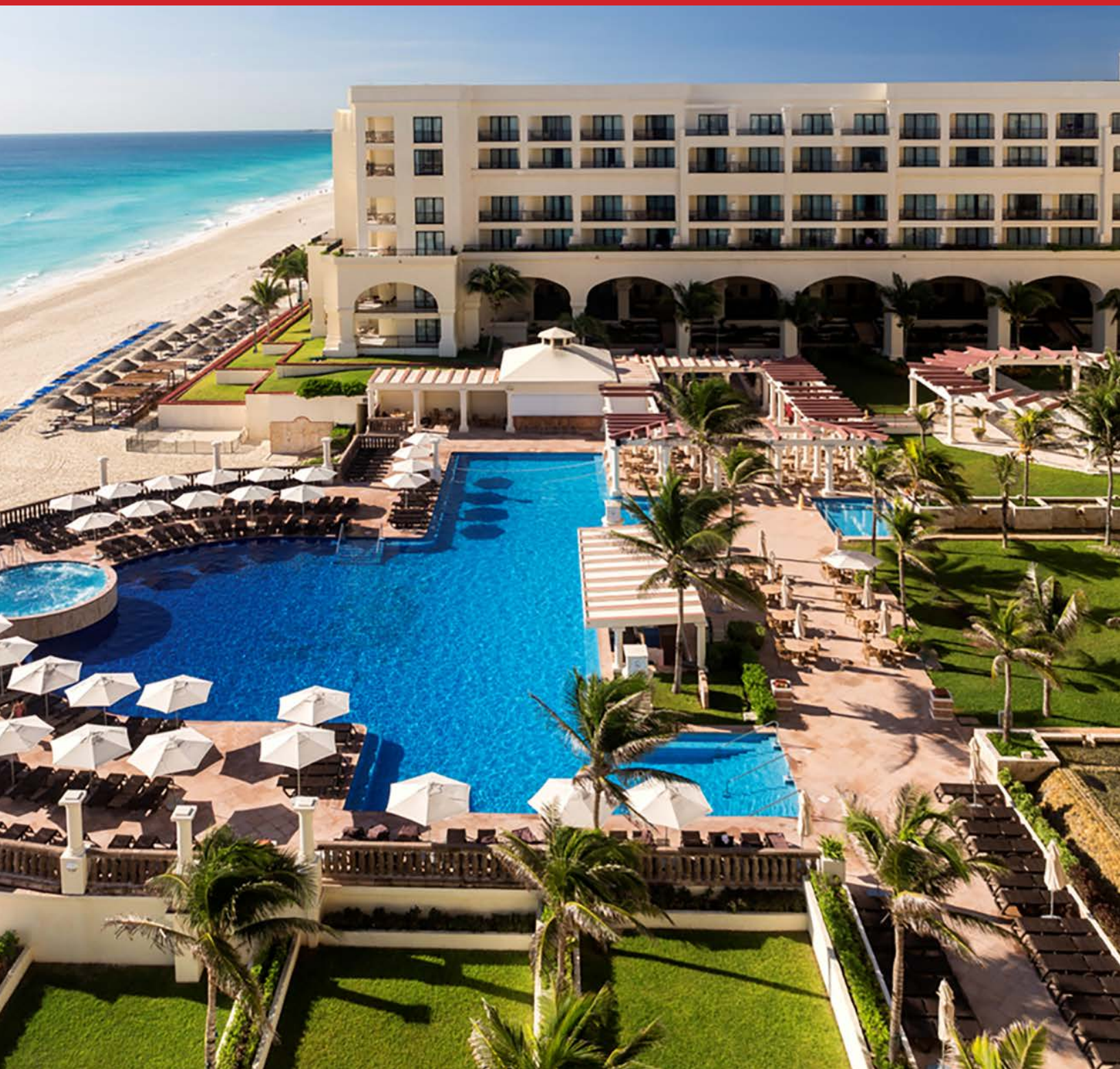
34TH ANNUAL MEETING OF THE SOCIETY FOR THERMAL MEDICINE

SYSTEMIC TREATMENT WITH LOCAL THERAPY

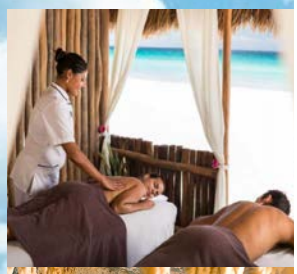
APRIL 29–MAY 2, 2017 • CANCÚN, MEXICO

2017 PROGRAM & ABSTRACT BOOK



Activities in Cancun

Activities offered at the CasaMagna Marriott Cancun Resort:



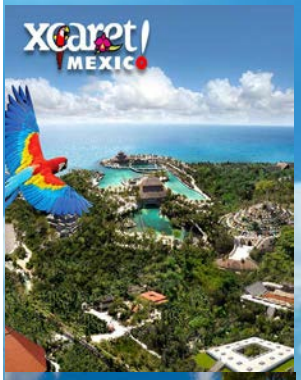
Jet-Ski Rentals, Boating, Horseback Riding, Snorkling or Scuba, Water-Skiing, Golf, and more!

On-Site Spa: Pamper yourself with massages, body wraps, facials, and other services.

On-property Beach, Outdoor Pool, and Whirlpool

Marriot Kid's Club: The Marriott Kid's Club offers organized daily activities for children from ages four to twelve. The club has a fee of $35.00 per participant.

Activities in the Cancun Area:

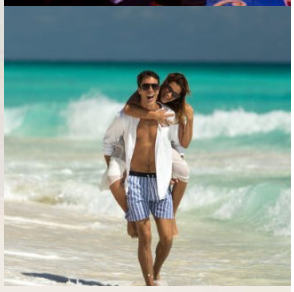


Mayan Ruins: Located just under two hours away from the Resort, both Chichen Itza and Tulum are ancient sights worth seeing!

Xcaret: A family friendly adventure park located about one hour from the Resort, it is perfect for cultural experiences, adult water activities and kid's activities.

Cancun Tarpon Fishing: Mexico is a great place to embrace fishing, boating, and watersports. Cancun Tarpon Fishing is located 1 mile outside of the resort.

360 Surf School: Cancun is a great place to learn to surf, 360 Surf School is located about 3 miles from the Resort.



Dinner Cruises: Cancun has many different themed dinner cruises in the area, a great activity for the family or adult groups to enjoy.

Downtown Cancun: Downtown Cancun is just 30-minutes from the Resort. Downtown offers great restaurants, clubs and shopping areas!

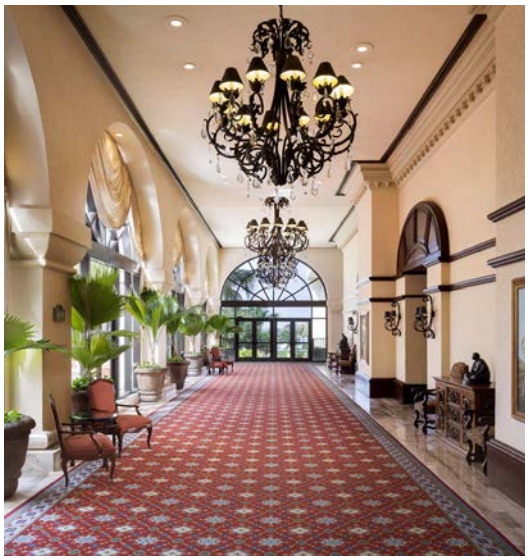
TABLE OF CONTENTS

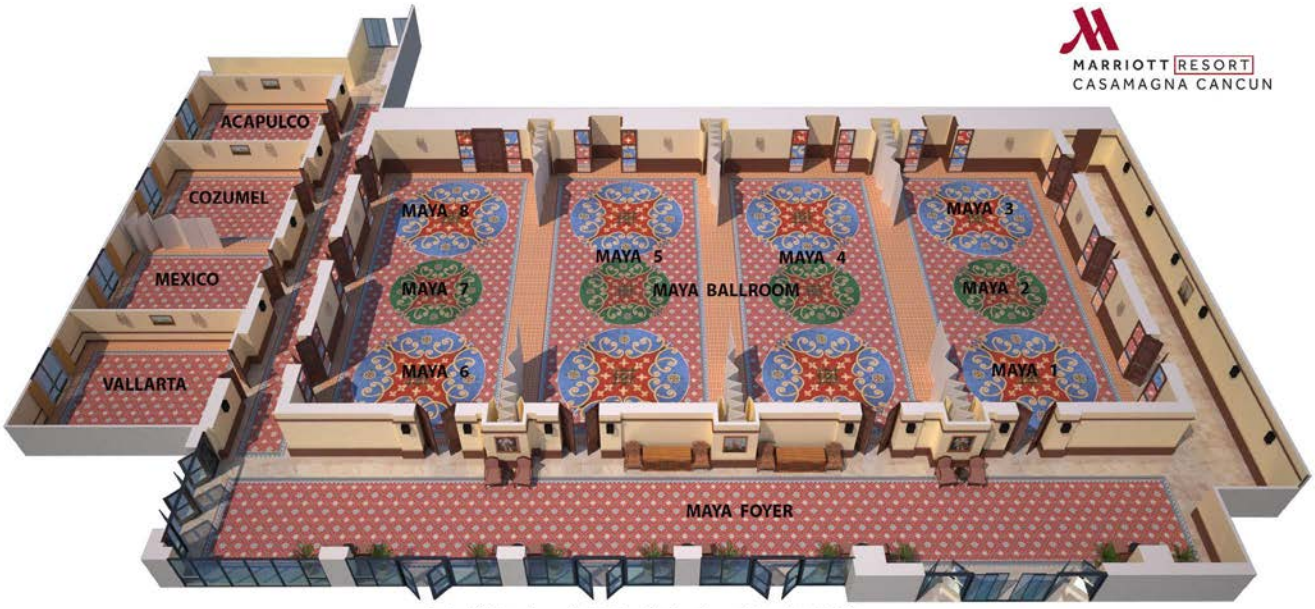
Meeting Info/Maps	2
Letter from the Program Chair	3–4
Thank You to Our Main Sponsor & Corporate Partners	5–7
2017 Planning Committee & Governing Council	12
IJH Editorial Board	13
2016 Taylor and Francis Editor's Award Winners	17
2017 JKTG Foundation Keynote Symposium – Keynote And Plenary Speakers	19–24
The George M. Hahn Award & Lecture – Dr. Mark W. Dewhirst	25–26
28th J. Eugene Robinson Award & Lecture – Prof. Gerard van Rhoon	27
2017 STM/JKTG Foundation New Investigator Awards	29–30
NCI/NIH – Cancer Nanotechnology Program – NIH updates	31
JKTG Foundation Refresher Workshop – The Physics, Biology, and Immunology of Thermal Nanomedicine	32
Presidential Symposium – Computational Modelling in Thermal Medicine	33
Program	35–62
Abstracts	63–228
Author Index	229–231

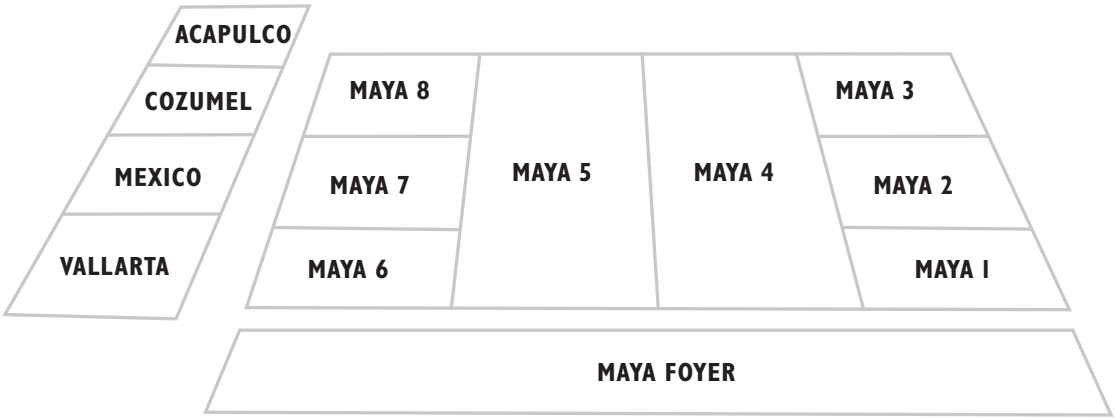
MEETING INFO/MAPS

Registration Desk Hours of Operation in the MAYA FOYER

Saturday, April 29	8:00am – 6:00pm
Sunday, April 30	7:00am – 6:00pm
Monday, May 1	7:00am – 5:00pm
Tuesday, May 2	7:00am – 5:00pm







Dear colleagues,

I want to welcome each of you to the 34th Annual Meeting of the Society for Thermal Medicine.

Many standard-of-care treatments address a local manifestation of disease. Surgery, radiation, and thermal therapies collectively represent a significant proportion of treatment options for many pathological conditions, especially cancer. Yet these modalities are often ('traditionally') considered inadequate for systemic conditions because the intervention lacks systemic impact.

ROBERT IVKOV, PHD

It is becoming accepted that hyperthermia is but one aspect of "Thermal Therapies", which cover the temperature range from cryotherapy to thermal ablation. Hyperthermia elicits a diverse array of biologic effects that can be used to augment the effectiveness of radiation and chemotherapies. Although this fact has been established for several decades, new discoveries regarding how hyperthermia inhibits DNA damage repair, how it affects intra- and extra-cellular signaling, and how hyperthermia can elicit immune-stimulatory effects have generated significant interest to exploit these phenomena for systemic disease management.

Our understanding of disease continues to evolve, with more recent efforts focusing on the involvement of the host immune system in both pathogenesis and progression. Cancer immunology has made tremendous advances in the past decade, and an understanding is developing that thermal therapies can generate systemic changes to alter the course of disease progression and aid long-term patient management.

The theme of the 34th Annual Meeting of the Society for Thermal Medicine focuses on the conceptual revolution towards realizing systemic treatment impact with local thermal interventions. Special sessions and a Refresher Workshop highlight the interconnectivity of local and systemic biological and immunological effects of heat stress, and how these interconnections can be exploited with new technologies.

Among the advances in thermal therapy technologies that will be featured are focused ultrasound, photothermal, radiofrequency and microwave, and nanoscale engineered technologies. Many of these technologies have improved tremendously and have advanced into clinical use through regulatory approvals in the USA, Europe and Asia making thermal therapies more accessible and commonplace. As these efforts have continued, there has been considerable improvement to refine computational modelling and treatment planning tools. Quality assurance is a critical feature of any successful clinical endeavor, with refined modelling and thermometry providing the foundation.

The 34th Annual Meeting features a special symposium highlighting the frontline of research in photothermal therapies for medicine occurring in our host country, Mexico. It is an objective of this meeting to expand the outreach and presence of our society and its mission throughout the Americas. I believe expansion to a wider range of countries will benefit our society and clinicians.

Another special symposium we have organized focuses on clinical modelling with companion animals. Canines, felines, and other mammals that

are commonplace in households develop spontaneous diseases, such as cancer, that remarkably mimic the etiology of human disease. Companion animals have long provided us with many benefits. In this symposium we will explore how companion animals can provide robust models to develop refined clinical trials designs and better therapeutics.

Our clinical trials updates and clinical applications symposium occupies three full sessions at this meeting, highlighting the continued growth of clinical applications. Results from new clinical trials and meta-analysis of prior clinical trials promise to reveal new insights to improving disease management with thermal therapies.

At the 34th Annual Meeting of the Society for Thermal Medicine, we will show the potential of thermal therapies to have systemic impact on disease.

With Regards,
ROBERT IVKOV, PHD

ROBERT IVKOV, PHD

Program Chair, President-Elect, Society for Thermal Medicine

Associate Professor, Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

Associate Editor, *International Journal of Hyperthermia*

A SPECIAL THANK YOU TO OUR MAIN SPONSOR

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

The JKTG Foundation is pleased to support the 34th Annual Meeting of the Society for Thermal Medicine. Enjoy the meeting!

The Jayne Koskinas Ted Giovanis Foundation for Health and Policy (JKTG) supports independent research, data analysis, events and other projects that improve health care and move health policy conversations beyond politics to achieve cost reduction, expand access and improve quality.

JKTGFoundation.org
@JKTGFoundation

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

Supported by the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, a Maryland private foundation dedicated to effecting change in health care for the public good. The opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and not necessarily those of the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, its directors, officers, or staff.

OUR CORPORATE PARTNERS

GOLD LEVEL

FOCUSED ULTRASOUND FOUNDATION

PHILIPS

SILVER LEVEL

heckel
hyperthermie

BRONZE LEVEL

nanoTherics

ZELTIQ

FRIENDS LEVEL

Celsius 42
Innovative Hyperthermie

COMBAT MEDICAL

FISO

micro mod

nB nanoScale Biomagnetics

SCIENTYMED

OTHER CONTRIBUTORS

iTheraMedical
Listening to Molecules

StressMarq Biosciences INC.

zurich med tech

34TH ANNUAL STM MEETING PLANNING COMMITTEE

Program Chair: Robert Ivkov, PhD, Johns Hopkins University School of Medicine Department of Radiation Oncology

Corporate Relations & Fundraising Chair: Zeljko Vujaskovic, MD, PhD, University of Maryland

Andris Bakuzis, PhD, Institute of Physics, Federal University of Goias, Brazil

Randy Burd, PhD, The University of Arizona Cancer Center

Erik Cressman, MD, PhD, University of Texas MD Anderson Cancer Center

Chris Diederich, PhD, University of California San Francisco

Steven Fiering, PhD, Geisel School of Medicine, Dartmouth College

Robert Griffin, PhD, University of Arkansas for Medical Sciences

Dieter Haemmerich, PhD, Medical University of South Carolina

Mark Hurwitz, MD, Thomas Jefferson University Hospitals

William Nau, PhD, Medtronic Minimally Invasive Therapies Group

Jason Stafford, MD, University of Texas MD Anderson Cancer Center

Paul Stauffer, PhD, Thomas Jefferson University

Christopher Lapine, STM Association Manager, Allen Press, Inc.

Joshua Hilbrand, Meeting Planner, K-State Conference Services

MISSION STATEMENT

The Society for Thermal Medicine is a 501(c)(3), non-profit organization whose mission is to significantly improve patient treatment outcomes by advancing the science, development and application of Thermal Therapy.

OUR SOCIETY STRIVES TO:

- Promote new discovery in thermal biology, physics/engineering, and medicine.
- Sponsor high quality forums for education of medical professionals in the practice of thermal medicine.
- Advocate for increased patient access to appropriate, high quality, thermal therapies.

GOVERNING COUNCIL

Society for Thermal Medicine (2016 –17)

PRESIDENT:
R. Jason Stafford, PhD
University of Texas MD Anderson Cancer Center
Houston, TX 77030

PRESIDENT-ELECT:
Robert Ivkov, PhD
Johns Hopkins School of Medicine
Baltimore, MD

VICE PRESIDENT-ELECT:
Michael Graner, PhD
University of Colorado
Aurora, CO

SECRETARY/TREASURER:
Dieter Haemmerich, PhD, DSc
Medical University of South Carolina
Charleston, SC

PAST PRESIDENT:
Erik N.K. Cressman, MD, PhD
University of Texas MD Anderson Cancer Center
Houston, TX

EDITOR-IN-CHIEF of *The International Journal of Hyperthermia*:
Mark W. Dewhirst, PhD, DVM
Duke University Medical Center
Durham, NC

Councilor: Biology /Chemical Sciences
2016–2017 Bonnie Hylander, PhD, Roswell Park Cancer Institute, Buffalo, NY

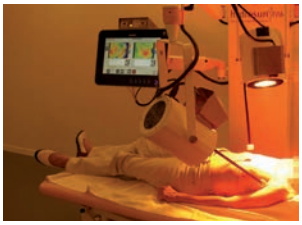
Councilor: Clinical/Medical Sciences
2016–2017 Rüdiger Wessalowski, PD Dr. med., Universitätsklinikum Düsseldorf, Düsseldorf, Germany

Councilor: Engineering/Physical Sciences
2016–2017 Rajiv Chopra, PhD, University of Texas Southwestern Medical Center, Dallas, TX

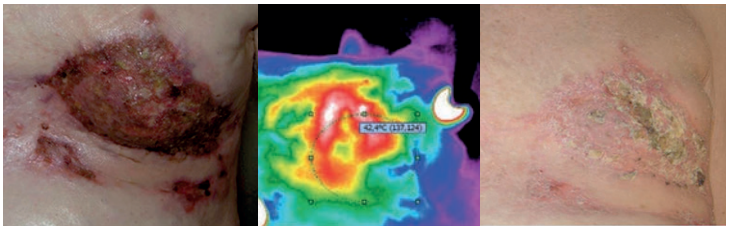
SPECIAL THANKS TO:
Society for Thermal Medicine Association Manager Christopher Lapine and Meeting Planner Joshua Hilbrand from Kansas State University Conference Services for their assistance with planning.

INTERNATIONAL JOURNAL OF HYPERTHERMIA BOARD MEMBERS

hydrosun-TWH 1500
Thermography-controlled Water-filtered infrared-A superficial Hyperthermia

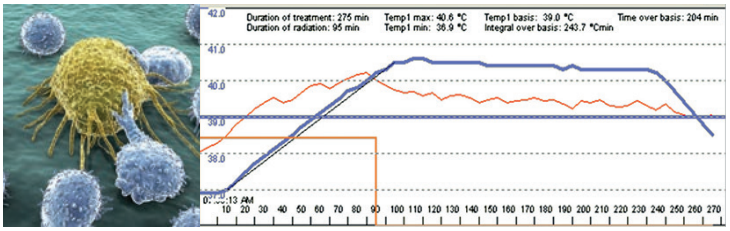


- Contact-free heating
- Real-time thermography measurement and control of superficial temperatures
- Effective in combination with tolerable, reduced radiation doses even for large and heavily pretreated target areas



heckel-HT3000
Whole Body Hyperthermia with Water-filtered infrared-A Radiation

- Stimulation of antitumor immune response
- Enhancement of perfusion and drug delivery
- Fever-range and extreme WBH
- Oncological and non-oncological indications (esp. chronic inflammation and infection)



Manufacturer:

hydrosun®
Hydrosun Medizintechnik GmbH
Mauchenerstr. 14, D-79379 Müllheim
info@hydrosun.de www.hydrosun.de

Distribution:

heckel
hyperthermie
heckel medizintechnik gmbh
Olgastr. 25, D-73728 Esslingen
Fon ++49 (0) 711-12 89 89-0 Fax ++49 (0) 711-12 89 89-20
info@heckel-medizintechnik.de www.hyperthermie.de

2016 TAYLOR AND FRANCIS EDITOR'S AWARD WINNERS

These chosen papers were selected by the Editorial Board of the *International Journal of Hyperthermia* as the best of Young Investigator papers (in their respective categories) that were published in 2016. Authors self-nominate themselves with the criteria being that they are less than 35 years of age. The editors have rigorous scoring criteria to help them select the winning papers.Our congratulations go to the following recipients of the 2016 awards:

PHYSICS/ENGINEERING

RAQUEL MARTÍNEZ-VALDEZ

Universidad Politécnica de Chiapas
Suchiapa,Chiapas,México

Design of a low power hybrid HIFU applicator for haemostasis based on acoustic propagation modeling

CLINICAL

ZACHARY ZIHUI YONG

Singapore General Hospital
Singapore, Singapore

Unresectability during open surgical exploration in planned cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

BIOLOGY

RACHEL WARDLOW

Oklahoma State University - Center for Veterinary Health Sciences
Stillwater, Oklahoma

Targeted antibiotic delivery using low temperature-sensitive liposomes and magnetic resonance-guided high-intensity focused ultrasound hyperthermia

Taylor & Francis
Taylor & Francis Group

2017 JKTG FOUNDATION KEYNOTE SYMPOSIUM
KEYNOTE AND PLENARY SPEAKERS

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

Supported by the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, a Maryland private foundation dedicated to effecting change in health care for the public good. The opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and not necessarily those of the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, its directors, officers, or staff.

KEYNOTE SPEAKER

DR. RICARDO BENTES DE AZEVEDO, PHD

University of Brasília, Brasilia, Brazil

"What does the future hold for PDT?"

SATURDAY, APRIL 29TH, 5:00PM–7:00PM / MAYA I-II-III-IV

DR. RICARDO BENTES AZEVEDO received his PhD degree from the University of Sao Paulo, Brazil with focused studies in Tissue and Cell Biology. He completed post-doctoral training at the National Institutes of Health (NIH) in Bethesda, Maryland, USA. Currently Dr. Azevedo is a scholar of the Brazilian National Council for Science and Technology (CNPq), he is the National Coordinator of the Brazilian Institute of Science and Technology (INCT) in Nanobiotechnology, and he holds a full Professor Chair in the Institute of Biological Sciences, at the University of Brasilia. The main focus of his research is biological and biomedical applications of nanostructured materials for drug delivery, imaging, and diagnosis. An area of intense interest in nanotechnology applications for Dr. Azevedo is the search for alternative treatments for cancer, microbial diseases, and treatment of environmental contamination using nanostructured materials as delivery agents of novel compounds derived from native plants and as mediators of complex chemical interactions. Dr. Azevedo's work has been cited over 3,000 times with over one hundred fifty published papers in varied scientific journals, including *Nature*, *Biomaterials*, *Journal of Biological Chemistry*, *Nanomedicine*, *Nanoscale*, *Journal of Biomedical Nanotechnology*, and many others.

2017 JKTG FOUNDATION KEYNOTE SYMPOSIUM

SATURDAY, APRIL 29TH, 5:00PM–7:00PM / MAYA I-II-III-IV

KEYNOTE SPEAKER

DR. INGRID HILGER, PHD

University Hospital Jena, Jena, Germany

"Future perspectives and challenges of magnetic hyperthermia tumor therapy"

SATURDAY, APRIL 29TH, 5:00PM–7:00PM / MAYA I-II-III-IV

PROF. DR. INGRID HILGER is head of the Department Experimental Radiology at the University Hospital Jena, Germany. Born in Argentina, she studied biology at the Christian-Albrechts-University in Kiel, Germany, and received her diploma in 1990. She performed several studies in biology in South America and Asia. Later on, she became interested in human biology and biochemistry and received her PhD at the University Hospital Hannover, Germany, in 1996. Since then, she focused her research activities to the areas of therapeutic nanotechnology and of in vivo meso/macroscopic optical molecular imaging and preclinical imaging in general. Since 2008, she is full professor at the University Hospital Jena, Germany. She was awarded the Walter Friedrich Prize in 2003 and an International Patent Innovation Prize in 2016. She is the spokesperson of the German Molecular Imaging Network and the German representative of the European Society of Molecular Imaging.

2017 JKTG FOUNDATION KEYNOTE SYMPOSIUM

SATURDAY, APRIL 29TH, 5:00PM–7:00PM / MAYA I-II-III-IV

KEYNOTE SPEAKER

DR. ELDER DE LA ROSA, PHD

Centro de Investigaciones en Óptica
Leon, Mexico

"The bright future of biophotonics in Mexico"

SATURDAY, APRIL 29TH, 5:00PM–7:00PM / MAYA I-II-III-IV

PROF. ELDER DE LA ROSA was born in Mexico in 1964. He received a PhD degree in 1998 from Centro de Investigaciones en Optica (CIO) and received a postdoctoral position at UNAM in 1999. He joined CIO in 2000 as a fulltime professor and has been the General Director since November 23, 2012. He is the founder of CIO's research group on Nanophotonics and Advanced Materials (NAFOMA). His research interests are linear and non-linear properties of advanced materials for photonic applications along with the synthesis and characterization of luminescence in nanostructured materials (oxides, semiconductors, metals) for lighting systems, solar cells, biosensing, biomedical applications, and preparation and characterization of luminescence in soft glasses (P_2O_5, TeO_2) doped with rare-earths for optic fiber amplifiers and lasers. He is SPIE fellow member since 2017, and member of SNI level III. He has published over 130 peer-reviewed scientific papers and has been cited more than 3000 times. He has also graduated 14 PhD and 13 MSc students. Prof. De la Rosa has been an invited editor from Optical Materials and Journal Nanoscience and Nanotechnology. Since 2004, he has annually organized the Topical Meeting on Nanoscience and Nanostructured Materials.

2017 JKTG FOUNDATION PLENARY SESSION I

SUNDAY, APRIL 30TH, 8:00AM–9:00AM / MAYA I-II-III-IV

PLENARY SPEAKER

DR. ELIZABETH REPASKY, MS., PHD

Roswell Park Cancer Institute, Buffalo, New York

"Chasing an Elusive Evidence-Based Rationale for Hyperthermia in the Cancer Clinic: Separating Fact from Fiction"

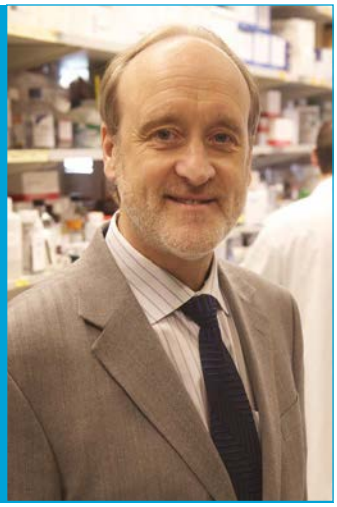
SUNDAY, APRIL 30TH, 8:00AM–9:00AM / MAYA I-II-III-IV

DR. ELIZABETH REPASKY is a Professor of Oncology, the William Huebsch Professor of Immunology, and a Program Leader for the Cell Stress and Biophysical Therapies Program at Roswell Park Cancer Institute (RPCI). Dr. Repasky's research program focuses on exploration of physiological responses which can be manipulated to alter the tumor microenvironment and improve the efficacy of cancer therapies, including immunotherapies. A major passion for her has been to understand the role of body temperature and the impact of mild thermal stress (hyperthermia and heat shock response) on anti-tumor immune activity, vascular function and metabolism. During her career, she has authored or co-authored over 170 cited publications. Dr. Repasky is a recent awardee of the J. Eugene Robinson Award from the Society for Thermal Medicine. Training and mentorship have been passions for her during her career and she has served as major advisor to 20 PhD students and 8 Postdoctoral Fellows who have gone on to become successful members of the research, academia or bio-tech communities. Several of her trainees are now members of the Society for Thermal Medicine.

2017 JKTG FOUNDATION PLENARY SESSION I

SUNDAY, APRIL 30TH, 8:00AM–9:00AM / MAYA I-II-III-IV

PLENARY SPEAKER



DR. ROBERT CLARKE, PHD, D.SC.

Georgetown University Medical Center
Washington, D.C.

"Modeling Endocrine Resistance in Breast Cancer - A Systems Biology Approach"

SUNDAY, APRIL 30TH, 8:00AM–9:00AM / MAYA I-II-III-IV

DR. ROBERT CLARKE is Professor of Oncology at Georgetown University (Washington, DC, U.S.A), Co-Leader of the Breast Cancer Program at the Georgetown Lombardi Comprehensive Cancer Center, and Dean for Research at Georgetown University Medical Center (GUMC). A Senior Editor for the journal, *Cancer Research*, Dr. Clarke serves on the boards of over a dozen international scientific journals. He regularly serves on state, national, and international grant peer-review study sections; completing his term as chair of an N.I.H. grant peer-review study section in 2008 (2002–2008; *National Center for Complementary and Alternative Medicine*) and again in 2013 (2011–2013; *Basic Mechanisms of Cancer Therapeutics*). Regularly invited to speak about his research at international and national meetings, he served a two year term as the elected NCI-SigmaXi Distinguished Lecturer (2012-2014). Dr. Clarke takes a systems biology approach to studying how hormones (endogenous and exogenous) and related factors affect breast cancer. He and his colleagues have recently defined a unified model of the hormonal regulation of breast cancer cell proliferation and cell death in response to estrogens, aromatase inhibitors, and antiestrogens. This signaling represents communication between endoplasmic reticulum and mitochondria, and reflects novel interactions among the unfolded protein response, autophagy, and cellular metabolism.

2017 JKTG FOUNDATION PLENARY SESSION II

MONDAY, MAY 1ST, 8:00AM–9:00AM / MAYA I-II-III-IV

PLENARY SPEAKER

DR. DENIS WIRTZ, PHD

Johns Hopkins University, Baltimore, Maryland

"Cancer Cell Biology in 3D"

MONDAY, MAY 1ST, 8:00AM–9:00AM / MAYA I-II-III-IV

DR. DENIS WIRTZ is the vice provost for research and a professor of chemical and biomolecular engineering at The Johns Hopkins University. He also directs the Johns Hopkins Physical Sciences-Oncology Center and co-directs the Cancer Nanotechnology Training Center, both National Cancer Institute-funded entities. Wirtz holds the T.H. Smoot Professorship in the Whiting School of Engineering's Department of Chemical and Biomolecular Engineering, and has secondary appointments in the School of Medicine's Departments of Oncology and Pathology. Wirtz earned his B.Sc. in Engineering Physics from the Université Libre de Bruxelles in Belgium and M.Sc. and Ph.D. degrees in Chemical Engineering from Stanford University. He studies the biophysical properties of healthy and diseased cells, including interactions between adjacent cells and the role of cellular architecture on nuclear shape and gene expression. Cell biophysics, single molecule manipulation, intracellular particle trafficking, instrument development, tissue engineering, and nanotechnology in biology and medicine are among his research interests. He has authored more than 200 peer-reviewed articles, and his research has been cited more than 14,000 times.

THE GEORGE M. HAHN AWARD & LECTURE

MONDAY, MAY 1ST, 3:30PM–6:00PM / MAYA I-II-III-IV

AWARD WINNER

MARK W. DEWHIRST, DVM, PHD, FASTRO, FAAAS

Duke University Medical Center
Durham, NC

MONDAY, MAY 1ST, 3:30PM–6:00PM / MAYA I-II-III-IV

The George M. Hahn Award is presented every other year to an investigator whose research has contributed in a significant way to new clinical applications in thermal therapy. This lecture is named in honor of Dr. George Hahn who received the first Robinson Award in 1989. Dr. Hahn led a highly productive clinical program grant at Stanford for many years and his fundamental work in the heat shock response and in how hyperthermia modifies chemotherapy sensitivity still stands today as foundational work. His highly productive career exemplifies the translational attributes of this award.

Hyperthermia and thermosensitive liposomes. For 19 of 23 years, I was PI of a program grant focused on applications of hyperthermia in the treatment of cancer (NIH/NCI 42745; Hyperthermia and Perfusion Effects in Cancer Therapy). We published well over 200 papers, which have been cited >9000 times. A major focus of our program was on establishment of principles and practice of thermal dosimetry. Much of this work led to the establishment of the original RTOG QA guidelines for invasive thermometry. The realization that invasive thermometry was too imprecise and impractical, led to our early testing of MR thermometry. Our group was the first to show that MR thermometry could be used to assess efficacy of thermoradiotherapy.

Our group published many papers related to the physiologic effects of hyperthermia. What set us apart from many other investigators was our emphasis in performing such measurements in the clinic, as opposed to pre-clinical models. An example was our demonstration that hyperthermia mediated reoxygenation of high grade soft tissue sarcomas was associated with thermoradiotherapy response[1]. Our early pre-clinical work showing that hyperthermia increases microvessel pore size led us to pursue the concept of using hyperthermia to increase nanoparticle drug delivery[2]. Our landmark paper showing that a novel thermosensitive liposome that exhibits rapid drug release upon reaching its transition temperature at 41.3°C[3] greatly accelerated work by our group and several others, to use this type of drug for traditional hyperthermia applications. The more recent discovery that this drug creates the enhanced drug delivery to tumor via intravascular drug release in the heated tissue highlights the unique feature of its drug delivery properties[4]. The application of this liposome with thermal ablative methods such as radiofrequency, microwave and HIFU, may be the first approved application for this drug delivery technology, where the rationale is to increase drug delivery to the periphery of ablated zones as a means to reduce marginal miss.

Companion Pet animal cancers as models for human cancer. My PhD thesis advisor was Edward Gillette, an early pioneer in the field of "Comparative Oncology", where the goal was to conduct innovative

high risk trials with canine cancers as a means to ask translational questions that could not be asked in human trials. Over the years, I was involved in the conduct of many clinical trials and in the oversight of physiologic correlative studies that were conducted as part of these trials. Over 70 papers were conducted by my group or in collaboration with Dr. Gillette. These papers garnered over 1200 citations. I conducted the first randomized phase III trial testing the value of hyperthermia as an adjuvant to radiotherapy, wherein 250 dogs with cancer were enrolled. This trial not only established the value of hyperthermia, but it also identified several key prognostic factors, including the importance of measuring thermal dose[5]. A key follow up trial was the first demonstration that prospective delivery of a prescribed thermal dose to companion dogs with soft tissue sarcomas lead to a significant improvement in progression free survival after thermoradiotherapy. This work was the first demonstration that the thermal equivalent dose formulation, devised by Sapareto and Dewey, could be used clinically to predict efficacy of thermoradiotherapy trials[6]. We also conducted the first phase I trial of a doxorubicin containing thermosensitive liposome in dogs with cancer[7]. These data were an important part of the FDA IND filing of this drug. The toxicity profile was valuable in setting the stage for human trials that followed. We also published several papers in which we used MRI/MRS to acquire physiologically relevant endpoints that we tested for their association with treatment outcome. Key papers in this series demonstrated that extracellular pH, DCE/MRI/MRS parameters are associated with progression free survival and metastatic rate in dogs with soft tissue sarcomas that were treated with thermoradiotherapy[8]. Importantly, on several occasions we identified similar prognostic factors in human trials[9]. Importantly, the Institute of Medicine and the NCI have now formally recognized the true value of companion canine cancers as being key to the cancer therapeutics development continuum[10].

CITATIONS

1 Brizel, D. M. et al. Radiation therapy and hyperthermia improve the oxygenation of human soft tissue sarcomas. *Cancer Research* **56**, 5347-5350 (1996). **127 citations**

2 Kong, G., Braun, R. D. & Dewhirst, M. W. Hyperthermia enables tumor-specific nanoparticle delivery: Effect of particle size. *Cancer Res*. **60**, 4440-4445 (2000).**392 citations**

3 Needham, D., Anyarambhatla, G., Kong, G. & Dewhirst, M. W. A new temperature-sensitive liposome for use with mild hyperthermia: Characterization and testing in a human tumor xenograft model. *Cancer Res*. **60**, 1197-1201 (2000).**436 citations**

4 Manzoor, A. A. et al. Overcoming Limitations in Nanoparticle Drug Delivery: Triggered, Intravascular Release to Improve Drug Penetration into Tumors. *Cancer Res*. **72**, 5566-5575, doi:10.1158/0008-5472.can-12-1683 (2012).**127 citations - designated "highly cited" by Thompson and Reuters**

5 Dewhirst, M. W., Sim, D. A., Sapareto, S. & Connor, W. G. IMPORTANCE OF MINIMUM TUMOR TEMPERATURE IN DETERMINING EARLY AND LONG-TERM RESPONSES OF SPONTANEOUS CANINE AND FELINE TUMORS TO HEAT AND RADIATION. *Cancer Research* **44**, 43-50 (1984).**168 citations**

6 Thrall, D. E. et al. Thermal dose is related to duration of local control in canine sarcomas treated with thermoradiotherapy. *Clinical Cancer Research* **11**, 5206-5214, doi:10.1158/1078-0432.ccr-05-0091 (2005).**50 citations**

7 Hauck, M. L. et al. Phase I trial of doxorubicin-containing low temperature sensitive liposomes in spontaneous canine tumors. *Clinical Cancer Research* **12**, 4004-4010, doi:10.1158/1078-0432.ccr-06-0226 (2006).**81 citations**

8 Lora-Michiels, M. et al. Extracellular pH and P-31 magnetic resonance spectroscopic variables are related to outcome in canine soft tissue sarcomas treated with thermoradiotherapy. *Clinical Cancer Research* **12**, 5733-5740, doi:10.1158/1078-0432.ccr-05-2669 (2006).**24 citations**

9 Dewhirst, M. W. et al. Relation between pO(2), P-31 magnetic resonance spectroscopy parameters and treatment outcome in patients with high-grade soft tissue sarcomas treated with thermoradiotherapy. *International Journal of Radiation Oncology Biology Physics* **61**, 480-491, doi:10.1016/j.ijrobp.2004.06.211 (2005).**19 citations**

10 LeBlanc, A. K. et al. Perspectives from man's best friend: National Academy of Medicine's Workshop on Comparative Oncology. *Science Translational Medicine* **8**, doi:10.1126/scitranslmed.aaf0746 (2016).

28TH J. EUGENE ROBINSON AWARD & LECTURE

MONDAY, MAY 1ST, 3:30PM–6:00PM / MAYA I-II-III-IV

AWARD WINNER

PROF. GERARD VAN RHOON, PHD

Erasmus MC Cancer Institute
Rotterdam, The Netherlands

MONDAY, MAY 1ST, 3:30PM–6:00PM / MAYA I-II-III-IV

The J. Eugene Robinson Award is presented annually to an investigator who has made outstanding contributions to the field of hyperthermic oncology in one or more of the three main disciplines: Medicine/Clinical, Biology/Physiology, and Physics/Engineering. It is the highest and most prestigious award of the Society for Thermal Medicine. The award is named after J. Eugene Robinson who was a pioneer of hyperthermia research from the 1960's through the 1980's and a strong proponent of combined radiation and hyperthermia for cancer therapy.

Gerard van Rhoon is trained as a physicist and obtained in 1994 his Ph.D. at the Lab. of Electromagnetic Research, Delft University of Technology on the feasibility of regional deep hyperthermia using radiofrequency electromagnetic fields. He has been involved in the clinical application of hyperthermia in cancer from the first hour and made pivotal contributions for integrating hyperthermia in regular health care in The Netherlands. His research activities aim at the development of the required technology to achieve a well-controlled localized heating of tumors at all sites in the human body. He has designed several high power RF measuring devices specifically for the measurement RF-fields in the near-field of RF-antennae to enhance quality assurance. His recent interest is the development of technology to enable thermal-ablation brachytherapy to treat patients using minimally invasive, precise therapy as a one stop-shop intervention using high quality, intelligent and augmented reality imaging guidance.

In 2011 he was appointed as Professor in Physical Aspects of Electromagnetic Fields & Health 2011 at the Erasmus MC Cancer Institute. From 2001–2016 he was a member of the Health Council of The Netherlands and chaired Committee 673: Electromagnetic Fields concerning EMF in society. He is a senior editor of the Int. J. of Hyperthermia and auditor for Physics in Medicine and Biology. In 2013 he was elected President of the European Society for Hyperthermic Oncology. Beginning in 2016, he has served as PI of the Academic Center of Excellence of Minimal Invasive Image Guided Therapy of Erasmus MC Cancer Institute and of the Intervention Radiotherapy Pillar of the dept. Radiation Oncology.

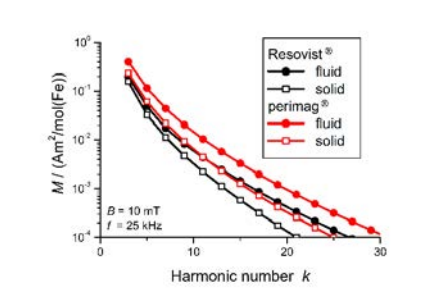
He is author of over 150 peer-reviewed publications and over 120 publications in books, proceedings and non-peer-reviewed journals. He received the first Lund Science Award in 1987, the Dr. BB Singh Award of the Indian Association of Hyperthermic Oncology & Medicine in 2008, the ESHO-BSD award in 2008 and the Dr. Sugahara Award in 2012.

micromod Partikeltechnologie GmbH

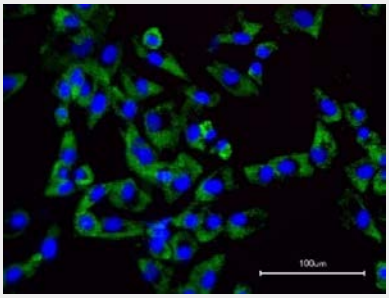
For more than **20 years** micromod has been the reliable supplier of particle-based system components for *in vitro* diagnostics, high-throughput screening, magnetic bio-separation, cell labeling as well as a partner in R&D of novel components for diagnosis (MPI, MRI) and cancer therapy (hyperthermia). A modern quality management according to EN ISO 13485 ensures a high quality standard in the development and production of **micro- and nanoparticles**.

perimag® - our new Magnetic Nanoparticles with Excellent Properties

- **as contrast agent for Magnetic Particle Imaging (MPI) and MRI**
- **for hyperthermia applications**
- **for homing and tracking of stem cells in regenerative medicine**



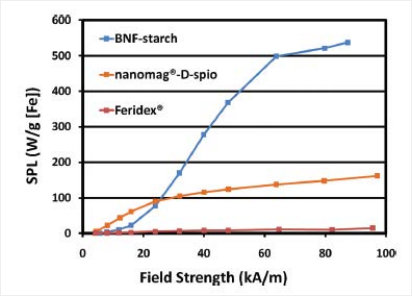
Magnetic Particle Spectra (MPS) of suspended and immobilized perimag® and Resovist®
(D. Eberbeck *et al. IEEE Transactions on Magnetics* 2013, 49 (1), 269-274.)



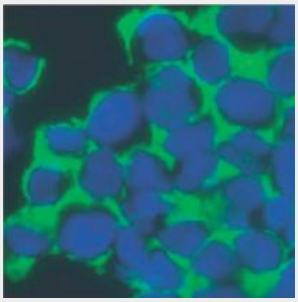
Labeling of hMSC with fluorescent perimag®
(nucleus: blue; perimag® in cytoplasm: green)
(T. Kilian et al. *Nanomedicine* 2016, 11 (15), 1957-1970.)

BNF - our established Bionized NanoFerrite with Excellent Properties

- **for targeted hyperthermia and MRI applications**
- **as tools in biosensor and lab-on-chip applications**



Specific power loss (SPL) vs field strength curve of BNF-Starch particles in comparison to other commercial magnetic nanoparticles
(D. E. Bordelon et al. *J. Appl. Phys.* 2011,109, 124904)



Immunofluorescence microscopy of CHLA-20 detecting human IgG and nuclear DAPI.
Cells were pretreated with anti-GD2-BNF conjugates
(D. Baiu et al. *Nanomedicine* 2015,10(19), 2973-2988)

www.micromod.de

2017 STM NEW INVESTIGATOR AWARDS

Jayne Koskinas Ted Giovanis | Foundation for Health and Policy

We are pleased to announce that The Society for Thermal Medicine, *with funding from the Jayne Koskinas Ted Giovanis Foundation for Health and Policy*, is providing travel grants to **15 New Investigators** to encourage participation at the 2017 STM annual meeting. Awardees will receive a $500 travel grant and gratis registration to the meeting. Travel Awards recipients are based upon a competitive evaluation of their submitted abstracts and New Investigator Award applications

HALE ARCA
Novel Photo-induced Chemotherapy Delivery Matrix for Support of Abdominal Organs following Cytoreductive Surgery

Wake Forest School of Medicine, Winston Salem, North Carolina USA

JAMES BARNETT
Temperature-dependent activation of DNA damage repair in human colorectal cancer cells

Johns Hopkins University School of Medicine, Baltimore, Maryland USA

STEVEN BROUSELL
Synergistic Immuno-Photothermal Nanotherapy (SYMPHONY): A Novel Treatment for Localized and Metastatic Bladder Cancer

Duke University, Durham, North Carolina USA

JULIANA CANO-MEJIA
Prussian blue nanoparticle-based photothermal therapy combined with checkpoint inhibition for photothermal immunotherapy of neuroblastoma

University of Maryland, Hyattsville, Maryland USA

BINGBING CHENG
Development of a remote acoustic sensing safety mechanism for biofilm eradication using alternating magnetic fields

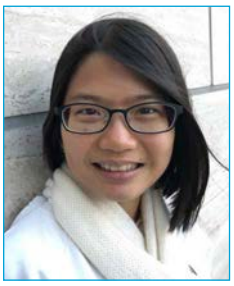
University of Texas Southwestern Medical Center, Dallas, Texas USA

EUN-YOUNG KOH
Development of the thermosensitizer for maximizing cancer treatment efficacy with the radiofrequency-induced hyperthermia

Jeonbuk National University, Jenonju-Si, Jeollabik-Do Republic of Korea

SATYA VVN KOTHAPALLI
Identification of clinical MR-HIFU hyperthermia treatment sites through validation of MR thermometry accuracy and precision in healthy volunteers

Washington University in Saint Louis, Saint Louis, Missouri USA



JESSIE LEE
Compact Ultrasound Applicator for Hyperthermia Treatment of the Transgenic Adenocarcinoma Mouse Prostate Model (TRAMP) with MR Thermometry in a 14T MRI Scanner

University of California San Francisco, San Francisco, CA USA

JASON MOLITORIS
Radiation Therapy plus External Thermal Therapy Results in Modest Toxicities with the Promise of Increased Efficacy: A Single Institutional Experience

University of Maryland Medical Center, Baltimore, Maryland USA

ANJAN MOTAMARRY
In vivo fluorescence imaging predicts drug uptake for temperature sensitive liposomal doxorubicin

Medical University of South Carolina, Charleston, South Carolina USA

IMALKA MUNAWEERA
Temperature-Sensitive Liposomal Ciprofloxacin for the Treatment of Biofilm on Prosthetic Joint Implants using Alternating Magnetic Fields

University of Texas Southwestern Medical Center, Dallas, Texas USA

ARLENE OEI
Hyperthermia affects both BRCA2-proficient and BRCA2-deficient cell lines

Department of Radiation Oncology, AMC, Amsterdam The Netherlands

ELIZABETH SWEENEY
Eliciting immunogenic cell death using Prussian blue nanoparticle-based photothermal therapy and the implications for cancer therapy

Children's National Health System, Washington, DC USA

LI TIAN
Co-delivery of nanoparticulated NVP BEZ-235 decreases cell proliferation of irreversible electroporation treated xenograft

The University of Texas MD Anderson Cancer Center, Houston, Texas USA

BETTINA WEIGELIN
Activating serial killers of cancer cells: Hyperthermia as supporting strategy for cancer immunotherapy

MD Anderson Cancer Center, Houston, Texas USA

NCI/NIH
CANCER NANOTECHNOLOGY PROGRAM – NIH UPDATES

MONDAY, MAY 1ST, 1:00PM–1:30PM / MAYA I-II-III-IV

SPEAKER

DR.CHRISTINA LIU, PHD PE

National Cancer Institute, National Institutes of Health Office of Cancer Nanotechnology Research, Bethesda, Maryland

Nanotechnology in Thermal Medicine-Current Status, Future Opportunities & NIH Grant Support

Christina H. Liu is a Program Director in the Office of Cancer Nanotechnology Research (OCNR), Center for Strategic Scientific Initiatives at the National Cancer Institute (NCI), National Institutes of Health (NIH), in Bethesda, Maryland. Currently, Christina manages nanotechnology projects and grants, participates in the development of new initiatives, and evaluates the effectiveness of programs within the Alliance for Nanotechnology in Cancer (the Alliance). She is a member of NCI's Nanotechnology Working Group and NIH's representative to the Nanotechnology Knowledge Infrastructure, under the U.S. National Nanotechnology Initiative. Detailed information about the NCI's Office of Cancer Nanotechnology Research and the Alliance is available at http://nano.cancer.gov/. Before joining NCI, Christina was the Program Director for the Molecular Imaging Program at the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and earlier, Program Officer for the Shared and High-End Instrumentation Programs (SIG/HEI) at the National Center for Research and Resources (NCRR, now under NIH's Office of Research Infrastructure Programs). Prior to joining NIH, Christina was a research scientist and faculty at the Massachusetts General Hospital/Harvard Medical School in Boston, MA. Her research focus was on the technical development of contrast-enhanced functional and molecular magnetic resonance imaging (MRI) to assess gene transcriptional changes in brain associated with drug addiction and stroke recovery. Christina earned her BS degree in Chemistry from the University of Washington, Seattle, WA and MS and PhD degrees in Chemical Engineering from Rice University and subsequently worked in the Petrophysical Interpretation Group in Baker Hughes Oil Service Company in Houston, TX, where magnetic resonance was used for oil exploration.

JKTG FOUNDATION REFRESHER WORKSHOP

THE PHYSICS, BIOLOGY, AND IMMUNOLOGY OF THERMAL NANOMEDICINE

SATURDAY, APRIL 29TH, 10:00AM–3:00PM / MAYA VI-VII

SPEAKERS

ANDRIS BAKUZIS
ROBERT IVKOV
MICHAEL GRANER
ELIZABETH REPASKY
GERARDO GOYA
FRED BUNZ

Thermal medicine involves multiple disciplines to deliver and control energy delivery to tissues with the objective to raise the local temperature for enhanced therapeutic benefit. Among the earlier embodiments translated to clinic, and still forming an operational treatment paradigm, are applications that utilize various energy sources to heat solid malignancies concomitant with radiation therapy to achieve better local control of cancer. While this embodiment of thermal medicine demonstrates significant benefits to cancer patients, even conferring improved overall survival, persisting challenges dampen enthusiasm for wider adoption. Some limitations are technological, but a principal objection to concomitant hyperthermia has been that its benefits are local, and thus unable to confer durable response, or 'cure'. It may be argued that much of this perception derives from the mechanistic focus of heat stress being limited to DNA-damage repair inhibition. Other biological, immunological, and physiological consequences of local and systemic heating have recently garnered significant attention to explore the effects of localized tumor damage that can elicit profound systemic responses to enhance long-term disease management. Thermal nanomedicine, a relatively recent entrant to the field has demonstrated potential utility in preclinical and clinical settings to improve energy deposition, imaging guidance of treatments, and for drug delivery. An aspect of nanostructured materials that is often ignored (or considered a nuisance to be minimized) is their inherent immunogenicity. Often resembling viruses in size and shape, nanoparticles offer significant potential to modulate biological and immunological responses to therapeutic intervention. The objective of this focused refresher workshop is to provide researchers and research trainees an overview of the many exciting facets of heat stress and thermal nanomedicine. Attendees will receive a refresher on subject matter integral to the 34th Annual Meeting of the Society for Thermal Medicine.

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

PRESIDENTIAL SYMPOSIUM – COMPUTATIONAL MODELLING IN THERMAL MEDICINE

TUESDAY, MAY 2ND, 11:30AM-1:00PM / MAYA I-II-III-IV / MAYA VI-VII

SPEAKERS R. JASON STAFFORD, PUNIT PRAKASH, DIETER HAEMMERICH, DAVID FUENTES

Thermal therapies embrace a diverse spectrum of disciplines including the biological, physical and clinical sciences. For over 30 years, the Society for Thermal Medicine has served as a proverbial 'melting pot' bringing scientists together to advance thermal therapies for patient benefit.

Computational modeling and simulation has played an ever increasingly important role within thermal medicine as the chief integrator of our biophysical and clinical theories and observations for translation into quantitative predictions. Biophysical models of heat generation and transfer for a diverse range of modalities – including hyperthermia and thermal ablation therapies - can be used to predict the distribution of temperature and integrated with appropriate feedback measurements. These models can be further expanded to investigate the impact of temperature on physiological or biological processes. Models based on observations of physiological or biological response to heat can be coupled with these biophysical models of heat transfer to predict effects of heating from new modalities as well as plan or guide treatment delivery. Computational modeling has brought thermal medicine from petri dish to patient as well as brought device from bench to bedside. Such models have been applied in various ways, including: (1) As a research tool to investigate biophysical effects, (2) integrated into the development of novel devices, and (3) for patient specific treatment planning of thermal therapies.

So, what has changed? As computational capacity and algorithms have advanced, and more user-friendly software tools have become available, so has the role of computational science within our discipline. Dynamic, data driven algorithms incorporating a variety of parametric and non-parametric methods and stochastic approaches to data assimilation produce increasingly more accurate predictions based on an accumulation of knowledge over time. Such predictions from these multiscale models can play a role in the investigation of physical or biological phenomena; development and validation of devices or procedures; treatment planning and simulation for patient selection; treatment guidance and control; as well as prediction of outcomes.

In this symposium, four outstanding society members working in the area of computational modeling and simulation of thermal therapy provide an overview of the role of computational science in thermal medicine. Essential and emerging techniques and the possibilities they facilitate, punctuated by examples from research will be presented as well as visions for the future.

PROGRAM

FRIDAY, APRIL 28TH

INTERNATIONAL JOURNAL OF HYPERTHERMIA STRATEGIC PLANNING MEETING

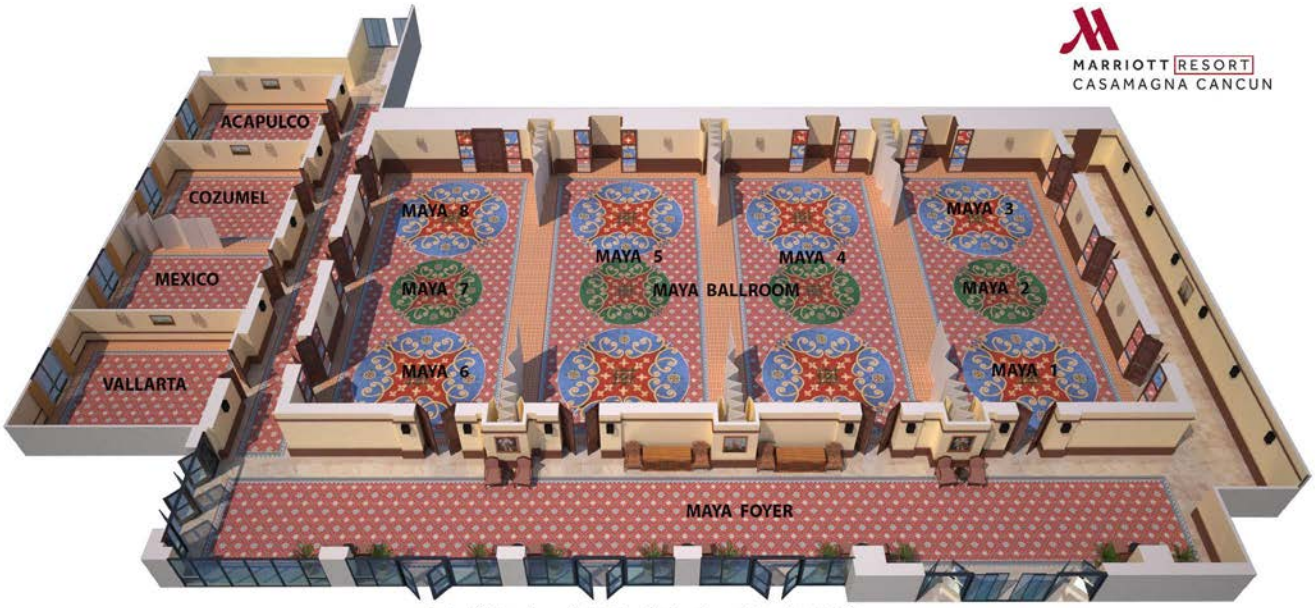
8:00AM–1:00PM MEXICO/COZUMEL

STM GOVERNING COUNCIL MEETING

2:00PM–3:30PM MEXICO/COZUMEL

STM 2018 PLANNING MEETING

4:00PM–5:30PM MEXICO/COZUMEL



SATURDAY, APRIL 29TH

REGISTRATION

8:00AM-6:00PM MAYA FOYER

OTHER STM COMMITTEE MEETINGS

8:00AM-11:00AM MEXICO/COZUMEL

STM FINANCE COMMITTEE MEETING

9:00AM-10:30AM VALLARTA

JKTG FOUNDATION REFRESHER WORKSHOP - THE PHYSICS, BIOLOGY, AND IMMUNOLOGY OF THERMAL NANOMEDICINE

10:00AM-3:00PM MAYA VI-VII CHAIR: ROBERT IVKOV

SAT 01 THE PHYSICS, BIOLOGY, AND IMMUNOLOGY OF THERMAL NANOMEDICINE
Andris Bakuzis[1], Robert Ivkov[2], Michael Graner[3], Elizabeth Repasky[4], Gerardo Goya[5], Fred Bunz[6]
[1]Federal University of Goiás, Goiânia, Goiás, Brazil, [2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [3]University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA, [4]Roswell Park Cancer Institute, Buffalo, New York, USA, [5]Universidad de Zaragoza, Zaragoza, Spain, [6]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

2017 JKTG FOUNDATION KEYNOTE SYMPOSIUM

5:00PM-7:00PM MAYA I-II-III-IV CHAIR: ROBERT IVKOV

SAT 02 THE BRIGHT FUTURE OF BIOPHOTONICS IN MEXICO
Elder De la Rosa
centro de investigaciones en optica, leon, gto, Mexico

SAT 03 FUTURE PERSPECTIVES AND CHALLENGES OF MAGNETIC HYPERTHERMIA TUMOR THERAPY
Ingrid Hilger
University Hospital Jena, Jena/Thuringia, Germany

SAT 04 WHAT DOES THE FUTURE HOLD FOR PDT?
Ricardo Azevedo
University of Brasília, Brasília - DF, Brazil

WELCOME RECEPTION

7:00PM-9:30PM TULUM TERRACE

SUNDAY, APRIL 30TH

REGISTRATION

7:00AM-6:00PM MAYA FOYER

BREAKFAST

7:00AM-8:00AM MAYA I-II-III-IV

PROGRAM CHAIR WELCOME

7:45AM-8:00AM MAYA I-II-III-IV

JKTG FOUNDATION PLENARY SESSION I

8:00AM-9:00AM MAYA I-II-III-IV CHAIR: MARK DEWHIRST

SUN 01 CHASING AN ELUSIVE EVIDENCE-BASED RATIONALE FOR HYPERTHERMIA IN THE CANCER CLINIC: SEPARATING FACT FROM FICTION
Elizabeth Repasky
Roswell Park Cancer Institute, Buffalo, New York, USA

BREAK AND EXHIBIT TIME

9:00AM-9:30AM MAYA FOYER

NANOTECHNOLOGY SESSION I: MHT - PHYSICS AND CELL INTERACTIONS

9:30AM-11:30AM MAYA I-II-III CHAIR: GERARDO GOYA & ONDREJ HOVORKA

SUN 02 NEW POSSIBILITIES FOR *IN VITRO* MAGNETIC HYPERTHERMIA BASED ON INTRACELLULAR NANOSTRUCTURES.
Gerardo Goya[1], Beatriz Sanz[1], Enio Lima Jr.[2], Emilio De Biasi[2], Rafael Cabreira-Gomes[3], Jerome Depeyrot[3]
[1]Instituto de Nanociencia de Aragon, Zaragoza, Spain, [2]Centro Atómico Bariloche/CONICET, S.C. de Bariloche, Argentina, [3]Complex Fluids Group, IF- UNB, Brasilia, Brazil

SUN 03 TOWARDS AN UNDERSTANDING OF HEATING EFFECTS AND MAGNETISATION RESPONSE OF MAGNETIC NANOPARTICLES ASSOCIATED WITH LIVE CELLS
Neil Telling[1], David Cabrera[1,2], Francisco Teran[2]
[1]Keele University, Stoke-on-Trent, UK, [2]IMDEA Nanoscience, Madrid, Spain

SUN 04 INORGANIC NANOPARTICLES FOR MAGNETIC HYPERTHERMIA: FROM THE SYNTHESIS TO THEIR IN VITRO AND IN VIVO CHARACTERIZATION
Teresa Pellegrino
Istituto Italiano di Tecnologia, Genoa, Italy

SUN 05 MAGNETIC DOMAINS INTERACTIONS AS FUNCTION OF PARTICLE SIZE IN MAGNETITE NANOPARTICLES

Ana Luisa Ramirez-Nuñez[1], Octavio Fuentes-Ramirez[1], Gerardo F. Goya[2], Jaime Santoyo-Salazar[3]
[1]Nanociencias y Nanotecnología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico, Mexico, [2]Instituto Universitario de Investigación en Nanociencia de Aragón (INA), Zaragoza, Spain, [3]Departamento de Física, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico, Mexico

SUN 06 REMOTE CONTROLLED DRUG DELIVERY ON ORAL CANCER TUMOR SITE IN MICE USING IRONPARTICLE AND FLUOROPHORE CONTAINING LIPOSOME AND ALTERNATING MAGNETIC FIELD

Oula Penate Medina[1], Tuula Penate Medina[1], Jana Humbert[1], Gerardo Goya[2], Mirko Gerle[1], Hanwen Zhu[1], Claus Glüer[1], Holger Kalthoff[1], Regine Willumeit Röhmer[1]
[1]Christian Albrechts Universität zu Kiel, Kiel, Germany, [2]Institute of Nanoscience of Aragon (INA) and Condensed Matter Physics Dept., , University of Zaragoza, Zaragoza, Spain

SUN 07 IMAGING-ASSISTED INDIVIDUAL DESIGNS OF HEATING PROTOCOLS FOR PROSTATIC TUMORS IN MAGNETIC NANOPARTICLE HYPERTHERMIA

Alexander LeBrun, Ronghui Ma, Charles Bieberich, Liang Zhu
University of Maryland Baltimore County, Baltimore, Maryland, USA

SUN 08 * DEVELOPMENT OF THE THERMOSENSITIZER FOR MAXIMIZING CANCER TREATMENT EFFICACY WITH THE RADIOFREQUENCY-INDUCED HYPERTHERMIA

Seong-Tshool Hong, Eun-young Koh
Department of Biomedical Sciences, Chonbuk National University Medical School, Jeonju, Chonbuk, Republic of Korea

PHYSICS SESSION I: EFFORTS TO IMPROVE QA FOR CLINICAL HYPERTHERMIA

9:30AM-11:30AM MAYA IV CHAIR: PAUL STAUFFER & GERARD VAN RHOON

SUN 09 QUALITY ASSURANCE AND CONTROL IS ESSENTIAL TO ENSURE GOOD CLINICAL RESULTS.

Gerard van Rhoon[1], Hana Dobsicek Trefna[2], Hans Crezee[3]
[1]Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [2]Chalmers University of Technology, Gothenborg, Sweden, [3]AMC, Amsterdam, The Netherlands

SUN 10 QUALITY ASSURED HYPERTHERMIA: THE PERSPECTIVE OF THE ESHO TECHNICAL COMMITTEE

Hana Dobsicek Trefna
Chalmers University of Technology, Gothenburg, Sweden

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

SUN 11 QUALITY ASSURANCE GUIDELINES FOR INTERSTITIAL HYPERTHERMIA

Hana Dob ícek Trefná[2], Manfred Schmidt[3], Gerard van Rhoon[5], H. Petra Kok[1], Ulf Lamprecht[4], Michael Ehmann[7], Jacek Nadobny[8], Sultan Abdel-Rahman[6], Vratislav Strnad[3], Andrzej Kukielka[12], Mark Hurwitz[9], Pirus Ghadjar[8], Zeljko Vujaskovic[11], Chris Diederich[10], Paul Stauffer[9], Hans Crezee[1]

[1]Academic Medical Center, Department of Radiation Oncology, Amsterdam, The Netherlands, [2]Chalmers University of Technology, Signals and Systems, Gothenburg, Sweden, [3]Universitätsklinikum Erlangen , Strahlenklinik, Erlangen, Germany, [4]University Hospital Tuebingen, Radiation Oncology, Tuebingen, Germany, [5]Erasmus MC Daniel den Hoed Cancer Center, Radiation Oncology, Rotterdam, The Netherlands, [6]Ludwig Maximilians University of Munich, Department of Internal Medicine III, Munich, Germany, [7]University Medical Centre Mannheim, Radiation Oncology, Mannheim, Germany, [8]Charité Universitätsmedizin Berlin, Radiation Oncology, Berlin, Germany, [9]Thomas Jefferson University, Philadelphia, USA, [10]UCSF, San Francisco, USA, [11]University of Maryland School of Medicine, Division of Translational Radiation Sciences, Baltimore, USA, [12]Amethyst Radiotherapy Centre, Ludwik Rydygier Memorial Hospital, Krakov, Poland, [13]Maria Sklodowska Curie Memorial Centre of Oncology, department of radiotherapy, Krakov, Poland

SUN 12 QUALITY ASSURANCE FOR THERMAL DOSIMETRY OF CLINICAL HYPERTHERMIA

Paul Stauffer, Dario Rodrigues, Mark Hurwitz
Thomas Jefferson University, Philadelphia, PA, USA

SUN 13 MAGNETIC RESONANCE THERMOMETRY BRINGS HYPERTHERMIA QUALITY ASSURANCE TO THE NEXT LEVEL

Tim Mulder, Sergio Curto, Daniel de Jong, Gerard van Rhoon
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

SUN 14 * IDENTIFICATION OF CLINICAL MR-HIFU HYPERTHERMIA TREATMENT SITES THROUGH VALIDATION OF MR THERMOMETRY ACCURACY AND PRECISION IN HEALTHY VOLUNTEERS

Satya V.V.N. Kothapalli[1], Michael B. Altman[2], Ari Partanen[3], Lifei Zhu[1], Galen Cheng[1], H. Michael Gach[2], Imran Zoberi[2], Dennis Hallahan[2], William Straube[2], Hong Chen[1,2]

[1]Department of Biomedical Engineering, Washington University in St. Louis, Saint Louis, Missouri, USA, [2]Department of Radiation Oncology, Washington University in St. Louis, Saint Louis, Missouri, USA, [3]Clinical Science MR Therapy, Philips, Andover, Massachusetts, USA

SUN 15 THE MANUFACTURER'S ROLE IN QUALITY ASSURANCE

Jason Ellsworth
Pyrexar Medical, Salt Lake City, Utah, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

BIOLOGY SESSION I : CELL STRESS

9:30AM-11:30AM MEXICO/COZUMEL CHAIR: MICHAEL GRANER & FRED BUNZ

SUN 16 EXTRACELLULAR HSP70 IS EXPORTED BY A MECHANISM INVOLVING INSERTION INTO LIPID MEMBRANES.

Antonio De Maio[1], David Cauvi[1], Dennis Hawisher[1], Ashley Rider[1], Bernardo Lara[1], Ricardo Capone[1], Nelson Arispe[2]

[1]University of California, San Diego, La Jolla, CA, USA, [2]Uniformed Services University, Bethesda, MD, USA

SUN 17 UNDERSTANDING THE CELLULAR RESPONSES TO CELL STRESS

Fred Bunz

Johns Hopkins Medicine, Baltimore, Maryland, USA

SUN 18 * TEMPERATURE-DEPENDENT ACTIVATION OF DNA DAMAGE REPAIR IN HUMAN COLORECTAL CANCER CELLS

James Barnett, Robert Ivkov, Fred Bunz

Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

SUN 19 * HYPERTHERMIA AFFECTS BOTH BRCA2-PROFICIENT AND BRCA2-DEFICIENT CELL LINES

Arlene L. Oei[1,2], Vidhula Ahire[1,2], Caspar M. van Leeuwen[2], Rosemarie ten Cate[1,2], Lukas J.A. Stalpers[1,2], Johannes Crezee[2], H. Petra Kok[2], Nicolaas A.P. Franken[1,2]

[1]Laboratory for Experimental Oncology and Radiobiology (LEXOR), AMC, Amsterdam, The Netherlands, [2]Department of Radiotherapy, AMC, Amsterdam, The Netherlands

SUN 20 STRESSING OUT THE NEIGHBORS: STRESED EXOSOMES ("SexOsomes"?) PASSAGE STRESS PHENOTYPES TO RECIPIENT CELLS

Michael Graner

University of Colorado Denver Anschutz Medical Campus, Aurora, CO, USA

LUNCH ON OWN AND RESORT TIME

11:30AM-2:00PM

PHOTODYNAMIC AND NOVEL COMBINATION THERAPIES SESSION I

2:00PM-3:30PM MAYA I-II-III CHAIR: GAL SHAFIRSTEIN & JULIANA CANO-MEJIA

SUN 21 THERANOSTIC MULTIPLEXED THERMOCHEMICAL ABLATION (MTCA): TRACKING DICHLOROACETATE USING MULTI-ENERGY COMPUTED TOMOGRAPHY

Rick Layman, Chunxiao Guo, Samuel Fahrenholtz, Dodge Baluya, Erik Cressman

MD Anderson Cancer Center, Houston, TX, USA

SUN 22 IMPROVING SBRT AND PROTON THERAPY WITH LOCAL HYPERTHERMIA TO SENSITIZE HYPOXIC AND RESISTANT CELLS

Robert J. Griffin[1], Ashish Ranjan[2], Azemat Jamshidi-Parsian[1], Ruud Dings[1], Cristina Munteanu[2], Salahuddin Ahmad[3], Terence Herman[3]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]Oklahoma State University, Stillwater, OK, USA, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

SUN 23 CONCURRENT THERMAL ABLATION AND INTERSTITIAL PHOTODYNAMIC THERAPY FOR CONTROLLING LOCALLY ADVANCED CANCER

Gal Shafirstein, Emily Oakley, Sasheen Hamilton, Michael Habitzruther, Joseph Spernyak, Lawrence Tworek, Alan Hutson, David Bellnier
Roswell Park Cancer Institute, Buffalo, NY, USA

SUN 24 * PRUSSIAN BLUE NANOPARTICLE-BASED PHOTOTHERMAL THERAPY COMBINED WITH CHECKPOINT INHIBITION FOR PHOTOTHERMAL IMMUNOTHERAPY OF NEUROBLASTOMA

Juliana Cano-Mejia[1,2], Rachel Burga[2,3], Elizabeth Sweeney[2], John Fisher[1,2], Catherine Bollard[2,3], Anthony Sandler[2], Conrad Russell Cruz[2,3], Rohan Fernandes[2]
[1]University of Maryland, College Park/MD, USA, [2]Children's National Medical Center, Washington/DC, USA, [3]The George Washington University, Washington/DC, USA

SUN 25 * CO-DELIVERY OF NANOPARTICULATED NVP BEZ-235 DECREASES CELL PROLIFERATION OF IRREVERSIBLE ELECTROPORATION TREATED XENOGRAFT

Li Tian[1], Yang Qiao[1], Saisree Ravi[2], Ashley Chang[4], Thomas Rogers[3], Marites Melancon[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Rice University, Houston, TX, USA, [3]Mississippi State University, Starkville, MS, USA, [4]McGovern Medical School, Houston, TX, USA

NANOTECHNOLOGY SESSION II: NANOTHERMOMETRY

2:00PM-3:30PM MAYA IV CHAIR: ANDRIS BAKUZIS & ROBERT GRIFFIN

SUN 26 LUMINESCENCE NANOTHERMOMETERS FOR PHOTOTHERMAL THERAPY

Carlos Jacinto[1], Daniel Jaque[2]
[1]Instituto de Física, Universidade Federal de Alagoas, Maceió-AL, 57072-900, Brazil, [2]Departamento de Física, Universidad Autonoma de Madrid, Madrid, Spain

SUN 27 MAGNETONANOTHERMOMETRY: PRESENT STATUS AND FUTURE PERSPECTIVES

Paulo De Morais
Anhui University, Hefei, Anhui, China

SUN 28 MRI THERMOMETRY FOR PHOTOTHERMAL THERAPY

R. Jason Stafford
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

SUN 29 * IN VIVO FLUORESCENCE IMAGING PREDICTS DRUG UPTAKE FOR TEMPERATURE SENSITIVE LIPOSOMAL DOXORUBICIN

Anjan Motamarry, Christian Rossman, Dieter Haemmerich
Medical University of South Carolina, SC, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

SUN 30 MAGNETIC HYPERTHERMIA IS MORE EFFICIENT THAN EXOGENOUS HEATING TO KILL NEUROBLASTOMA CELLS

Beatriz Sanz[1,2], M. Pilar Calatayud[1], Teobaldo E. Torres[1,4], Mónica L. Fanarraga[5], M. Ricardo Ibarra[1,3], Gerardo F. Goya[1,3]

[1]Instituto de Nanociencia de Aragón (INA), Universidad de Zaragoza, Zaragoza, Spain, [2]nB nanoScale Biomagnetics S.L., Zaragoza, Spain, [3]Departamento de Física de la Materia Condensada, Facultad de Ciencias, Universidad de Zaragoza, Zaragoza, Spain, [4]Laboratorio de Microscopias Avanzadas (LMA), Universidad de Zaragoza, Zaragoza, Spain, [5]Grupo de Nanomedicina-IDIVAL, Universidad de Cantabria, Santander, Spain

SUN 31 MAGNETIC HYPERTHERMIA AND MR IMAGING USING G4 PAMAM DENDRIMER COATED FE_3O_4 NANOPARTICLES

Marzieh Salimi[1,3], Saeed Sarkar[1], Reza Saber[2], Alimohamad Alizadeh[3], Hamid Delavari[4]

[1]Department of medical physics and Biomedical Engineering, Tehran university of medical sciences,, Tehran, Iran, [2]Department of modern technologies, Tehran university of medical sciences, Tehran, Iran, [3]Cancer institute, Emam Khomeini hospital, Tehran university of medical sciences, Tehran, Iran, [4]Department of Materials Engineering, Tarbiat Modares University, Tehran, Iran

CLINICAL HYPERTHERMIA SESSION I: CLINICAL TRIALS UPDATES

2:00PM-3:30PM MEXICO/COZUMEL CHAIR: ZELJKO VUJASKOVIC & RUDI WESSALOWSKI

SUN 32 CHEMOTHERAPY AND HYPERTHERMIA FOR LOCALIZED SOFT TISSUE SARCOMA: UP-DATE WITH LONG-TERM FOLLOW-UP

Rolf Issels, Lars Lindner

Klinikum Grosshadern- University of Munich, Munich, Germany

SUN 33 RESULTS OF RANDOMIZED STUDIES ON HYPERTHERMIA IN ONCOLOGY

O.K. Kurpeshev[1], J. van der Zee[2], A.V. Orlova[1]

[1]A.Tsyb Medical Radiological Research Center, Obninsk, Russia, [2]Erasmus MC Cancer Institute, Rotterdam, The Netherlands

SUN 34 REGIONAL HYPERTHERMIA FOR TREATMENT OF PEDIATRIC OVARIAN GERM CELL TUMORS

Ruediger Wessalowski[1], Gabriele Calaminus[2], Eunike Velleuer[1], Oliver Mils[1], Stefan Schönberger[2], Dominik T. Schneider[3], Rotem Lanzman[4], Eugen Ruckhäberle[5], Ivo Leuschner[6], Ulrich Göbel[7]

[1]Heinrich-Heine-University, Medical Faculty, Clinic for Pediatric Oncology, Hematology and Clinical Immunology, Duesseldorf, Germany, [2]University Children's Hospital, Department of Pediatric Hematology and Oncology, Bonn, Germany, [3]Pediatric Clinic, Municipal Hospital, Dortmund, Germany, [4]Heinrich-Heine-University, Medical Faculty, Institute of Diagnostic Radiology, Duesseldorf, Germany, [5]Heinrich-Heine-University, Medical Faculty, Department of Gynecology and Obstetrics, Duesseldorf, Germany, [6]University of Kiel, Pediatric Pathology, Kiel, Germany, [7]Heinrich-Heine-University, Medical Faculty, Pediatric Surveillance Unit (ESPED), Duesseldorf, Germany

SUN 35 A SYSTEMATIC REVIEW AND META-ANALYSIS OF HYPERTHERMIA AND RADIOTHERAPY IN MANAGEMENT OF LOCALLY RECURRENT BREAST CANCERS

Niloy Datta[1], Emsad Puric[1], Dirk Klingbiel[2], Silvia Ordóñez[1], Stephan Bodis[1]

[1]Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland, [2]Swiss Group for Clinical Cancer Research (SAKK), Coordinating Centre, Bern, Switzerland

SUN 36 * NOVEL PHOTO-INDUCED CHEMOTHERAPY DELIVERY MATRIX FOR SUPPORT OF ABDOMINAL ORGANS FOLLOWING CYTOREDUCTIVE SURGERY

Hale Arca, Nicole Levi

Department of Plastic and Reconstructive Surgery, Wake Forest University Health Sciences, Winston-Salem, NC, USA

SUN 37 * RADIATION THERAPY PLUS EXTERNAL THERMAL THERAPY RESULTS IN MODEST TOXICITIES WITH THE PROMISE OF INCREASED EFFICACY: A SINGLE INSTITUTIONAL EXPERIENCE

Jason Molitoris[1], JW Snider[1], Tejan Diwanji[1], Arpit Chhabra[1], Travis Dobbin[1], Valerie Smith[1], Andrew Cox[1], Shifeng Chen[2], Mariana Guerrero[2], Zeljko Vujaskovic[2]

[1]Dept of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, USA, [2]Dept of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA

BREAK AND EXHIBIT TIME

3:30PM-4:00PM MAYA FOYER

CLINICAL MODELLING WITH COMPANION ANIMALS

4:00PM-6:00PM MAYA I-II-III CHAIR: MARK DEWHIRST & JACK HOOPES

SUN 38 STATUS OF CURRENT RESOURCES AND EXPERIENCES WITH NATURALLY OCCURRING CANCER IN COMPANION ANIMALS: BIOLOGY, IMMUNOLOGY AND EXPERIMENTAL THERAPEUTICS.

Rodney Page

Flint Animal Cancer Center, Colorado State University, Fort Collins, CO, USA

SUN 39 AN HISTORICAL PERSPECTIVE ON THE VALUE OF COMPANION CANINE CANCERS IN EXPERIMENTAL THERAPEUTICS TRIALS- ADVANTAGE FROM THE DOG'S AND HUMAN'S POINT OF VIEW

Mark Dewhirst

Duke University, Durham, NC, USA

SUN 40 HYPO-FRACTIONATED RADIATION, MAGNETIC NANOPARTICLE HYPERTHERMIA AND VIRAL IMMUNOTHERAPY TREATMENT OF SPONTANEOUS CANINE TUMORS

P. Jack Hoopes[1], Karen Moodie[1], Margaret Crary-Burney[1], Alicia Petryk[4], James Petryk[1], Shawntel Sechrist[3], David Gladsione[1], Ashish Rajan[5], Robert Wagner[1], Alicea Bursey[1], Nichole Steinmetz[2], Steven Fiering[1]

[1]Dartmouth College, Hanover, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]St. Johnsbury Animal Hospital, St. Johnsbury, VT, USA, [4]University of Bridgeport, Bridgeport, CT, USA, [5]Oklahoma State University, Stillwater, OK, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

SUN 41 VALIDATION OF PROCASPASE-3 AS A PREFERENTIAL THERAPEUTIC TARGET FOR TREATMENT OF BRAIN CANCER THROUGH THE INCLUSION OF PET DOGS AS A COMPARATIVE TUMOR MODEL

Lisa Schlein[1], Edward Roy[1], Stephane Lezmi[4], Jayme Looper[3], Michael Podell[1], Peter Dickinson[2], Paul Hergenrother[1], Timothy Fan[1]

[1]University of Illinois, Urbana, USA, [2]University of California, Davis, USA, [3]Louisania State University, Baton Rouge, USA, [4]Ipsen Pharmaceuticals, Paris, France

SUN 42 IMAGE-GUIDED CATHETER-BASED ULTRASOUND THERMAL ABLATION OF TUMORS IN GENETICALLY ENGINEERED ONCOGENIC PIGS

E. Clif Burdette[1], Goutam Ghoshal[1], Emery Williams[1], Paul Neubauer[1], Lance Frith[1], Patrick Roady[2], Laurie Rund[2], Larry Schook[2]

[1]Acoustic MedSystems, Inc., Savoy, IL, USA, [2]University of Illinois, Urbana-Champaign, Urbana, IL, USA

BIOLOGY SESSION II: MECHANISMS AND AGENTS OF CELL STRESS TO ENHANCE THERAPY

4:00PM-6:00PM MAYA IV CHAIR: RANDY BURD & PREETHI KORANGATH

SUN 43 IMMUNOBIOLOGY OF LARGE HEAT SHOCK PROTEIN AND ITS BINDING RECEPTOR IN DISEASE PATHOGENESIS AND THERAPEUTIC APPLICATIONS

Xiangyang Wang[1], John Subjeck[2]

[1]Virginia Commonwealth University, Richmond, VA, USA, [2]Roswell Park Cancer Institute, Buffalo, NY, USA

SUN 44 MILD HYPERTHERMIA IMPROVES PERFUSION AND ANTIMICROBIAL EFFICACY IN MOUSE MODEL OF STAPHLOCOCCUS AUREUS ABSCESS

Ashish Ranjan, Rachel Wardlow, Jerry Malayer, Kaustuv Sahoo

Oklahoma State University, Stillwater, Oklahoma, USA

SUN 45 LIDOCAINE-INDUCED POTENTIATION OF THERMAL DAMAGE IN KERATINOCYTE, FIBROBLAST, AND BASAL CELL CARCINOMA CELL LINES

Martin Purschke, Adam Raff, Carina Thomas, Rox Anderson

Massachusetts General Hospital / Harvard Medical School, Boston, MA, USA

SUN 46 SENSITIZATION OF THEMORADIATION WITH CISPLATIN AND SMALL MOLECULES (PARP1- AND DNAPKCS INHIBITORS) TO IMPROVE CERVICAL CANCER TREATMENT.

Vidhula Ahire[1,2], Arlene Oei[1,4], Caspar van Leeuwen[2], Hans Rodermond[1,2], Lukas Stalpers[2], Przemek Krawczyk[3], Johannes Crezee[2], Petra Kok[2], Nicolaas Franken[1,2]

[1]Laboratory for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental Molecular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [3]Dept. of Cell Biology and Histology, Amsterdam, The Netherlands, [4]The Johns Hopkins University School of Medicine, Baltimore, United States Minor Outlying Islands

SUN 47 HISTOLOGICAL EVALUATION OF CELLULAR CHANGES IN HEALTHY BONE AFTER MRI GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND: AN ACUTE AND CHRONIC STUDY IN PIGS

Karolina Piorkowska[1], Gino R. Somers[2,3], James Drake[1,4], Adam C Waspe[1,6]

[1]Centre for Image Guided Innovation and Therapeutic Intervention, The Hospital for Sick Children, Toronto, Canada, [2]Department of Pathology, The Hospital for Sick Children, Toronto, Canada, [3]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada, [4]Department of Neurosurgery, The Hospital for Sick Children, Toronto, Canada, [5]Department of Medical Imaging, University of Toronto, Toronto, Canada

SUN 48 MULTI-ENERGY COMPUTED TOMOGRAPHY (MECT) IMAGING OF ENDOVASCULAR ABLATION: THERMOEMBOLIZATION IN AN EX-VIVO PORCINE KIDNEY MODEL

Rick Layman, Chunxiao Guo, Samuel Fahrenholtz, Dodge Baluya, Erik Cressman

MD Anderson Cancer Center, Houston, TX, USA

PHYSICS SESSION II: THERAPEUTIC METHODS WITH EM ENERGY

4:00PM-6:00PM MEXICO/COZUMEL CHAIR: HANA DOBSICEK-TREFNA & DARIO RODRIGUES

SUN 49 SUPERFICIAL HYPERTHERMIA TREATMENT PLANNING FOR RECTANGULAR WAVEGUIDES WITH CUSTOM CONFORMAL WATERBOLUS

Dario Rodrigues[1], Mark Hurwitz[1], Randolph Sinahon[2], Lyndsey Sbarro[2], Paul Stauffer[1]

[1]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [2]Department of Biomedical Engineering, Drexel University, Philadelphia, PA, USA

SUN 50 COMPOSITE SCAFFOLDS FOR THERMAL ABLATION OF METASTATIC CANCER CELLS

Navid Manuchehrabadi, Francisco Pelaez, Priyatanu Roy, Harishankar Natesan, Heather Fong, Kevin Zeng, Emilian Racila, John Bischof, Samira Azarin

University of Minnesota, Minneapolis, Minnesota, USA

SUN 51 AIR POCKETS IN THE URINARY BLADDER REDUCE THERMAL DOSE DURING RADIOFREQUENCY HYPERTHERMIA TREATMENT

Gerben Schooneveldt, Petra Kok, Debby Geijsen, Akke Bakker, Jean de la Rosette, Maarten Hulshof, Theo de Reijke, Hans Crezee

Academisch Medisch Centrum, Amsterdam, The Netherlands

SUN 52 PRECLINICAL SURVIVAL STUDY DEMONSTRATING SAFE AND EFFECTIVE HEATING OF IN-VIVO PORCINE PANCREAS WITH NOVEL MULTI-APPLICATOR COIL INDUCTIVE THERMAL TREATMENT SYSTEM (TTX)

Pierre Floriano[1], Randall Jones[2], Yong Pang[2], William Riehle[2], Paul Stauffer[3], Kelly Lechtenberg[4], Teresa Schieber[4], Robin Schroeder[4], Charles Anderson[1]

[1]NeoTherma Oncology, Wichita, KS, USA, [2]ScanMed, Omaha, NE, USA, [3]Thomas Jefferson University, Philadelphia, PA, USA, [4]Midwestern Veterinary Services, Inc., Oakland, NE, USA

SUN 53 MANAGEMENT OF LOCALIZED CANCER USING SLEEVED DUAL SLOT ANTENNA MICROWAVE ABLATION TECHNIQUE

Ephraim Nwoye, Z. Ayo Ibitoye, Moses Aweda

University of Lagos, Nigeria, Lagos, Nigeria

SUN 54 DESIGNED AND EXPERIMENTAL VALIDATION OF A SLEEVED ANTENNA FOR MICROWAVE ABLATION

Ayo Ibitoye, Ephraim Nwoye, Adebayo Aweda
College of Medicine, University of Lagos, Lagos, Nigeria

SUN 55 FOCUSING WITH MICROWAVE HYPERTHERMIA ARRAY APPLICATORS: FREQUENCY MATTERS

Hana Dobsicek Trefna[1], Björn Martinsson[1], Julia Ravanis[1], Martin Torstensson[1], Petra Kok[2], Mikael Persson[1]
[1]Chalmers University of Technology, Gothenburg, Sweden, [2]AMC Medical Centre, Amsterdam, The Netherlands

POSTER SESSION & COMPETITION

6:00PM-8:00PM MAYA V-VI-VII-VIII

POS 1 HEAT-TARGETED DRUG DELIVERY USING THE COMBAT BRS DEVICE FOR TREATING BLADDER CANCER

Thomas Longo, Steven Brousell, Joseph Fantony, Mark Dewhirst, Paolo Maccarini, Ivan Spasojevic, Brant Inman
Duke University, Durham,NC, USA

POS 2 MODELING THE ELECTRICAL-THERMAL PERFORMANCE OF INTERNALLY COOLED WET (ICW) ELECTRODES FOR RF ABLATION

Macarena Trujillo, Jose Bon, Enrique Berjano
Universidad Politécnica de Valencia, Valencia, Spain

POS 3 HYPERTHERMIA COMBINED WITH HYDROGEL PROMOTED APOPTOSIS VIA VARIOUS BIOLOGICAL MECHANISMS IN SKIN AND PROSTATE CANCER CELL LINES COMPARISON WITH NORMAL CELL LINES

Bihter Yavuz[1,2], Gülengül Duman[1], Onur Cem Namli[1], Berrin Erdag[2]
[1]Yeditepe University, Istanbul, Turkey, [2]TUBITAK MAM, Gebze/ Kocaeli, Turkey

POS 4 OBSERVATION OF LIPID CRYSTALLIZATION IN HUMAN FAT CELLS

Like Zeng, George Frangineas
ZELTIQ Aesthetics, Inc, Pleasanton, CA, USA

POS 5 INTRAABDOMINAL TEMPERATURE CHANGES BY APPLICATION OF RADIOFREQUENCY DEVICE (REMISSION1°C)

Hyung Joon Han[1], Tae-Jin Song[1], Won-Jin Park[2]
[1]Korea University Ansan Hospital, Ansan/Gyeonggi-di, Republic of Korea, [2]WonJin Aesthetic Surgery Clinic, Seoul/Seoul, Republic of Korea

POS 6 ROLE OF HIF-1α IN THE RESPONSE OF TUMORS TO THE COMBINATION OF HYPERTHERMIA AND RADIATION IN VIVO

Wonwoo Kim1, Mi-Sook Kim1,2
1Radiation Non-clinic Center, Korea Institute of Radiological & Medical Sciences, Seoul, Republic of Korea, 2Department of Radiation Oncology, Korea Institute of Radiological & Medical Sciences, Seoul, Republic of Korea

POS 7

MAGNETIC NANOSTRUCTURES OVERLAID WITH GOLD FOR APPLICATIONS IN COMPUTED TOMOGRAPHY AND MAGNETOHYPERTHERMIA

Elis Regina Siqueira, Breno Coelho, Marcelo Souza, Paulo César Morais, Ricardo Azevedo, Alicia Ombredane

University of Brasilia, Brasília, Distrito Federal, Brazil

POS 8

SENSITIVITY ANALYSIS FOR MODELING RF ABLATION USING COMPLEX FINITE ELEMENT METHOD

Juan Monsalvo, Manuel Garcia, Harry Millwater, Yusheng Feng

The University of Texas at San Antonio, San Antonio, Texas 78249, USA

POS 9

SEMI-GREEN SYNTHESIS AND CHARACTERIZATION OF SUPERPARAMAGNETIC FE_3O_4-MNPS WITH AQUEOUS EXTRACTS FROM C. VERUM AND NATURAL EXTRACT FROM V. PLANIFOLIA.

A.L. Ramírez-Núñez[1], J. Santoyo-Salazar[1], L.F. Jiménez-García[2], B. Sanz[3], G.F. Goya-Rossetti[3]

[1]CINVESTAV-IPN, México, Mexico, [2]UNAM, México, Mexico, [3]Instituto de Nanociencia de Aragón (INA), Universidad de Zaragoza, España, Spain

POS 10

UPTAKE AND RETENTION OF ANTIBODY CONJUGATED FERRITE NANOPARTICLES - A STUDY USING XENOGRAFT MODELS OF HER2 POSITIVE BREAST CANCER

Preethi Korangath, James Barnett, Anirudh Sharma, Jacqueline Stewart, Elizabeth Henderson, Shu-han Yu, Sri Kamal Kandala, Rajeev Hatwar, Mohammed Hedayati, Brian Simons, Saraswati Sukumar, Robert Ivkov

Johns Hopkins University, Baltimore, MD, USA

POS 11

PHOTODYNAMIC THERAPY CAN CURE NATURAL CUTANEOUS HEMANGIOSARCOMA IN DOGS

Martha Rocha, Carolina Lucci, João Paulo Longo, Luis Muehlmann, Ricardo Azevedo

University of Brasilia, Brasilia, DF, Brazil

POS 12

PROCESSING AND PHYSICAL PROPERTIES OF GD-DTPA COMPLEX-FUNCIONALIZED MAGNETIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

Sandra Irene Eguía Eguía[1], Octavio Fuentes Ramírez[1], Lorenzo Gildo Ortíz[1], Patricia Maldonando Altamirano[2], Jorge Ricardo Aguilar Hernández[2], Jaime Santoyo Salazar[3]

[1]Doctorado en Nanociencias y Nanotecnología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Zacatenco, Ciudad de México, Mexico, [2]Escuela Superior de Física y Matemáticas, Instituto Politécnico Nacional, Ciudad de México, Mexico, [3]Departamento de Física, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Zacatenco, Ciudad de México, Mexico

POS 13

MULTIPLE INJECTIONS OF MAGNETIC IRON OXIDE NANOPARTICLES IN MICE: TOXICITY STUDY

Monica Pereira Garcia, Vanessa Carvalho Moreiraa, Mariana Marzullo Pedreirab, Jaqueline Rodrigues Silva, Ricardo Bentes Azevedo

University of Brasilia, Brasília,DF, Brazil

POS 14

ANTI-TUMOR EFFECT OF HYPERTHERMIA IN COMBINATION WITH THE EXTRACT OF FERMENTED SOYBEAN

Kimiko Yoshimizu[1], Tohru Takahaashi[2], Takeo Hasegawa[3], Itsuo Yamamoto[4], Haeun Cho[5]
[1]Garden Clinic nakamachi, Tokyo, Japan, [2]Kansai Medical University, Hirakata, Osaka, Japan, [3]Louis Pasteur Center for Medical Research, Kyoto, Japan, [4]Kyouei Hyperthermia Co, Ltd, Iwaki, Japan, [5]University of Minnesota, Minneapolis, MN, USA

POS 15

EFFECTS OF VARIATIONS IN BLOOD PERFUSION AND ANATOMY ON MODELLED TEMPERATURE DISTRIBUTION DURING WIRA HYPERTHERMIA

Michael Jackson[1,2], Victoria Timchenko[2], Zain Khan[2], Olivia Ng[2]
[1]Prince of Wales Hospital, Randwick, NSW, Australia, [2]University of New South Wales, Kensington, NSW, Australia

POS 16

ARRHENIUS KINETIC ANALYSIS OF DYNAMIC MR SIGNAL CHANGES IN A PROTEIN COAGULATION PHANTOM

Chris MacLellan[1], Ken-Pin Hwang[1], R. Jason Stafford[1,2]
[1]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas, USA

POS 17

MAGNETIC HYPERTHERMIA CONTROLLED RELEASE OF DOXORUBYCIN FROM MAGNETIC FOLATE-TARGETED LIPOSOMES

Emilio Ramos Cintra, Marcilia Viana Pavam Gonçalves, Relton Romeis Oliveira, Thais Leite Nascimento, Andris Figueiroa Bakuzis, Eliana Martins Lima
Universidade Federal de Goias, Goiania,GO, Brazil

POS 18

THERMOCHROMIC PAINT FORMULATION AND PHANTOM TO OPTIMIZE THERAPEUTIC ULTRASOUND EXPOSURES FOR BONE CANCER THERAPY

Ayele H Negussie[1], Navid Farr[1], Ari Partanen[1,2], Li Piin Sung[3], Avinash Eranki[4], Andrew S Mikhail[1], Brad J Wood[1]
[1]Center for Interventional Oncology Radioloy and Imaging Sciences, CC, NIC, NIH, 9000 Rockville Pike, Bethesda, MD, USA, [2]Clinical Science MR Therapy, Philips,, Andover, Massachusetts, USA, [3]National Institute of Standards and Technology, Gaithersburg, MD, USA, [4]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Health System, Washinton, DC, USA

POS 19

METAL FOAM BASED REWARMING OF VITRIFIED SYSTEMS

Navid Manuchehrabadi[1], Meng Shi[2], Aiden Carley Clopton[1], Jinbin Qui[2], Feng Xu[2], Tian Jian Lu[2], John Bischof[1]
[1]University of Minnesota, Minneapolis, Minnesota, USA, [2]Xi'an Jiaotong University, Xian Shi, Shaanxi Sheng, China

POS 20

COMBINING DOXORUBICIN AND HYPERTHERMIA INCREASES CYTOTOXICITY IN HCT116 CELLS.

Sanem Ozayral, Anirudh Sharma, Robert Ivkov
Johns Hopkins University School of Medicine, Maryland, USA

POS 21

COMBINED MAGNETIC HYPERTHERMIA AND IONIZING RADIATION INDUCES AN ABSCOPAL EFFECT.

Jacqueline Stewart, Mikko Helenius, Anilchandra Attaluri, Elliot Mackrell, Anusha Badathala, Monica Garcia, Viviana Barquet, Sai Gargi, Preethi Korangath, Robert Ivkov
Johns Hopkins University, Baltimore, MD, USA

POS 22

3D PRINTED TISSUE-MIMICKING THERMOCHROMIC PHANTOM OF THE LUMBAR SPINE FOR PRE-CLINICAL TESTING OF MRGFUS ABLATIONS OF THE FACET JOINT AND MEDIAL BRANCH NERVE

Hari Trivedi, Derrick Gillan, Matthew Adams, Aaron Losey, Chris Diederich, Eugene Ozhinsky, Matthew Bucknor, Viola Rieke
University of California, San Francisco, San Francisco, USA

POS 23

TISSUE FRACTIONATION USING MICROSECOND-LONG HIFU PULSES ON A CLINICAL MR-HIFU SYSTEM

Avinash Eranki[1,2], Navid Farr[2], Ari Partanen[3], Karun V.Sharma[1], Christoper T.Rossi[1], AeRang Kim[1], David Woods[2], Pavel Yarmolenko[1], Peter C.W.Kim[1], Bradford J.Wood[2]
[1]Childrens National Health System, Washington, DC, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]Philips, Andover, MA, USA

POS 24

THE LINEAR-QUADRATIC FORMULA TO MODEL HYPERTHERMIC RADIOSENSITIZATION OF CARCINOMA CELLS IN VITRO

Taylor Ibelli, Anilchandra Attaluri, Budri Abubaker-Sharif, Haoming Zhou, Madhav Seshadri, Monica Garcia, Robert Ivkov
Johns Hopkins University, Baltimore, Maryland, USA

POS 25

POTENTIAL PATHWAY OF HEPG2 CELLS TOWARD DEATH WITH HYPERTHERMIA AND ROS INDUCED BY MAGNETIC HYDROXYAPATITE NANOPARTICLES AND ALTERNATING MAGNETIC FIELDS

Chun Ting Yang[1,2], Keng Yuan Lee[1], Fan Qi Meng[1], Robert Ivkov[2], Feng Huei Lin[1]
[1]National Taiwan University, Taipei, Taiwan, [2]Johns Hopkins University School of Medicine, Baltimore, USA

POS 26

INVESTIGATING THE IMPACT OF ALTERNATING MAGNETIC FIELD EXPOSURES ON BIOFILM GROWN ON METALLIC SURFACES:IMPLICATIONS FOR TREATMENT OF PROSTHETIC JOINT INFECTION

Sumbul Shaikh, Imalka Munaweera, Yonatan Chatzinoff, Bingbing Cheng, Cecil Futch, James Howard, Seth Daly, David Greenberg, Rajiv Chopra
UT Southwestern Medical Center, Dallas, Tx, USA

POS 27

A CASE REPORT OF RECURRED HEPATOCELLULAR CARCINOMA PATIENT TREATED WITH RADIO-FREQUENCY HYPERTHERMIA IN CONJUNCTION WITH SORAFENIB

Jee-Hye Kim[1], Jong-Hoon Lee[2], Jong-Cheon Joo[3], Jeong-Bok Lee[1], Chong-Kwan Cho[1], Hwa-Seung Yoo[1]
[1]Daejeon University, Daejeon, Republic of Korea, [2]Woosuk University, Jeonju, Republic of Korea, [3]Wonkwang University, Jeonju, Republic of Korea

POS 28

MODELING AND MEASUREMENT OF HEATING PATTERNS OF A HIFU APPLICATOR: PRELIMINARY RESULTS

Raquel Martinez[1], A. Ramos[2], A. Vera[3], L. Leija[3]
[1]Department of Biomedical Engineering, Polytechnic University of Chiapas, Chiapas, Mexico, [2]Group of R&D "Systems and Ultrasonic Technologies", Institute for Physical and Information Technologies, CSIC, Madrid, Spain, [33]Electrical Engineering Department, Bioelectronics Section, CINVESTAV-IPN, Mexico City, Mexico

MONDAY, MAY 1ST

REGISTRATION

7:00AM-6:00PM MAYA FOYER

BREAKFAST

7:00AM-8:00AM MAYA I-II-III-IV

JKTG FOUNDATION PLENARY SESSION 2

8:00AM-9:00AM MAYA I-II-III-IV CHAIR: ROBERT IVKOV

MON 1 MODELING ENDOCRINE RESISTANCE IN BREAST CANCER - A SYSTEMS BIOLOGY APPROACH

Robert Clarke

Georgetown University Medical Center, Washington DC, USA

BREAK AND EXHIBIT TIME

9:00AM-9:30AM MAYA FOYER

BIOLOGY SESSION III - IN SITU CANCER VACCINATION

9:30AM-11:30AM MAYA I-II-III CHAIR: STEVEN FIERING & MIKKO HELENIUS

MON 2 *IN SITU* VACCINATION TO TREAT CANCER USING PLANT-DERIVED VIRAL LIKE NANOPARTICLES FROM COMPEA MOSAIC VIRUS

Steven Fiering[1], Patrick Lizotte[1], Mee Rie Sheen[1], Sourabh Shukla[2], Jack Hoopes[1], Nicole Steinmetz[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [2]Case Western Reserve University, Cleveland OH, USA

MON 3 AMPLIFYING THE IMMUNE CONSEQUENCE OF RADIATION-INDUCED CANCER CELL DEATH TO CONTROL DISTANT TUMORS

Jason Baird[1], Marka Crittenden[1,2], Gwen Kramer[1], Shelly Bambina[1], David Friedman[1], Michael Gough[1]

[1]Earle A. Chiles Research Institute, Portland, OR, USA, [2]The Oregon Clinic, Portland, OR, USA

MON 4 LARGE RADIATION FRACTION SIZE, HYPERTHERMIA AND VIRAL –LIKE NANOPARTICLE ENHANCEMENT OF THE ABSCOPAL EFFECT IN A SPONTANEOUS CANINE ORAL MELANOMA MODEL

P. Jack Hoopes[1], Karen Moodie[1], Alicia Petryk[2], James Petryk[1], Nicole Steinmetz[4], Robert Wagner[1], Margaret Crary-Burney[1], Alicea Bursey[1], Ashish Rajan[3], Steven Fiering[1]

[1]Dartmouth, Lebanon, NH, USA, [2]University of Bridgeport, Bridgeport, CT, USA, [3]Oklahoma State University, Stillwater, OK, USA, [4]Case Western Reserve Univeristy, Cleveland, OH, USA

MON 5 * ELICITING IMMUNOGENIC CELL DEATH USING PRUSSIAN BLUE NANOPARTICLE-BASED PHOTOTHERMAL THERAPY AND THE IMPLICATIONS FOR CANCER THERAPY

Elizabeth E. Sweeney, Rachel A. Burga, Juliana Cano-Mejia, Rohan Fernandes

Children's National Health System, Washington, DC, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

MON 6 COMBINATION OF FOCAL NANOPARTICLE HEAT THERAPY AND RADIOTHERAPY CREATES IMMUNOLOGICAL RESPONSE GREATER THAN ITS PARTS

Mikko Helenius[1], Jackie Stewart[1], Shu-Han Yu[1], Preethi Korangath[1], James Barnett[1], Anirudh Sharma[1], Sri Kamal Kandala[1], Charles Drake[3,4], Angelo M. De Marzo[2,3], Robert Ivkov[1]
[1]Johns Hopkins University School of Medicine, Department of Radiation Oncology, Baltimore, MD, USA, [2]Johns Hopkins University School of Medicine, Department of Pathology, Baltimore, MD, USA, [3]Johns Hopkins University School of Medicine, Department of Urology, Buchanan Brady Urological Institute, Baltimore, MD, USA, [4]Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

MON 7 B16 CANCER ANTIGEN RELEASE AND PRESENTATION DEPENDS ON FOCAL THERAPY CONDITIONS

Qi Shao, Stephen O'Flanagan, Jackson Raynor, Brandon Burbach, Samira Azarin, Yoji Shimizu, John Bischof
University of Minnesota, MN, USA

PHOTOTHERMAL THERAPIES - PRECLINICAL AND CLINICAL OPPORTUNITIES

9:30AM-11:30AM MAYA IV CHAIR: DAVID WOODRUM & EDWARD ABRAHAM

MON 8 GALECTIN-1-BASED TUMOR-TARGETING FOR PHOTOTHERMAL THERAPY

Samir Jenkins[1], Dmitry Nedosekin[1], Ruud Dings[1], Jingyi Chen[2], Robert Griffin[0]
[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

MON 9 MRI-GUIDED LASER ABLATION FOR SYMPTOMATIC, PERIPHERAL LOW-FLOW VASCULAR ANOMALIES: FEASIBILITY, SAFETY, AND EFFECTIVENESS IN 22 PATIENTS.

David Woodrum, Scott Thompson, Matthew Callstrom, Emily Bendel, Lori Cranston, Krzysztof Gorny, Michael McKusick
Mayo Clinic, Rochester, MN, USA

MON 10 REAL-TIME MONITORING OF INDOCYANINE GREEN PHOTOTHERMAL ABLATION USING PHOTOACOUSTIC IMAGING

Nicholas Benvenuto[1], Houra Taghavi[3], Trevor Mitcham[3], Erik Cressman[2], Rahul Sheth[2], Richard Bouchard[3]
[1]Sidney Kimmel Medical College, Philadelphia, PA, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Imaging Physics, Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

MON 11 OPTIMIZING INFRARED HYPERTHERMIA, PHOTOBIOMODULATION, IONIZING RADIATION TECHNIQUES, AND ADJUVANT THERAPEUTICS IN THE SALVAGE OF RECURRENT STAGE IV PROSTATE CANCER.

Edward Abraham[1], Van Woo[1], Robert Griffin[2]
[1]Artesian Cancer Center, Claremore, OK, USA, [2]Radiation Oncology, UAMS, Little Rock, AR, USA

MON 12 WATER-FILTERED INFRARED-A HYPERTHERMIA FOR SUPERFICIAL, WIDESPREAD BREAST CANCER RECURRENCES: CHANCES, LIMITATIONS AND OPEN QUESTIONS

Peter Vaupel[1], Markus Notter[2]
[1]Dept. Radiation Oncology,Klinikum rechts der Isar, Munich, Germany, [2]Dept. Radiooncology, Lindenhofspital, Berne, Switzerland

MON 13 EFFECTS OF VARIABLE POWER ON TISSUE ABLATION DYNAMICS DURING MAGNETIC RESONANCE GUIDED LASER-INDUCED THERMAL THERAPY

Sean Munier, Nitesh Patel, Shabbar Danish
Department of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, USA

MON 14 A HETEROGENEOUS TISSUE MODEL FOR TREATMENT PLANNING IN LASER INDUCED THERMAL THERAPY

Drew Mitchell, Christopher MacLellan, Samuel Fahrenholtz, John Hazle, Jason Stafford, David Fuentes
The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

CLINICAL HYPERTHERMIA SESSION II - NEW OPPORTUNITIES FOR ONCOLOGY

9:30AM-11:30AM MEXICO/COZUMEL CHAIR: MARK HURWITZ & DIETER MANSTEIN

MON 15 EXPANDING USE OF HYPERTHERMIA IN TODAY'S ONCOLOGY CLINIC: INITIAL IMPRESSIONS FROM THE THOMAS JEFFERSON THERMAL ONCOLOGY PROGRAM

Mark Hurwitz, Dario Rodrigues, Pramilla Anne, Voichita Bar-Ad, Paul Stauffer
Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

MON 16 CONCURRENT PENCIL BEAM SCANNING PROTON THERAPY AND HYPERTHERMIA: INITIAL CLINICAL EXPERIENCE

James Snider, III[1], Arpit Chhabra[1], Tejan Diwanji[1], Jason Molitoris[1], Lolly Johnson[1], Mandy Clevenger[1], William Regine[2], Zeljko Vujaskovic[2]
[1]University of Maryland Medical Center-Maryland Proton Treatment Center, Baltimore, MD, USA, [2]University of Maryland School of Medicine-Maryland Proton Treatment Center, Baltimore, MD, USA

MON 17 IMAGE-GUIDED TARGETED DOXORUBICIN DELIVERY WITH HYPERTHERMIA TO OPTIMZE LOCO-REGIONAL CONTROL IN BREAST CANCER; STUDY DESIGN OF THE I-GO FEASIBILITY STUDY

Josanne de Maar[1], Roel Deckers[1], Britt Suelmann[1], Manon Braat[1], Sabine Linn[2,1], Chrit Moonen[1], Elsken van der Wall[1]
[1]University Medical Center Utrecht, Utrecht, The Netherlands, [2]Netherlands Cancer Institute, Amsterdam, The Netherlands

MON 18 A PILOT CLINICAL STUDY ON CRYO-THERMAL THERAPY OF LIVER CANCER

Wentao Li[1], Zan Shen[2], Guangzhi Wang[1], Xinhong He[1], Lichao Xu[1], Kangwei Zhang[3], Kun He[3], Ping Liu[3], Aili Zhang[3], Guangyuan Zhang[4], Yonggang Wang[2], Shengping Wang[5], Weijun Peng[5], Lisa X. Xu[3]
[1]Department of Interventional Radiology, Fudan University Shanghai Cancer Center, shanghai, China, [2]Department of Oncology, Shanghai Jiaotong University Affiliated Sixth People's Hospital, shanghai, China, [3]School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, shanghai, China, [4]Department of Radiology, Shanghai Proton and Heavy Ion Center, shanghai, China, [5]Department of Radiology, Fudan University Shanghai Cancer Center, shanghai, China

MON 19 COMPARISON OF INDUCED BIOLOGICAL EFFECTS OF MODULATED ELECTROHYPERTHERMIA TO CONVENTIONAL CAPACITIVE HYPERTHERMIA
Oliver Szasz
St. Istvan University, Biotechnics Department, Budaors, Hungary

MON 20 OUTCOMES AND TOXICITY DATA OF EXTERNAL THERMAL THERAPY (ETT) CONCURRENT WITH EXTERNAL BEAM RADIATION THERAPY (EBRT) IN THE MANAGEMENT OF NON-MELANOMA SKIN CANCERS
Arpit Chhabra, James Snider, Zeljko Vujaskovic
University of Maryland Medical Center, Baltimore, MD, USA

MON 21 TARGETABILITY OF ADULT SOFT TISSUE SARCOMAS FOR MILD HYPERTHERMIA TREATMENTS USING MAGNETIC RESONANCE IMAGING-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND
Jochen Cammin[1], Satya V.V.N. Kothapalli[2], Hong Chen[2], Ari Partanen[3], Imran Zoberi[1], Michael B. Altman[1]
[1]Washington University in St. Louis, Department of Radiation Oncology, St. Louis, MO, USA, [2]Washington University in St. Louis, Department of Biomedical Engineering, St. Louis, MO, USA, [3]Philips, Clinical Science MR Therapy, Andover, MA, USA

STM BUSINESS MEETING AND WORKING LUNCH

11:30AM-1:00PM MAYA I-II-III-IV

NCI/NIH - CANCER NANOTECHNOLOGY PROGRAM - NIH UPDATES

1:00PM-1:30PM MAYA I-II-III-IV CHAIR: ROBERT IVKOV

MON 22 NANOTECHNOLOGY IN THERMAL MEDICINE-CURRENT STATUS, FUTURE OPPORTUNITIES & NIH GRANT SUPPORT
Christina Liu
National Institutes of Health, Bethesda, MD, USA

IMMUNOBIOLOGY AND IMMUNOTHERAPY: PRECLINICAL AND CLINICAL OPPORTUNITIES

1:30PM-3:00PM MAYA I-II-III CHAIR: ELIZABETH REPASKY & RICARDO BENTES DE AZEVEDO

MON 23 * SYNERGISTIC IMMUNO-PHOTOTHERMAL NANOTHERAPY (SYMPHONY): A NOVEL TREATMENT FOR LOCALIZED AND METASTATIC BLADDER CANCER
Steven Brousell, Yang Liu, Paolo Maccarini, Gregory Palmer, Wiguins Etienne, Yulin Zhao, Chen-Ting Lee, Xiumei Ma, Tuan Vo-Dinh, Brant Inman
Duke University, Durham, NC, USA

MON 24 * ACTIVATING SERIAL KILLERS OF CANCER CELLS: HYPERTHERMIA AS SUPPORTING STRATEGY FOR CANCER IMMUNOTHERAPY
Esther Wagena[2], Stefan Kuehberger[2], Daphne Craenmehr[2], Bettina Weigelin[1,2]
[1]MD Anderson Cancer Center, Houston, TX, USA, [2]Radboud University Medical Center, Nijmegen, The Netherlands

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

MON 25 ADRENERGIC SIGNALING IMPAIRS ACTIVATION OF CD8^{+}T CELLS BY BLOCKING METABOLIC REPROGRAMMING

Guanxi Qiao, Mark Bucsek, Elizabeth Repasky, Bonnie Hylander
Roswell Park Cancer Institute, Buffalo.NY, USA

MON 26 THE MICROBIOME IS HIGHLY RELEVANT TO IMMUNE THERAPY. CAN THERMAL THERAPY AFFECT BOTH THE MICROBIOME AND IMMUNE THERAPY?

Joan Bull
The University of Texas McGovern School of Medicine, Houston, Texas, USA

MON 27 RETHINKING SPONTANEOUS HYPOTHERMIA IN HUMAN SEPSIS.

Monique T Fonseca[1], Abner C Rodrigues[2], Luana C Cezar[1], Andre Fujita[2], Francisco G Soriano[3], Alexandre A Steiner[1]
[1]Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil, [2]Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil, [3]Medical School, University of São Paulo, São Paulo, Brazil

NANOTECHNOLOGY SESSION III - MAGNETIC HYPERTHERMIA MODELLING

1:30PM-3:00PM MAYA IV CHAIR: ONDREJ HOVORKA & GERARDO GOYA

MON 28 THE EFFECT OF AGGREGATION OF MAGNETIC NANOPARTICLES ON PERFORMANCE OF THERANOSTIC APPLICATIONS IN MEDICINE

Ondrej Hovorka
University of Southampton, Southampton, UK

MON 29 LOCAL VS GLOBAL HEATING IN MAGNETIC NANOPARTICLE HYPERTHERMIA

Cristina Munoz Menendez[1,2], Sergiu Ruta[1], Roy Chantrell[1]
[1]University of York, York, UK, [2]University of Santiago de Compostela, Santiago de Compostela, Spain

MON 30 NANOPARTICLE HEATING TO IMPROVE THERAPEUTICS, DIAGNOSTICS AND REGENERATIVE MEDICINE

John Bischof
University of Minnesota, Departments of Mechanical and Biomedical Engineering, Minneapolis, MN, USA

MON 31 MAGNETIC NANOPARTICLES IN VISCOUS MEDIA - HEATING AND REORIENTATION UNDER AC FIELDS

David Serantes[1,2]
[1]The University of York, York, UK, [2]Universidade de Santiago de Compostela, Santiago de Compostela, Spain

MON 32 PHYSICAL ASPECTS OF MAGNETIC NANOPARTICLE HYPERTHERMIA

Nikolai Usov[1,2], Vadim Tarasov[1]
[1]National University of Science and Technology «MISiS», Moscow, Russia, [2]Pushkov Institute of Terrestrial Magnetism, Ionosphere and Radio Wave Propagation RAS, Troitsk, Moscow, Russia

MON 33 OPTIMIZING CANCER MAGNETIC-RESONANCE NANO-THERANOSTIC HYPERTHERMIA BY MAGNETIC NANOPARTICLES

Chencai Wang
University of California, Los Angeles, Los Angeles, CA, USA

CLINICAL HYPERTHERMIA SESSION III - CASE STUDIES AND NON-ONCOLOGY APPLICATIONS

1:30PM-3:00PM MEXICO/COZUMEL CHAIR: ERIK CRESSMAN & ROLF ISSELS

MON 34 TRANSURETHRAL HIGH INTENSITY ULTRASOUND FOR TREATMENT OF STRESS URINARY INCONTINENCE (SUI): SIMULATION STUDIES WITH PATIENT SPECIFIC MODELS

Dong Liu[1], Matthew Adams[1], Clif Burdette[2], Chris Diederich[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Acoustic MedSystems Inc, Savoy, IL, USA

MON 35 CHARACTERIZING UTERINE FIBROID TISSUE PROPERTIES FOR THERMAL THERAPIES

Christopher Dillon, Margit Janát-Amsbury, Allison Payne
University of Utah, Salt Lake City, Utah, USA

MON 36 THERMOREGULATION BY AGE: A CARDIOVASCULAR MRI STUDY

A. Colleen Crouch, Joan Greve
University of Michigan, Ann Arbor, MI, USA

MON 37 PHASE I TRIAL OF MR-HIFU MILD HYPERTHERMIA WITH RADIATION AND CHEMOTHERAPY FOR RECURRENT RECTAL CANCER: SECOND PATIENT

William Chu[1,3], Samuel Pichardo[5,6], Yuexi Huang[1,2], Robert Staruch[4], Ari Partanen[5], Merrylee McGuffin[1], Gregory Czarnota[1,2], Kullervo Hynynen[2,3]
[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Sunnybrook Research Institute, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Philips Research, Cambridge, MA, USA, [5]Philips Healthcare, Andover, MA, USA, [6]Thunder Bay Regional Research Institute, Thunder Bay, ON, Canada, [7]Lakehead University, Thunder Bay, ON, Canada

MON 38 WOUND CARE MANAGEMENT FOLLOWING RE-IRRADIATION (EBRT) AND CONCURRENT HYPERTHERMIA (ETT)

Nasarachi Onyeuku, Tejan Diwanji, James Snider, Pradip Amin, Zeljko Vujaskovic
University of Maryland, Baltimore, MD, USA

MON 39 IMMUNOTHERAPY IN COMBINATION WITH THERMORADIOTHERAPY FOR THE TREATMENT OF REFRACTORY MELANOMA

Dan Kunaprayoon, Zeljko Vujaskovic
University of Maryland, Baltimore, MD, USA

BREAK AND EXHIBIT TIME

3:00PM-3:30PM MAYA FOYER

ANNOUNCEMENT OF 2017 JKTG FOUNDATION NITA RECIPIENTS, POSTER AWARDS, AND STM ROBINSON AND HAHN AWARD PRESENTATIONS

3:30PM-6:00PM MAYA V-VI-VII-VIII CHAIR: DIETER HAEMMERICH

PRE-BANQUET RECEPTION

6:30PM-7:30PM SEASIDE GARDEN

J. EUGENE ROBINSON AWARD BANQUET

7:30PM-9:30PM SEASIDE GARDEN

TUESDAY, MAY 2ND

REGISTRATION

7:00AM-5:00PM MAYA FOYER

BREAKFAST

7:00AM-8:00AM MAYA I-II-III-IV

JKTG FOUNDATION PLENARY SESSION 3

8:00AM-9:00AM MAYA I-II-III-IV CHAIR: ROBERT IVKOV

TUES 1 CANCER CELL BIOLOGY IN 3D
Denis Wirtz
Johns Hopkins University, Baltimore, MD, USA

BREAK AND EXHIBIT TIME

9:00AM-9:30AM MAYA FOYER

NANOTECHNOLOGY SESSION IV - IN VIVO PRECLINICAL MODELS OF MAGNETIC HYPERTHERMIA

9:30AM-11:30AM MAYA I-II-III CHAIR: ROBERT IVKOV & INGRID HILGER

TUES 2 HOST IMMUNE STATUS DETERMINES THE UPTAKE AND RETENTION OF TARGETED ANTIBODY CONJUGATED NANOPARTICLES.
Preethi Korangath, James Barnett, Anirudh Sharma, Jacqueline Stewart, Elizabeth Henderson, Shu-han Yu, Sri Kamal Kandala, Rajeev Hatwar, Mohammed Hedayati, Brian Simons, Saraswati Sukumar, Robert Ivkov
Johns Hopkins University, Baltimore, MD, USA

TUES 3 EFFECT OF HYPERTHERMIA DURATION ON MR-HIFU MEDIATED DOXORUBICIN DELIVERY FROM THERMOSENSITIVE LIPOSOMES: IN VIVO BIODISTRIBUTION AND COMPARISON WITH NUMERICAL MODELS
Robert Staruch[1,2], Sumbul Shaikh[1], Chenchen Bing[1], Joris Nofiele[1], Debra Szczepanski[1], Yu Hong[1], Michelle Wodzak[1], Dieter Haemmerich[3], Noelle Williams[1], Theodore Laetsch[1,4], Rajiv Chopra[1]
[1]UT Southwestern Medical Center, Dallas, TX, USA, [2]Philips Research, Cambridge, MA, USA, [3]Medical University of South Carolina, Charleston, SC, USA, [4]Children's Health, Dallas, TX, USA

TUES 4 LYSO-THERMOSENSITIVE LIPOSOMAL DOXORUBICIN FOR TREATMENT OF BLADDER CANCER
Andrew Mikhail[1], Ayele Negussie[1], William Pritchard[1], Dieter Haemmerich[2], David Woods[1], Ivane Bakhutashvili[1], Juan Esparza-Trujillo[1], John Karanian[1], Sam Brancato[1], Piyush Agarwal[1], Bradford Wood[1]
[1]National Institutes of Health, Bethesda, MD, USA, [2]Medical University of South Carolina, Charleston, SC, USA

TUES 5 BNF-IGG NANOPARTICLE BASE MAGNETIC HYPERTHERMIA FOR TARGETED BREAST CANCER THERAPY

Chun Ting Yang[1,2], Preethi Korangath[2], Jackie Stewart[2], Anirudh Sharma[2], Sri Kandala[2], James Barnett[2], Feng Huei Lin[1], Robert Ivkov[2]

[1]National Taiwan University, Taipei, Taiwan, [2]Johns Hopkins University School of Medicine, Baltimore/Maryland, USA

TUES 6 CHARACTERIZATION OF A DUAL DRUG-LOADED STEALTH NANOSCALE LIPOSOMAL CARRIER FOR DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

Fred Lam[1], Stephen Morton[1], Jeffrey Wyckoff[1], Amanda Maffa[1], Elena Balkanska-Sinclair[3], Paula Hammond[1], Scott Floyd[3], Michael Yaffe[1,2]

[1]Koch Institute for Integrative Cancer Resarch at MIT, Cambridge, USA, [2]Harvard Medical School, Boston, USA, [3]Duke University School of Medicine, North Carolina, USA

TUES 7 EXPLOITING SYNTHETIC LETHALITY WITH NANOTECHNOLOGY: A NEW PARADIGM TO TARGET P53 MUTANT TUMORS.

Yi Wen Kong[1], Erik Dreaden[1], Sandra Morandell[1], Mohiuddin Quadir[3], Paula Hammond[1], Michael Yaffe[1,2]

[1]Massachusetts Institute of Technology, Cambridge, Massachusetts, USA, [2]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, [3]North Dakota State University, Fargo, North Dakota, USA

TUES 8 A COMPREHENSIVE HISTOLOGICAL ANALYSIS OF NANOPARTICLE TARGETING IN HER2+ BREAST CANCER

Elizabeth Henderson, Preethi Korangath, Brian Simons, Robert Ivkov

Johns Hopkins University School of Medicine, Baltimore, MD, USA

PHYSICS SESSION III - THERAPEUTIC OPPORTUNITIES WITH ULTRASOUND AND OTHER ENERGY SOURCES

9:30AM-11:30AM MAYA IV CHAIR: CHRIS DIEDERICH & JESSIE LEE

TUES 9 * COMPACT ULTRASOUND APPLICATOR FOR HYPERTHERMIA TREATMENT OF THE TRANSGENIC ADENOCARCINOMA MOUSE PROSTATE MODEL (TRAMP) WITH MR THERMOMETRY IN A 14T MRI SCANNER

Jessie Lee, Matthew Adams, Peter Jones, Eugene Ozhinsky, Viola Rieke, John Kurhanewicz, Chris Diederich

University of California - San Francisco, San Francisco, CA, USA

TUES 10 MR-GUIDED HIFU-INDUCED HYPERTHERMIA FOR LOCAL DRUG DELIVERY IN BREAST CANCER: MR THERMOMETRY EVALUATION AND PRECLINICAL VALIDATION

Roel Deckers[1], Charles Mougenot[1], Josanne S. De Maar[1], Manon N.G. Braat[1], Britt B.M. Suelmann[2], Sabine C. Linn[3], Elsken Van der Wall[2], Clemens Bos[1], Lambertus W. Bartels[1], Chrit T.W. Moonen[1]

[1]Imaging Division, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands, [3]Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

TUES 11 REAL-TIME SPATIOTEMPORAL CONTROL OF TRANSCRANIAL FOCUSED ULTRASOUND *IN VIVO*

Dalong Liu[1,2], Kyle Schaible[1], Walter Low[1], Emad Ebbini[1]

[1]University of Minnesota Twin Cities, Minneapolis, MN, USA, [2]Siemens Health Solutions, Seattle, WA, USA

TUES 12 INTEGRATING CATHETER-BASED THERAPEUTIC ULTRASOUND WITH DEPLOYABLE REFLECTORS AND FLUID LENSES TO ENHANCE FOCAL GAIN AND PENETRATION DEPTH.

Matthew Adams[1], Vasant Salgaonkar[1], Graham Sommer[2], Chris Diederich[1]

[1]UC San Francisco, San Francisco, CA, USA, [2]Stanford University Medical Center, Palo Alto, CA, USA

TUES 13 IMPROVEMENT OF SPATIAL RESOLUTION FOR TEMPERATURE IMAGING WITH 1°C ACCURACY FROM 50 TO 2MM² USING A STOCHASTIC-SIGNAL FRAMEWORK ON MEASURED ULTRASONIC IMAGES

Martin Arthur, Jason Trobaugh

Washington University in St. Louis, St. Louis, MO, USA

TUES 14 TRANSURETHRAL ULTRASOUND TO INDUCE COLLAGEN REGENERATION FOR TREATMENT OF STRESS URINARY INCONTINENCE (SUI)

Goutam Ghoshal[1], Emery Williams[1], Paul Neubauer[1], Patrick Roady[3], Corrine Bromfield[3], Clifford Shipley[3], Laurie Rund[3], Chris Diederich[2], E. Clif Burdette[1]

[1]Acoustic MedSystems, Inc., Savoy, IL, USA, [2]University of California at San Francisco, San Francisco, CA, USA, [3]University of Illinois, Urbana-Champaign, Urbana, IL, USA

TUES 15 ELECTROTHERMAL MODEL OF PULSED RADIOFREQUENCY ABLATION FOR PAIN RELIEF: COMPUTER STUDY AND IN VITRO VALIDATION

Elzbieta Ewertowska[1], Borja Mercadal[2], Victor Muñoz[3], Antoni Ivorra[2,5], Macarena Trujillo[4], Enrique Berjano[1]

[1]Department of Electronic Engineering, Universitat Politécnica de Valéncia, Valencia, Spain, [2]Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain, [3]Neurotherm Spain, Barcelona, Spain, [4]Instituto Universitario de Matemática Pura y Aplicada, Universitat Politécnica de Valéncia, Valencia, Spain, [5]Serra Húnter Fellow Programme, Generalitat de Catalunya, Spain

EMERGING PHOTONICS IN MEDICINE IN MEXICO

9:30AM-11:30AM MEXICO/COZUMEL CHAIR: GUILLERMO AGUILAR & SANTIAGO CAMACHO-LOPEZ

TUES 16 WINDOWS TO THE BRAIN (WTTB): A NEW PLATFORM FOR DIAGNOSIS AND THERAPY OF BRAIN PATHOLOGIES AND AN EXAMPLE OF BINATIONAL COLLABORATION BETWEEN USA-MEXICO

Guillermo Aguilar[1,2], Santiago Camacho-Lopez[2,1], Juan Hernandez-Cordero[3], Ruben Ramos-Garcia[4]

[1]University of California Riverside, Riverside, CA, USA, [2]CICESE, Ensenada, BC, Mexico, [3]UNAM, Mexico City, Mexico, [4]INAOE, Puebla, Pue, Mexico

TUES 17 BIOPHOTONICS: A GROWING NETWORK IN MÉXICO WHICH AIMS TO ADDRESS HEALTH ISSUES

Santiago Camacho-Lopez[1], Ruben Ramos-Garcia[2]

[1]CICESE, Ensenada, Baja California, Mexico, [2]INAOE, Puebla, Puebla, Mexico

TUES 18 BIOMEDICAL PHOTONIC DEVICES USING PHOTOTHERMAL POLYMER MEDIA
Reinher Pimentel-Domínguez, Juan Hernández-Cordero
Instituto de Investigaciones en Materiales, UNAM, Cd. Universitaria, CD Mx, Mexico

TUES 19 THERMOGRAPHY OF THE PLANTAR SKIN OF OVERWEIGHT AND OBESE INDIVIDUALS.
Francisco-J Renero-C
INAOE, Puebla, Mexico

PRESIDENTIAL SYMPOSIUM - COMPUTATIONAL MODELLING IN THERMAL MEDICINE

11:30AM-1:00PM MAYA I-II-III-IV CHAIR: JASON STAFFORD

TUES 20 SOCIETY OF THERMAL MEDICINE 2017 PRESIDENT'S SYMPOSIUM: COMPUTATIONAL MODELING AND SIMULATION IN THERMAL MEDICINE
R. Jason Stafford[1], Dieter Haemmerich[2], Punit Prakash[3], David Fuentes[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Medical University of South Carolina, Charleston, SC, USA, [3]Kansas State University, Manhattan, KS, USA

NANOTECHNOLOGY SESSION V - DRUG DELIVERY METHODS

1:00PM-2:30PM MAYA I-II-III CHAIR: TIMO TEN HAGEN & BONNIE HYLANDER

TUES 21 EVALUATION OF DOXORUBICIN-LOADED GOLD NANOSPHERES COMBINED WITH PHOTOTHERMAL ABLATION FOR LIVER CANCER
Rahul Sheth[1], Xiaoxia Wen[2], Junjie Li[2], Marites Melancon[1], Chun Li[2], Sanjay Gupta[1]
[1]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [2]Cancer Systems Imaging, Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

TUES 22 DEVELOPMENT OF A HEAT-TRIGGERED RELEASE FORMULATION OF CYCLOPHOSPHAMIDE FOR USE IN A PEDIATRIC PATIENT POPULATION
Michael Dunne, Christine Allen
University of Toronto, Toronto, Ontario, Canada

TUES 23 FOLIC ACID TARGETED NANOPARTICLES FOR DETECTION, TARGETING, AND THERMAL TREATMENT OF PERITONEALLY DISSEMINATED COLORECTAL CANCER
Eleanor McCabe-Lankford, April Brown, Bryce McCarthy, Margarita Peterson, Nicole Levi-Polyachenko
Wake Forest University Health Sciences, Winston-Salem, NC, USA

TUES 24 HOW TO IMPROVE CHEMOTHERAPY WITH THERMOSENSITIVE NANOCARRIERS.
Timo ten Hagen
Erasmus MC, Rotterdam, The Netherlands

TUES 25 HYPERTHERMIA MODULATED DELIVERY OF NAB-PACLITAXEL FOR THE TREATMENT OF MELANOMA
Mai Xu[1], Xing Liu[2], Albert C Lockhart[1], Robert J. Myerson[3], Imran Zoberi[3], Hong Chen[3], Lifei Zhu[3], Andrea Wang-Gillam[1]
[1]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA, [2]Department of Colorectal Surgery, Fujian Medical University Union Hospital, Fuzhou, China, [3]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri, USA

TUES 26 A DRUG RELEASE ANALYSIS SYSTEM (DRAS) FOR ALTERNATING MAGNETIC FIELD MEDIATED DRUG RELEASE FROM NANOPARTICLES

Mahendran Subramanian, Carlton Neville Jones
nanoTherics Limited, Staffordshire, UK

NOVEL TECHNOLOGY AND COMBINATION THERAPIES - TREATING INFECTIOUS DISEASES

1:00PM-2:30PM MAYA IV CHAIR: RAJIV CHOPRA & MARK SMELTZER

TUES 27 EMPLOYING HIGH-FREQUENCY ALTERNATING MAGNETIC FIELDS FOR THE NON-INVASIVE TREATMENT OF PROSTHETIC JOINT INFECTIONS

Rajiv Chopra, Sumbul Shaikh, Yonatan Chatzinoff, Imalka Munaweera, Bingbing Cheng, Seth Daly, Yin Xi, James Howard, Cecil Futch, Chenchen Bing, David Greenberg
UT Southwestern Medical Center, Dallas, Texas, USA

TUES 28 NANOTECHNOLOGY: A TINY SOLUTION TO THE BIG PROBLEM OF BIOFILM-ASSOCIATED BACTERIAL INFECTIONS?

Mark Smeltzer[2], Daniel Meeker[2], Jingyi Chen[1]
[1]Univerisity of Arkansas, Fayetteville, AR, USA, [2]University of Arkansas for Medical Sciences, Little Rock, AR, USA

TUES 29 * DEVELOPMENT OF A REMOTE ACOUSTIC SENSING SAFETY MECHANISM FOR BIOFILM ERADICATION USING ALTERNATING MAGNETIC FIELDS

Bingbing Cheng[1], Yonatan Chatzinoff[1], Omar Wyman[1], Debby Szczepanski[1], Sumbul Shaikh[1], Chenchen Bing[1], John Shelton[2], Cameron Perry[2], Jim Richardson[2], David Greenberg[4], Rajiv Chopra[1,3]
[1]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [3]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA, [4]Department of internal medicine and microbiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

TUES 30 * TEMPERATURE-SENSITIVE LIPOSOMAL CIPROFLOXACIN FOR THE TREATMENT OF BIOFILM ON PROSTHETIC JOINT IMPLANTS USING ALTERNATING MAGNETIC FIELDS

Imalka Munaweera[1], Sumbul Shaikh[1], Yonatan Chatzinoff[1], Danny Maples[2], Nandhini Sethuraman[2], Adane Nigatu[2], Ashish Ranjan[2], David Greenberg[3], Rajiv Chopra[1]
[1]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA, [2]Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA, [3]Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

TUES 31 PHOTOTHERMAL NANO-COMPOSITE FOR AUGMENTING ANTIBIOTIC EFFICACY

Nicole Levi-Polyachenko, Anila Pullagura
Wake Forest Unviersity Health Sciences, Winston-Salem, NC, USA

*** DENOTES JKTG/STM NITA AWARD RECIPIENT**

TUES 32 GENERATION OF PHOTOTHERMAL EFFECTS FROM GOLD NANOCAGES FOR THE TARGETED TREATMENT OF STAPHYLOCOCCUS AUREUS BIOFILMS

Daniel Meeker[1], Karen Beenken[1], Jingyi Chen[2], Mark Smeltzer[1]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

TUES 33 LASER INDUCED PRECISION HEATING FOR IMPROVED BACTERIAL DESTRUCTION WITH GENTAMICIN

Kenneth Vogel, Anila Pullagura, Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA

PHYSICS SESSION IV - THERMOMETRY, TREATMENT MODELLING, AND QA

1:00PM-2:30PM MEXICO/COZUMEL CHAIR: DIETER HAEMMERICH & CASPAR VAN LEEUWEN

TUES 34 THERMORADIOTHERAPY PLANNING: MEASUREMENT, ANALYSIS AND IMPLEMENTATION OF THE IMPACT OF TIME-INTERVAL, TEMPERATURE AND RADIATION DOSE USING BIOLOGICAL MODELING

Caspar van Leeuwen[1], Arlene Oei[1,2], R. ten Cate[1,2], Nicolaas Franken[1,2], Arjan Bel[1], Lukas Stalpers[1], Johannes Crezee[1], H. Petra Kok[1]

[1]Academic Medical Center, Department of radiation Oncology, Amsterdam, The Netherlands, [2]Academic Medical Center, Laboratory for Experimental Oncology and Radiobiology (LEXOR)/ Center for Experimental Molecular Medicine, Amsterdam, The Netherlands

TUES 35 ANALYSIS OF THE SPECIFIC ABSORPTION RATE (SAR) COVERAGE DURING SUPERFICIAL HYPERTHERMIA TREATMENT WITH AN ARRAY OF TWO CFMA ANTENNAS

Akke Bakker, Jasmijn Vink, Nathalie Zandbergen, Remko Zweije, Petra Kok, Hans Crezee

Academic Medical Center, Amsterdam, The Netherlands

TUES 36 INTEGRATED SYSTEM FOR SMALL-ANIMAL HYPERTHERMIA INVESTIGATIONS UNDER ULTRA-HIGH FIELD MRI GUIDANCE: AUTOMATIC CONTROL OF TISSUE TEMPERATURE

Pegah Faridi, Sergio Curto, Tej Shrestha, Marla Pyle, Leila Maurmann, Deryl Troyer, Stefan Bossmann, Punit Prakash

Kansas State University, Manhattan, KS, USA

TUES 37 ON-LINE ADAPTIVE HYPERTHERMIA TREATMENT PLANNING DURING LOCOREGIONAL HEATING TO IMPROVE TUMOR TEMPERATURES AND REDUCE HOT SPOTS

H.P. Kok, L. Korshuize - Van Straten, A. Bakker, R. De Kroon - Oldenhof, E.D. Geijsen, L.J.A. Stalpers, J. Crezee

Academic Medical Center, Department of radiation oncology, Amsterdam, The Netherlands

TUES 38 NON-INVASIVE HEATING OF JOINT IMPLANT BIOFILMS IN ALTERNATING MAGNETIC FIELDS: FACTORS AFFECTING UNIFORMITY

Yonatan Chatzinoff[1], David Greenberg[1], Ji Chen[2], Rajiv Chopra[1]

[1]UT Southwestern Medical Center, Dallas, Tx, USA, [2]University of Houston, Houston, Tx, USA

TUES 39 MRI-BASED REAL-TIME CHARACTERIZATION OF THERMOEMBOLIZATION

Samuel Fahrenholtz[1], Chunxiao Guo[2], Joshua Yung[1], Ken Hwang[1], R. Jason Stafford[1], Erik Cressman[2]
[1]Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA,
[2]Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

TUES 40 THERMAL-STRUCTURAL CHARACTERIZATION OF NON-INVASIVE SELECTIVE CRYOLIPOLYSIS, A COMPREHENSIVE NUMERICAL STUDY

Reza Monazami[1,2], Dieter Manstein[1,2]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Harvard Medical School, Boston, MA, USA

BREAK AND EXHIBIT TIME

3:00PM-3:30PM MAYA I-II-III-IV

CLOSING PROGRAM

3:30PM-4:30PM MAYA I-II-III-IV

MEETING ADJOURNED

5:00PM

SAT 01

THE PHYSICS, BIOLOGY, AND IMMUNOLOGY OF THERMAL NANOMEDICINE

Andris Bakuzis[1], Robert Ivkov[2], Michael Graner[3], Elizabeth Repasky[4], Gerardo Goya[5], Fred Bunz[6]

[1]Federal University of Goiás, Goiânia, Goiás, Brazil, [2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [3]University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA, [4]Roswell Park Cancer Institute, Buffalo, New York, USA, [5]Universidad de Zaragoza, Zaragoza, Spain, [6]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Thermal medicine involves multiple disciplines to deliver and control energy delivery to tissues with the objective to raise the local temperature for enhanced therapeutic benefit. Among the earlier embodiments translated to clinic, and still forming an operational treatment paradigm, are applications that utilize various energy sources to heat solid malignancies concomitant with radiation therapy to achieve better local control of cancer. While this embodiment of thermal medicine demonstrates significant benefits to cancer patients, even conferring improved overall survival, persisting challenges dampen enthusiasm for wider adoption. Some limitations are technological, but a principal objection to concomitant hyperthermia has been that its benefits are local, and thus unable to confer durable response, or 'cure'. It may be argued that much of this perception derives from the mechanistic focus of heat stress being limited to DNA-damage repair inhibition. Other biological, immunological, and physiological consequences of local and systemic heating have recently garnered significant attention to explore the effects of localized tumor damage that can elicit profound systemic responses to enhance long-term disease management. Thermal nanomedicine, a relatively recent entrant to the field has demonstrated potential utility in preclinical and clinical settings to improve energy deposition, imaging guidance of treatments, and for drug delivery. An aspect of nanostructured materials that is often ignored (or considered a nuisance to be minimized) is their inherent immunogenicity. Often resembling viruses in size and shape, nanoparticles offer significant potential to modulate biological and immunological responses to therapeutic intervention. The objective of this focused refresher workshop is to provide researchers and research trainees an overview of the many exciting facets of heat stress and thermal nanomedicine. Attendees will receive a refresher on subject matter integral to the 34th Annual Meeting of the Society for Thermal Medicine.

SAT 02

THE BRIGHT FUTURE OF BIOPHOTONICS IN MEXICO

Elder De la Rosa

centro de investigaciones en optica, leon, gto, Mexico

Biophotonics focus on the use of photonics principles, engineering and technology to view and analyze molecules, cells or living tissue for critical problems in biotechnology, biology and medicine. Properties are based on the interaction of light with matter that result on absorption, fluorescence, reflection and scattering, which tell us about composition and structure of matter. The market volume in 2012 was $48.4 billion euros and expected $85.5 for 2020 dominated for diagnostic and food safety. Such market size highlights the relevance of biophotonics industry. Here in this work, we discuss a general overview about biophotonics activities in México, in particular we present some result on bionanophotonics applications for single molecule detection, imaging cells and tissue, and drug delivery including the design of theranostic nanoparticles for diagnostic and therapy, performed in our laboratory at Centro de Investigaciones en Optica (Optical Research Center).

SAT 03

FUTURE PERSPECTIVES AND CHALLENGES OF MAGNETIC HYPERTHERMIA TUMOR THERAPY

Ingrid Hilger

University Hospital Jena, Jena/Thuringia, Germany

Up to now, many researchers suggested magnetic hyperthermia as a valuable tool to supplement and improve conventional cancer treatment methods. It is based on the accumulation of iron oxide nanoparticles in the tumour region and the exposure of the target organ to an alternating magnetic field. One advantage of this method is that heating can be applied interstitially and not from outside the body. The method is minimally-invasive, since only the application of the magnetic material is required, and heating can ideally be selectively localized at the tumour area.

Particularly iron oxide nanoparticles are smart vehicles for magnetic hyperthermia. Iron oxide nanoparticles with specific physicochemical and magnetic features can distinctly impact tumour cellular function upon exposure of target cells to an alternating magnetic field. Among the different strategies to apply the magnetic material, the intratumoral application is favoured, since it allows a distinct control of the amounts to be deposited. In contrast, the often claimed feasibility of targeting iron oxide nanoparticles via the vascular system and/or the local tumour vascularization (active nanoparticle targeting) has not been properly validated so far. This is mainly due to the action of diverse physiological parameters in the body, which will be discussed in detail in this talk. An ideal technique to monitor the presence of iron oxide nanoparticles inside the tumours might be CT imaging. Iron oxide nanoparticles are also ideal vehicles for the attachment of drugs, making it possible of combining magnetic hyperthermia with chemotherapy by utilization of only one carrier.

SAT 04

WHAT DOES THE FUTURE HOLD FOR PDT?

Ricardo Azevedo

University of Brasília, Brasília - DF, Brazil

Photodynamic therapy (PDT) is a modality of treatment that uses light to activate a drug called photosensitizer to generate Reactive Oxygen Species (ROS) that kills nearby cells and microorganisms. Currently, PDT is used mainly for cancer treatment; however other diseases can be treated with it, such as superficial skin fungus diseases, cutaneous leishmaniases, among others, what is of great importance given the seriousness that drug-resistant pathogens have now become. The main advantages of PDT rely on the fact that it has no long-term side effects; It's less invasive, quicker than surgery and is mainly done as an outpatient. Also, it is lower cost than other treatments and can be repeated several times, if needed. The main drawbacks of PDT are it cannot reach deep organs and therefore cannot be used for cancer metastasis, for example; also it can cause skin sensitivity to light. A few photosensitizer are already approved by the FDA and other regulatory organs worldwide. However, there is a second generation of them being tested in clinical trials for different diseases that can go deeper than their first generation counterpart; cause minimal or no skin sensitivity and may be quickly removed from healthy cells. Many of the first and second generation of photosensitizer are being associated with nanomaterials as a carrier. This association is thought to improve the efficacy of the PDT since it can better protect the drug; diminish the amount of injected drug; allow the use of hydrophobic photosensitizers, and so on. This kind of system, in which the photosensitizer is associated with carriers, is often referred to as third-generation photosensitizer. It is worth to call attention that published papers by different groups have been pointed out that, on the contrary of chemotherapy and radiotherapy, PDT can stimulate the immune system instead of suppressing it, depends upon photosensitizer, cell localization, tumor type, among others factors. Work on ways to improve this feature of PDT will help the patient to fight against possible metastasis. Finally but not less important is the real possibility of using PDT along with other therapies to turn it more effective.

SUN 01

CHASING AN ELUSIVE EVIDENCE-BASED RATIONALE FOR HYPERTHERMIA IN THE CANCER CLINIC: SEPARATING FACT FROM FICTION

Elizabeth Repasky

Roswell Park Cancer Institute, Buffalo, New York, USA

The number of different thermal therapy applications for cancer and for other pathologies has grown precipitously in the past 35 years, largely because of applications involving HIPEC, Isolated limb perfusion/ infusion, thermal ablation, ultrasound-based heating, internal heating devices, heat-generating nanoparticles and heat sensitive liposomes, and more recently, mild whole body heat treatments using water-filtered IR-A-radiation. At the same time, the number of sites performing "traditional" local hyperthermia using external devices which deliver electromagnetic energy to raise internal temperature of the tumor volume, typically in the range of 42-45°C, has grown smaller. This presentation will examine the strengths, and weaknesses, of the rationales which are typically given for design of the clinical application of several types of thermal therapies, including local (or local-regional) hyperthermia. Quite often, the rationale cited derives from in vitro studies, or animal studies which utilize surface heating procedures, (which involves direct heating of the skin and other normal tissues) rather than generating heat at the site of tumor. Other evidence strongly suggests that current clinical protocols are not optimized in terms of schedule of heating with radiation or chemotherapy, and do not take full advantage of the potential of thermal therapies to stimulate anti-tumor immunity or vascular changes which enhance delivery of cells and therapeutic molecules. The fact that there is still real benefit resulting from addition of heat in current clinical applications should provide optimism that considerable additional benefit could be achieved by designing clinical trials based upon evidence-based rationales that exploit the most beneficial properties of thermal manipulations.

SUN 02

NEW POSSIBILITIES FOR *IN VITRO* MAGNETIC HYPERTHERMIA BASED ON INTRACELLULAR NANOSTRUCTURES.

Gerardo Goya[1], Beatriz Sanz[1], Enio Lima Jr.[2], Emilio De Biasi[2], Rafael Cabreira-Gomes[3], Jerome Depeyrot[3]

[1]Instituto de Nanociencia de Aragon, Zaragoza, Spain, [2]Centro Atómico Bariloche/CONICET, S.C. de Bariloche, Argentina, [3]Complex Fluids Group, IF- UNB, Brasilia, Brazil

The magnetic dynamics of a single-domain magnetic nanoparticle (MNP) under ac magnetic fields is well understood. There is a large set of experimental data on MNPs dispersed in viscous fluids that can be explained by classical theory, from the Stoner-Wohlfarth model to the Landau-Lifshitz stochastic equations. However, the impact of different nano-assemblies like aggregates, clusters or chains of MNPs on the power absorption has only recently started to be assessed. We have increased the heating efficiency in vitro by tailoring both the magnetic properties of MNPs and their interactions. The values of the physical parameters of MNPs such as magnetic anisotropy and dipolar interactions were screened for maximum power absorption, using numerical simulation of the magnetic dynamics under ac magnetic fields so that the heating efficiency is preserved in the intracellular environment. The output of this protocol is the largest *in vitro* specific power absorption (SPA) values reported so far. Our results demonstrate the need of precise experimental data about the actual size, shape and structure of intracellular clusters to validate theoretical models about the role of dipolar interactions or cluster topology on power absorption.

SUN 03

TOWARDS AN UNDERSTANDING OF HEATING EFFECTS AND MAGNETISATION RESPONSE OF MAGNETIC NANOPARTICLES ASSOCIATED WITH LIVE CELLS

Neil Telling[1], David Cabrera[1,2], Francisco Teran[2]

[1]Keele University, Stoke-on-Trent, UK, [2]IMDEA Nanoscience, Madrid, Spain

Magnetic hyperthermia is an experimental thermal cancer treatment that uses magnetic nanoparticles to channel the energy from an external high-frequency alternating magnetic field. As heating can only occur where nanoparticles are present, the technique is truly local and significant effects can be obtained by accumulating nanoparticles within tumors. Previous encouraging results have shown that magnetic hyperthermia using concentrated particle suspensions can reduce tumor volume, and can increase survival times in clinical trials when combined with radiotherapy. However in order to obtain true cellular level thermal treatment, much recent work has focused on labelling individual cancer cells with magnetic nanoparticles, either by binding them to cell membranes or through internalisation routes such as endocytosis. In principle these particles should then be able to heat the cells directly to trigger cell death. However the results of such experiments to date have been somewhat disappointing because it seems the magnetic and consequently heating properties of the nanoparticles can change once they are associated with cells. In this talk I will review the physical mechanisms behind the magnetic nanoparticle based heating effects of relevance to localised hyperthermia treatment in cancer. In particular I will discuss how developing a full understanding of the interactions of nanoparticles with their local environment is essential to achieve effective cellular level heating within real biological systems, and the current limitations that constrain progress in this area. Within this context I will describe the results of our recent work using a.c. magnetic susceptometry and magnetometry to probe the high-frequency magnetic response of nanoparticles under different environmental conditions, including in-situ measurements of nanoparticles associated with live cells. I will also discuss how nanoparticle surfaces can evolve when in contact with biological media and how such processes affect their interaction with cells. Overall our results suggest that the magnetic response and consequently heating efficiency of the nanoparticles is sensitive to a combination of local environmental conditions, and intrinsic physical nanoparticle properties such as magnetic anisotropy. Such knowledge should inform on the design elements of future methodologies for optimising and enhancing the performance of cellular level magnetic hyperthermia.

SUN 04

INORGANIC NANOPARTICLES FOR MAGNETIC HYPERTHERMIA: FROM THE SYNTHESIS TO THEIR *IN VITRO* AND *IN VIVO* CHARACTERIZATION

Teresa Pellegrino

Istituto Italiano di Tecnologia, Genoa, Italy

Chemotherapy together with surgery are the main modalities to treat tumors in clinic. Although there are several FDA approved chemotherapeutic agents, such as doxorubicin cisplatin, paclitaxel etc. they all show together with beneficial actions against tumor cells also various degree of side effects due to their non-specific action against healthy cells.

On the other hand, the use of heat to reduce tumor mass is very ancient. Nowadays, many techniques allow to precisely focalizing the heat in very specific body regions resulting in treatments that are more efficient and minimize side effects. Magnetic nanoparticles can act as heat mediators under oscillating magnetic fields in the so-called "magnetic hyperthermia". The field of magnetic hyperthermia has received a renewed interest since the colloidal syntheses by non-hydrolytic methods have revealed several merits over conventional wet chemical hydrolytic processes in terms of controlled size, size distribution and crystallinity of magnetic materials.
All these parameters indeed affect structural and magnetic properties of nanomaterials and thus their heat performances. Here, I will first focus on our recent progress on the combination of cubic shape iron oxide magnetic nanoparticles with thermo-responsive coating to achieve both magnetic hyperthermia and heat-mediated drug delivery. I will cover all topics from the synthesis, to the functionalization and characterization, to the drug loading and *in vitro* characterization, to the *in vivo* long-term study (up to 5 months after hyperthermia treatment) on xenograft tumor murine model. In addition, our bio-distribution studies at the iron dose needed for hyperthermia have indicated the absence of toxicity of such thermo-responsive iron oxide nanocubes and the *in vivo* degradation of the materials over three months.

I will also provide a comparative magnetic hyperthermia study based on iron oxide nanocubes and another type of nanocubes made of spinel cobalt ferrites providing also in this case the *in vitro* and *in vivo* study. Finally, I will show a recent work performed with the aim to combine magnetic hyperthermia with photo-ablation.

Keywords: magnetic nanoparticles, thermo-responsive polymers, drug delivery, magnetic hyperthermia, photoablation

Acknowledgements: The author acknowledges the Italian AIRC project (Contract No. 14527), the Cariplo foundation (Contract No. 2013 0865), the EU- Horizon 2020 MSCA RISE call, (COMPASS project – 691185) and the European Research Council (ERC) (starting grant ICARO project, Contract N. 678109) for supporting this research.

SUN 05

MAGNETIC DOMAINS INTERACTIONS AS FUNCTION OF PARTICLE SIZE IN MAGNETITE NANOPARTICLES

Ana Luisa Ramirez-Nuñez[1], Octavio Fuentes-Ramirez[1], Gerardo F. Goya[2], Jaime Santoyo-Salazar[3]

[1]Nanociencias y Nanotecnología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico, Mexico, [2]Instituto Universitario de Investigación en Nanociencia de Aragón (INA), Zaragoza, Spain, [3]Departamento de Física, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico, Mexico

Nowadays, superparamagnetic magnetite (Fe_3O4) nanoparticles have been used in functional systems as target, carrier, and hyperthermia source for specific applications mainly drug delivery, contrast agents and magnetic hyperthermia cancer treatment. The control, direction and accumulation of these functional systems are dependent of physical properties of (a) magnetite nanoparticles as core and (b) bioactive coatings as shell, in "core-shell" configuration. Superparamagnetic magnetite nanoparticles have magnetic single-domains, which can be oriented to applied magnetic field direction. Also these nanoparticles have low coercitivity with magnetic remanence near to zero. The functionalizated systems can be stimulated by external magnetic field AC in order to generate an energy change, from magnetic vibrational action of magnetic domains to thermal energy. In this work, magnetite nanoparticles have been obtained by co-precipitation and analyzed as function of particle size (10, 15, 20, 25, 30, 35 and 40nm) by Magnetic Force Microscopy, MFM. Results showed uniaxial interactions, which depend of particle size, morphology, neighboring interactions and magneto-static energy over the surface of nanoparticles. Also, these interactions can change as function of particle concentrations. Finally, magnetite nanoparticles have been functionalizated with different organic shell to reach cell viability near to 90%. Perspectives for these functional systems are the hyperthermia testing in-vitro and in-vivo.

SUN 06

REMOTE CONTROLLED DRUG DELIVERY ON ORAL CANCER TUMOR SITE IN MICE USING IRONPARTICLE AND FLUOROPHORE CONTAINING LIPOSOME AND ALTERNATING MAGNETIC FIELD

Oula Penate Medina[1], Tuula Penate Medina[1], Jana Humbert[1], Gerardo Goya[2], Mirko Gerle[1], Hanwen Zhu[1], Claus Glüer[1], Holger Kalthoff[1], Regine Willumeit Röhmer[1]

[1]Christian Albrechts Universität zu Kiel, Kiel, Germany, [2]Institute of Nanoscience of Aragon (INA) and Condensed Matter Physics Dept., , University of Zaragoza, Zaragoza, Spain

Several small molecules have to short circulation time in the blood. Liposomal delivery systems have been used to compensate this phenomenon in drug delivery and in imaging. Often liposomal drugs remain entrapped inside the liposomes. We developed magnetoenzymatic sensitive liposome (MESL) carrier systems for imaging and targeted release of multifunctional nanotheranostic agents. The method utilizes alternating magnetic fields (AMF) and liposomal nanoparticles enzymatically sensitized to apoptosis, tumor and inflammation processes.. We have used this phenomenon to develop more advanced image guided tumor and inflammation targeting and therapy methods utilizing apoptotic enzyme secretion in the target tissues.

The liposomal construct was assembled as ICG and iron nanoparticle containing MESL nanocarrier. Characterisationj of liposome was done in Uni Kiel.. Preliminary in vivo imaging studies were performed at the Molecular Imaging North Competence Center. Liposome payload accumulation was tested by using optical imaging (NightOwl and FMT 2500). ROI analysis was used to assess targeting to the tumor In preliminary in vivo experiments 40 orthotopic xenograft SCC tongue carcinoma were used in from tumor models and mice were used per cell line for imaging, targeting and PK parameter assessment. All administrations were IV injections. The liposome accumulation was studied by using ICG fluorophores encapsulated in to the liposomes. The dye content in a target organ was assessed by using ICG fluorescence or absorbance. At the study endpoint a surgical microscope was used to examine the tumors of the mouse. After in vivo imaging the organs of the animals were harvested and optical microscopy, histology, operative microscopy was assessed. Several time points were selected according to the previous liposomal imaging studies. Cisplatin was chosen as a model drug for further drug delivery function.

There were clear increase in the accumulation of available drug in the AMF +liposome treated mice versus control..AMF treated MESL liposomes were able to deliver 10 times more signal than the free ICG. The amounts of fluorophore accumulated in the tumor were sufficient that the tumors were able to be seen and identified by using operative microscope fitted with fluorescent filters.

There was clear synergy in using AMF and enzymatic activation in tandem. MRI and optical methods can be used to assess and develop this platform for further refinement. This method offers total improved way to do imaging and drug delivery and has possible perspectives to be clinically translated

SUN 07

IMAGING-ASSISTED INDIVIDUAL DESIGNS OF HEATING PROTOCOLS FOR PROSTATIC TUMORS IN MAGNETIC NANOPARTICLE HYPERTHERMIA

Alexander LeBrun, Ronghui Ma, Charles Bieberich, Liang Zhu

University of Maryland Baltimore County, Baltimore, Maryland, USA

Magnetic nanoparticles subjected to an alternating magnetic field can generate heat. This approach has high cell-killing potential in cancer treatment because it can deliver confined thermal energy to tumours. Unfortunately, nanoparticle spreading in tumours is difficult to model due to tumour heterogeneity and complex intra-tumoural transport processes. In this study, we have utilized a microCT system to study nanoparticle distribution in PC3 human prostate cancer xenografts in mice. Nanoparticle deposition patterns unique to individual tumour groups were visualized and quantified. Among three infusion rates (3-5 μL/min), the infusion rate of 3 μL/min was identified to result in the most repeatable nanoparticle distribution in PC3 tumours, with less than 8% variation in nanoparticle distribution volume. For an alternating magnetic field of 5 kA/m at 190 kHz, the calibrated and calculated total energy deposition rate in tumours was 0.38 W from the 0.1 cc nanofluid injected. The observed similarity in total energy deposition rates in all three infusion rate groups suggests improvement in minimizing nanoparticle leakage from the tumours. Individual tumour geometry and nanoparticle distribution obtained from the microCT scans were then generated and exported for heat transfer simulation. Thermal damage regions were simulated to determine optimal treatment protocols. The time needed for complete thermal damage to a tumour ($\sim$ 650 mm^3 in volume) was determined to be approximately 12 minutes or 25 minutes if one uses the Arrhenius integral Ω equal to 1 or 4 as the damage threshold, when the infusion rate is 3 μL/min. Although the two larger infusion rate groups with longer heating time can still cause thermal damage to the entire tumour, the collateral thermal damage would have exceeded the design criterion of 5%, while the assessment criterion was acceptable only in the 3 μL/min infusion rate group. Finally, heating protocols were implemented in PC3 xenograft tumours in mice using *in vivo* magnetic nanoparticle hyperthermia. We demonstrated that the designed 25 minutes heating on tumour tissue was effective to cause irreversible thermal damage to PC3 tumours within three days after the heating. Reducing the heating time to 12 minutes resulted in an initial shrinkage, however, tumours recurred within the observation period of 56 days. Results of the histological analysis showed vast regions of apoptotic and necrotic cells, consistent with the significant temperature elevation. These data, obtained by testing imaging based theoretical simulation in animal models, provide new approaches for individualized heat treatment designs for cancer patients.

SUN 08

DEVELOPMENT OF THE THERMOSENSITIZER FOR MAXIMIZING CANCER TREATMENT EFFICACY WITH THE RADIOFREQUENCY-INDUCED HYPERTHERMIA

Seong-Tshool Hong, Eun-young Koh

Department of Biomedical Sciences, Chonbuk National University Medical School, Jeonju, Chonbuk, Republic of Korea

One therapeutic approach to treat cancer is hyperthermia in which malignant tissues are exposed to high temperature. Although various physical methodologies have been developed to induce heat in malignant tissues, the hyperthermia using radiofrequency electromagnetic wave to induce heat is the most frequently used method currently in oncology. However, the therapeutic efficacy of the radiofrequency-induced hyperthermia by itself is marginal so that the radiofrequency-induced hyperthermia is typically used with chemotherapy or radiotherapy to treat cancer in modern standard cancer treatments. Therefore, development of a method to amplify the therapeutic efficacy of the radiofrequency-induced hyperthermia is required for the radiofrequency-induced hyperthermia to become another therapeutic option for cancer. Metal ions, such as ferric ion, have a very strong dipole moment, which means that the metal ions can interact well to generate heat. Considering the characteristics of metals ions, it would be an ideal thermosensitizer for radiofrequency-induced hyperthermia if non-toxic biological metal ion, such as ferric ion, could be specifically delivered to cancer. Here, I report that transferrin containing ferric ions can be used as an ideal thermosensitizer for the radiofrequency-induced hyperthermia. Ferric ions loaded in transferrin were 1.8 times more actively transferred into cancer cells than non-malignant normal cells in vitro. As is the case of in vitro experiment, ferric ions loaded in transferrin were specifically accumulated in the tumor tissue of tumor xenografted mice so that the concentration of ferric ions were 1.5 ~ 3.7 times higher than normal tissues. Because ferric ions were specifically accumulated in the tumor tissue of tumor xenografted mice, ferric ions reacted with the electromagnetic wave-dependent hyperthermia to generate high heat. Therefore, increase in the temperature of the tumor tissue was 2.4 fold higher in the tumor xenografted mice under the 13.56 MHz radiofrequency-induced hyperthermia after injecting transferrin compared to the 13.56 MHz radiofrequency-induced hyperthermia without transferrin injection. Surprisingly, the overall anticancer efficacy of the 13.56 MHz radiofrequency-induced hyperthermia using transferrin as a thermosensitizer was much better than paclitaxel's efficacy, and was able to completely eradicate cancer in the tumor xenografted mice.

SUN 09

QUALITY ASSURANCE AND CONTROL IS ESSENTIAL TO ENSURE GOOD CLINICAL RESULTS.

Gerard van Rhoon[1], Hana Dobsicek Trefna[2], Hans Crezee[3]

[1]Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [2]Chalmers University of Technology, Gothenborg, Sweden, [3]AMC, Amsterdam, The Netherlands

The drive behind for the need to update many Hyperthermia Quality Assurance guidelines is twofold and reflects improved clinical studies and innovations in hyperthermia technology during the last decades.

Until recently the available, quality assurance guidelines for the clinical application of hyperthermia dated back several decades. These guidelines were designed reflecting the experience and expertise from the early days of hyperthermia. Since then, numerous improvements in equipment have been made available and more importantly advanced hyperthermia treatment planning (HTP) has been introduced. The latter resulted in a greatly enhanced ability to fully understand the interaction of the electromagnetic fields emitted by the hyperthermia applicators with the anatomy of the patient. In fact the advanced modelling enabled the currently ongoing transition from empirical to objective HTP guided adaptive temperature optimization of the hyperthermia treatment.

Ample evidence can be found in literature showing that quality of the hyperthermia treatment is related to clinical outcome. In several early clinical studies poor quality of the hyperthermia treatment has been claimed to be the cause of the inability to demonstrate a benefit of adding hyperthermia to radiotherapy. More convincing is however, that many studies have been published demonstrating a positive dose effect relationship in patients treated with radiotherapy and hyperthermia. In these studies thermal dose, i.e. quality of the hyperthermia treatment, was reported using a variety of measured temperature parameters or using various technical parameters.

Conclusion: The recently published new Quality Assurance guidelines for superficial and loco-regional deep hyperthermia have been designed to reflect today's standard of technology and the current evidence on thermal dose effect relationships. Wide adoption of these guidelines can be further promoted by organization of audits and site-visits.

SUN 10

QUALITY ASSURED HYPERTHERMIA: THE PERSPECTIVE OF THE ESHO TECHNICAL COMMITTEE

Hana Dobsicek Trefna

Chalmers University of Technology, Gothenburg, Sweden

Quality assurance (QA) guidelines are essential to provide uniform execution of clinical trials and treatment in the application of hyperthermia. The ESHO technical committee (ESHO-TC) has set out to provide QA guidelines for a number of different hyperthermia applications. The intention of the QA documents is to provide definitions for a good hyperthermia treatment and to identify which hyperthermia systems can adequately heat the tumor volume for different tumor sites. In other words, the guidelines are inclusive for all heating techniques, which have been demonstrated to be capable of adequate heating of the (tumor) target. These system characteristics should be well documented.

In this way, participation in clinical trials is open for all participants providing they have **both** implemented the QA guidelines **and** strictly follow the specific requirements of the clinical study protocol to apply hyperthermia to the defined clinical target. Hence it is the responsibility of every institute to characterize its hyperthermia equipment and make the data available to the ESHO technical committee (ESHO-TC).

As a follow-up of the development of these QA guidelines and using the experimental and clinical information obtained via the implementation of the QA guidelines, the ESHO-TC will investigate the possibility to compose a public list of device types with a description of the potential tumor size, depth and location that can be heated.

Conclusions: The goal of the ESHO-TC is to establish QA guidelines for the application of hyperthermia. The QA guidelines for administration of deep and superficial hyperthermia were recently published; the interstitial guidelines are in preparation while QA guidelines for hyperthermia treatment planning are in the pipeline.

SUN 11

QUALITY ASSURANCE GUIDELINES FOR INTERSTITIAL HYPERTHERMIA

Hana Dobšícek Trefná[2], Manfred Schmidt[3], Gerard van Rhoon[5], H. Petra Kok[1], Ulf Lamprecht[4], Michael Ehmann[7], Jacek Nadobny[8], Sultan Abdel-Rahman[6], Vratislav Strnad[3], Andrzej Kukielka[12], Mark Hurwitz[9], Pirus Ghadjar[8], Zeljko Vujaskovic[11], Chris Diederich[10], Paul Stauffer[9], Hans Crezee[1]

[1]Academic Medical Center, Department of Radiation Oncology, Amsterdam, The Netherlands, [2]Chalmers University of Technology, Signals and Systems, Gothenburg, Sweden, [3]Universitätsklinikum Erlangen , Strahlenklinik, Erlangen, Germany, [4]University Hospital Tuebingen, Radiation Oncology, Tuebingen, Germany, [5]Erasmus MC Daniel den Hoed Cancer Center, Radiation Oncology, Rotterdam, The Netherlands, [6]Ludwig Maximilians University of Munich, Department of Internal Medicine III, Munich, Germany, [7]University Medical Centre Mannheim, Radiation Oncology, Mannheim, Germany, [8]Charité Universitätsmedizin Berlin, Radiation Oncology, Berlin, Germany, [9]Thomas Jefferson University, Philadelphia, USA, [10]UCSF, San Francisco, USA, [11]University of Maryland School of Medicine, Division of Translational Radiation Sciences, Baltimore, USA, [12]Amethyst Radiotherapy Centre, Ludwik Rydygier Memorial Hospital, Krakov, Poland, [13]Maria Sklodowska Curie Memorial Centre of Oncology, department of radiotherapy, Krakov, Poland

Interstitial hyperthermia (IHT) is a hyperthermia method using arrays of needle shaped applicators or applicators in tubes implanted into the target volume. The heating characteristics of IHT set it apart from other hyperthermia methods, warranting dedicated QA guidelines. Existing QA guidelines for clinical application of IHT are over 25 years old and our goal is to establish new QA guidelines for IHT, similar to the recently established QA guidelines for clinical application of deep and superficial hyperthermia.

The technical committee (TC) of the European Society of hyperthermic Oncology (ESHO) set out to formulate new QA IHT guidelines with participation of experienced members of the Society for Thermal Medicine (STM). We decided to focus on application of IHT for mild hyperthermia in the 40-45°C temperature range, aiming at indirect cell kill by radiosensitisation and chemosensitisation.

Guidelines are given for preparation, planning, execution and documentation of treatments. The strong thermal gradients associated with the very localized heating of IHT impose specific minimum requirements on implant geometry, needle spacing and thermometry. Implants need to be planned to match both radiotherapy and hyperthermia requirements as IHT is generally applied in combination with brachytherapy, using the same catheter implant. Accurate dose distribution data (CEM43, T50, T90) need to be recorded, correcting for potential overestimation and underestimation associated with the measurement location.

Conclusion: The new IHT QA guidelines reflect the current standard and ensure that a uniform application and registration of interstitial hyperthermia treatments within clinical trials based on current knowledge and clinical experience.

SUN 12

QUALITY ASSURANCE FOR THERMAL DOSIMETRY OF CLINICAL HYPERTHERMIA

Paul Stauffer, Dario Rodrigues, Mark Hurwitz

Thomas Jefferson University, Philadelphia, PA, USA

Introduction:

Accurate temperature measurements are essential to good thermal dosimetry of clinical hyperthermia (HT). In addition to accuracy, the distribution of temperature throughout the tumor target is of critical importance. Typical tools used to monitor HT include: single or multiple sensor temperature probes located in fixed positions; cyclically moving thermal mapping sensors; and infrared thermography. These techniques record temperatures at the skin surface or inside the body when probes are placed via interstitial or intracavitary catheters. In recent years, there has been increased attention to non-invasive thermometry approaches such as magnetic resonance thermal imaging (MRTI) and microwave radiometry. These methods provide extremely useful volumetric temperature distribution data from deep in the body but generally have poorer absolute temperature accuracy: on the order of 1°C versus 0.2°C for traditional temperature probes. There are appropriate clinical applications as well as limitations for the use of these thermometric tools, which must be considered carefully in the quality assurance (QA) of hyperthermia treatments.

Results:

This presentation will describe basic QA considerations for each of the major thermometry approaches, which must be evaluated and balanced to provide reliable monitoring and control of quality hyperthermia treatments. Proper interpretation of measured temperatures within a clinical distribution is critically important to ensure quality HT, so strategies will be defined for sensor placement and interpretation of readings in typical clinical configurations. Recommended probe placements include sampling different regions of heterogeneous tumor volumes including scars, skin folds and contoured or irregular anatomy likely to perturb applicator heating patterns. For heating systems with increasingly accurate computer treatment planning predictions of temperature distributions, there are opportunities for smart interpolation of temperature distributions and self-correcting thermal simulations based on real-time feedback during treatment.

Conclusion:

The presentation will end with an overview summary of typical clinical thermal monitoring approaches with expected accuracy, spatial and temporal resolution, and importantly, a list of confounding factors that must be managed to maintain reliability of temperature feedback with each approach.

SUN 13

MAGNETIC RESONANCE THERMOMETRY BRINGS HYPERTHERMIA QUALITY ASSURANCE TO THE NEXT LEVEL

Tim Mulder, Sergio Curto, Daniel de Jong, Gerard van Rhoon

Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Quality assurance (QA) is defined as the systematic evaluation of system performance. In general the objective is to perform QA with the most advanced measuring tools available in order to allow a quantitative decision based on objective criteria whether a system operates according to specifications. HT applicators require formal QA to ensure accurate, precise and consistent treatments.

Most commonly used HT QA measurement techniques to evaluate hyperthermia system performance rely on temperature probes, infrared (IR) cameras, Diode E-field sheets, single E-field sensors and lamp phantoms. Although, these techniques in principle provide objective, quantitative information they have serious drawbacks for pre-treatment quality control. Limitations include invasiveness (all), a limited set of points or single plane measurements (temperature probes and single E-field sensors), poor spatial or temporal resolution (IR cameras, E-field sheets, lamps), long sampling time (scanning devices) and a limited dynamic range (lamps). As a result the decision whether a system meets the QA assurance demands, is often based on either a low number of data points covering only a small volume of the whole energy distribution or at best on a qualitative 2D registration of the E-field distribution in one of the major cross-sectional planes of the phantom.

In contrast, magnetic resonance thermometry (MRT) offers a non-invasive 3D view of temperature distribution, thereby being the only system that provides the ability to register 3D energy distribution in solid anatomical phantoms.

For the introduction of the Pyrexar BSD2000 3D MR HT applicator in combination with the GE 450w MR scanner at the Erasmus MC Cancer Institute in Rotterdam, the proton resonance frequency shift (PRFS) method was used to acquire temperature maps. We made an anthropomorphic phantom as well as several cylindrical phantoms to check different properties of the system and to match the HTP simulations to the MRT. By carefully controlling positioning the phantom in the applicator we were able to verify phase and amplitude steering resolution with the MR-compatible Sigma Eye applicator and to demonstrate it to be accurate at sub-cm level. Further, the 3D imaging of the temperature distribution in anthropomorphic phantoms with MRT facilitates investigating the sensitivity of translating hyperthermia treatment planning settings to clinically relevant conditions and resembles a major step forward in adaptive image guided hyperthermia.

SUN 14

IDENTIFICATION OF CLINICAL MR-HIFU HYPERTHERMIA TREATMENT SITES THROUGH VALIDATION OF MR THERMOMETRY ACCURACY AND PRECISION IN HEALTHY VOLUNTEERS.

Satya V.V.N. Kothapalli[1], Michael B. Altman[2], Ari Partanen[3], Lifei Zhu[1], Galen Cheng[1], H. Michael Gach[2], Imran Zoberi[2], Dennis Hallahan[2], William Straube[2], Hong Chen[1,2]

[1]Department of Biomedical Engineering, Washington University in St. Louis, Saint Louis, Missouri, USA, [2]Department of Radiation Oncology, Washington University in St. Louis, Saint Louis, Missouri, USA, [3]Clinical Science MR Therapy, Philips, Andover, Massachusetts, USA

Introduction: Magnetic resonance imaging-guided high-intensity focused ultrasound (MR-HIFU), a well-established noninvasive thermal ablation technique, has great potential for precise, localized, and deep-penetration mild hyperthermia treatment. However, the treatment duration (30-60min) within a narrow therapeutic window (41-43°C) pose challenges on MR thermometry. As a first step toward effective clinical translation of MR-HIFU hyperthermia, this study identified preferable treatment sites based on accuracy and precision of MR thermometry performed in healthy volunteers.

Methods: In this study, a clinical MR-HIFU system (Sonalleve V2, Philips) was used together with a clinical MRI scanner (Ingenia 1.5T, Philips). Fifteen healthy volunteers (age 18-45y, weight 45-90kg) were recruited and they were positioned above the HIFU table's acoustic window. A HIFU-compatible 3-channel pelvic receive coil was secured over the target anatomy, and used in tandem with a 2-channel receive coil integrated in the table. A dynamic multi-slice FFE-EPI sequence (TR=41ms; TE=19ms; voxel=$2.5\times2.5\times7mm^2$; FOV=$400\times400mm^2$; flip angle=20°) was utilized for real-time MRI (without HIFU sonication) together with the proton resonance frequency shift method for temperature mapping. Eight volunteers were subjected to a shorter (5 min) scanning protocol targeting the upper body, pelvis, and lower extremities (thigh and calf). Seven subsequent volunteers were subjected to a longer (30 min) scanning protocol targeting the lower extremities. The precision of MR thermometry was quantified as the temporal temperature uncertainty (temporal standard deviation for each pixel) within an $18\times18mm^2$ ROI. The accuracy of MR thermometry (absolute error between measured temperatures and body temperature; 37°C) was quantified within the same ROI. Uncertainty and absolute error < 1°C were used as criteria for acceptable thermometry.

Results: MR thermometry measurements based on 5-min scans of the chest, pelvis, and lower extremities had uncertainties of 2.53°C±0.48°C, 1.89°C±0.50°C, and 0.50°C±0.04°C, respectively, and absolute errors of 0.63°C±0.63°C, 2.88°C±0.87°C, and 0.08°C±0.13°C, respectively. Measurements based on 30-min scans of the lower extremities indicated the uncertainty and absolute error of MR thermometry to be 0.52°C±0.13°C and 0.12°C±0.06°C, respectively. No statistically significant differences ($p<0.05$) were found between 5-min and 30-min scans for lower extremities.

Conclusion: This study constitutes the first evaluation of MR thermometry performance at different anatomical locations for long scan times that are relevant for clinical MR-HIFU hyperthermia. Respiration, cardiac and digestive-related motion pose technical challenges to hyperthermia application in the chest and pelvis. Among the three anatomical sites, only the lower extremities had satisfactory temperature accuracy and precision according to the chosen criteria.

SUN 15

THE MANUFACTURER'S ROLE IN QUALITY ASSURANCE

Jason Ellsworth

Pyrexar Medical, Salt Lake City, Utah, USA

Introduction

The product manufacturer plays an important role in supporting the academic and clinical community in current best practices.

Body

Manufacturers have a duty to create, support, and promote best practices in quality assurance. The industry produces the product features that make quality assurance possible. To do this effectively, it is critical to stay in touch with the clinical and academic communities using the products daily.

The hyperthermia industry is focused on several key quality parameters that relate to the design and support of the physical product:

1. Thermometry calibration and verification
2. RF power measurement and control accuracy
3. Applicator SAR pattern data and verification
4. Phantom use and standardization
5. Data standardization in display, storage, and accessibility

In some cases academia will validate an existing design provided by industry. At other times, the academic community may propose further research. Such recommendations have driven temperature measurement technology from point measurements, to mapped measurements, to volumetric temperature imaging.

Manufacturers provide for the implementation of the recommended quality standards. This frequently results in modifications to existing products, development of new products, updates to user instructions, or recommendations for additional equipment. As technology develops, it is imperative to distinguish between recommendations derived from available products and the underlying functional use requirements driving those recommendations. Attentive tracking and translating of quality assurance recommendations can lead to state-of-the-art implementation. Superior quality assurance begins with quality design. A more robust, accurate, capable product provides for enhanced quality assurance.

Conclusion

The manufacturer is critical to effective quality assurance. Partnering with the clinical and academic communities and staying apprised of the constantly changing landscape of technology requirements facititate effective development of products capable of superior clinical outcomes.

SUN 16

EXTRACELLULAR HSP70 IS EXPORTED BY A MECHANISM INVOLVING INSERTION INTO LIPID MEMBRANES.

Antonio De Maio[1], David Cauvi[1], Dennis Hawisher[1], Ashley Rider[1], Bernardo Lara[1], Ricardo Capone[1], Nelson Arispe[2]

[1]University of California, San Diego, La Jolla, CA, USA, [2]Uniformed Services University, Bethesda, MD, USA

Cells respond to extreme conditions or stresses by the expression of heat shock proteins (hsp). These proteins are involved in the stabilization of basic cellular processes to preserve cell viability and to guaranty the return to cellular homeostasis. In addition, they protect cells from subsequent insults in a time-dependent fashion that has been called stress tolerance. Although hsp participate as molecular chaperones in the cytosol and other subcellular compartments, they have also been found outside cells. These extracellular hsp act as signaling molecules directed at activating a systemic response to stress, which has been named "the Stress Observation System." Extracellular hsp are released either by a passive mechanism after necrosis or by an active mechanism independent of cell death. In the later mechanism, hsp are likely exported associated with membrane vesicles. Therefore, the first step in the secretion of hsp is the incorporation into the plasma membrane. Using a variety of *in vitro* approaches, we have shown that the insertion of Hsp70, the most stress-inducible hsp, into membranes is spontaneous and specific for negatively charged phospholipids, such as phosphatidylserine. In addition, the protein oligomerizes within the lipid bilayer forming an ion conductance pathway. Thus, Hsp70 display a unique characteristic of assembling into lipid membranes, which may play a role in their export as well as extracellular function.

SUN 17

UNDERSTANDING THE CELLULAR RESPONSES TO STRESS

Fred Bunz

Johns Hopkins Medicine, Baltimore, Maryland, USA

Many types of exogenous stimuli can activate the intracellular signalling pathways that control cell number and ultimately maintain tissue homeostasis. Among the most intensively studied are the pathways triggered by DNA damage. A coordinated human DNA damage response (DDR) is mediated by an evolutionarily conserved signalling network composed of upstream sensors, transducers, and downstream effectors. Intensive research over the past 10 years has revealed how proximal serine/threonine protein kinases of the DDR are activated by double strand DNA breaks and DNA replication intermediates, and how these signals control cell cycle arrest, DNA repair, and apoptosis. Proteomic analyses of the numerous substrates modified by the DDR have suggested much broader cellular roles for this signalling network. This prediction has been validated by more recent studies demonstrating a broad range of upstream stimuli, including heat, mechanical perturbation, and infection, as well as new downstream responses, including inflammation and the induction of genes that mediate the interferon responses. This presentation will provide a concise overview of these new concepts.

SUN 18

TEMPERATURE-DEPENDENT ACTIVATION OF DNA DAMAGE REPAIR IN HUMAN COLORECTAL CANCER CELLS

James Barnett, Robert Ivkov, Fred Bunz

Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Background: Heat stress is known to affect the DNA damage response (DDR) pathways. This repair network is essential for genomic stability, replication, cellular homeostasis and normal physiological development. The DDR is an extensive system of signaling pathways that responds to double strand breaks (DSB), single strand breaks (SSB) and the more complex DNA structures that may arise during replication. It remains unclear whether heat stress can induce real DNA strand breaks or causes stalling during replication that leads to damage. The objective of the current study is to elucidate temperature-time effects on the activation of DDR signal transduction pathways involving the cell-cycle checkpoint kinases CHEK1 and CHK2.

Methods: HCT116 cells were exposed to elevated temperatures from 42 to 45 °C, and control at 37 °C, for 30 minutes. Response, relative to controls, was measured by clonogenic survival assays, immunoblotting, and immunofluorescence microscopy. Western blots were obtained to detect the presence of phosphorylated CHEK1, CHK2, p53, and histone H2AX. Immunofluorescence analysis was conducted to detect localization of -H2AX and cleaved Caspase 3 sites within the cell nuclei. In ongoing studies, agarose gel electrophoresis will be performed to assess the extent of DNA fragmentation induced by hyperthermia, and comet assays will be conducted to distinguish single- and double-strand breaks. Fluorescence in situ hybridization (FISH) will be used to assess the expression of the common chromosomal fragile site Fra3b following partial inhibition of DNA replication.

Results: A significant decrease in clonogenic survival was observed at temperatures above 43 °C. Dramatic changes in cell signaling events were also observed at 44 °C, which were not apparent following exposure to 43 °C, implying a profound transition occurs between 43-44 °C that affects DNA damage signaling. A biphasic trend was observed that involved latent phosphorylation of CHEK1 and the pronounced dephosphorylation of CHK2 during 12 hours after exposure at 44 °C. Gamma-H2AX activation was observed at these higher temperatures, comparable to exposure to ionizing radiation at a dose of 2 Gy. By contrast, exposure at temperatures below 44 °C produced none of these effects. Results of comet assay and FISH analysis will be presented to provide further evidence of altered DNA integrity.

Conclusion: These data demonstrate that cell exposure to temperatures between 43 and 44 °C is accompanied by the perturbation of DNA replication, which triggers a DNA damage response.

SUN 19

HYPERTHERMIA AFFECTS BOTH BRCA2-PROFICIENT AND BRCA2-DEFICIENT CELL LINES

Arlene L. Oei[1,2], Vidhula Ahire[1,2], Caspar M. van Leeuwen[2], Rosemarie ten Cate[1,2], Lukas J.A. Stalpers[1,2], Johannes Crezee[2], H. Petra Kok[2], Nicolaas A.P. Franken[1,2]

[1]Laboratory for Experimental Oncology and Radiobiology (LEXOR), AMC, Amsterdam, The Netherlands, [2]Department of Radiotherapy, AMC, Amsterdam, The Netherlands

Background: Poly(ADP-ribose)polymerase1 (PARP1) is an important enzyme in regulating DNA replication. Inhibition of PARP1 can lead to collapsed DNA forks which cause genomic instability, making DNA more susceptible to the development of fatal DNA double strand breaks. PARP1-induced DNA damage is generally repaired by homologous recombination (HR), for which BRCA2 proteins are essential. Therefore, BRCA2-deficient tumor cells are susceptible to treatment with PARP1-inhibitors (PARP1-*i*). Recently BRCA2 was shown to be temporarily downregulated by hyperthermia (HT), thereby inactivating HR for several hours.

Methods: In this study we investigated whether HT exclusively interferes with HR by testing the hyperthermic radiosensitization on BRCA2-proficient and deficient cells. After elucidating the equitoxicity of PARP1-*i* on BRCA2-proficient and deficient cells, cell survival, apoptosis, DNA damages (-H2AX foci and comet assay) and cell cycle distribution after different treatments were investigated.

Results: Results confirmed that sensitivity to PARP1-*i* strongly depends on the BRCA2 status. Both BRCA2-proficient and deficient cells show radiosensitization by HT, indicating that HT does not exclusively act by inhibition of HR. In all cell lines, the addition of HT to radiotherapy and PARP1-*i* resulted in the lowest cell survival, the highest levels of DNA damages and apoptotic levels compared to duo-modality treatments.

Conclusions: Concluding, HT not only inhibits HR, HT is also capable of radiosensitizing BRCA2-deficient cells. Thus, combining hyperthermia with PARP1-*i* may boost the effectiveness of treatments for BRCA2-mutation carriers. The combination therapy would be effective for all patients with PARP1-*i* regardless of their BRCA status.

SUN 20

STRESSING OUT THE NEIGHBORS: STRESED EXOSOMES ("SEXOSOMES"?) PASSAGE STRESS PHENOTYPES TO RECIPIENT CELLS

Michael Graner

University of Colorado Denver Anschutz Medical Campus, Aurora, CO, USA

Cancer cells undergo a number of stresses, many of them self-inflicted, but often do not appear to suffer the consequences of those stresses. In some cases, the stress responses may actually prove beneficial to the tumor cells, providing them with potent resilience to their less-than-hospitable environments. Two consistent tumor stress responses are the Heat Shock Response (HSR), and the Unfolded Protein Response (UPR). The latter is an endoplasmic reticulum-based stress-management system with sensors, transducers, and effectors that result in a transcriptional and translational landscape rearrangement leading to resolution of the stress, or cellular apoptosis. However, tumors may incorporate the HSR and UPR into their stress portfolio to survive or even thrive amidst their environmental insults. We propose that exosomes from stressed cells (stressed exosomes, or "sexosomes") are able to induce stress response phenotypes in recipient, unstressed cells, thus enabling stress responses without having to experience the actual stress. Our analysis in this report goes to the molecular level, monitoring proteome changes in glioma cells when those cells are exposed to exosomes released from UPR-stressed cells. We find high overlap in the proteomes of stressed cells and unstressed cells that receive "sexosomes", suggesting that tumors may unify their overall stress responses despite their inherent heterogeneity. The implications for general tumor biology, and in particular, therapeutic resistance, are highlighted.

SUN 21

THERANOSTIC MULTIPLEXED THERMOCHEMICAL ABLATION (MTCA): TRACKING DICHLOROACETATE USING MULTI-ENERGY COMPUTED TOMOGRAPHY

Rick Layman, Chunxiao Guo, Samuel Fahrenholtz, Dodge Baluya, Erik Cressman

MD Anderson Cancer Center, Houston, TX, USA

Introduction

Multiplex thermochemical ablation (MTCA) has recently been proposed as a therapeutic procedure for solid tumors such as hepatocellular carcinoma. The application exploits the substantial exotherm arising from acid/base neutralization and imposes an acute severe osmotic stress. In the multiplex variant, the acid is dichloroacetic acid (DCA). DCA has anti-tumor activity due to its ability to reverse Warburg metabolism, thereby serving dual roles as both reactant and drug. A challenge with MTCA, as with all therapies, is monitoring and evaluating the treatment. In this work, we demonstrate the utility of multi-energy computed tomography (MECT) for tracking DCA. We take advantage of the presence of chlorine atoms in reaction product DCA given the higher effective atomic number of chlorine (Z) relative to the native tissues and the local concentration gradient. These factors enable enhanced contrast sensitivity and thus monitoring MTCA using MECT.

Methods

Fresh ex vivo porcine liver was used. DCA and NaOH were used at concentrations up to 4M with 1 mL injection volumes. MECT images were acquired using a dual source CT scanner. Acquisition parameters were Tube A 80 kV, 545 mA; Tube B 140 kV with a tin filter, 233 mA, pitch 0.6 and 0.6x128 collimation. Images were reconstructed at 0.5x0.25mm with iterative reconstruction (I41f, strength 2). Software was used to post-process the images with the energy window set to 40 keV. Visualization was further improved with thresholding to differentiate DCA and normal liver tissue. Gross pathology of the treatment areas were obtained for evaluation of the ablation zone.

Results

With low keV image processing the salt was clearly identified in the tissues without any added contrast agent. A gradient at the margins of the ablation was depicted with resolution down to 1-2 mm. Images correlated well with gross pathology accurately characterizing the extent of the ablation area.

Conclusion

This work clearly demonstrates the contrast sensitivity of MECT to monitor MTCA therapies. This is particularly remarkable considering the effective atomic number of the salt is not significantly different from the native liver tissue. MECT further enables the application of MTCA by offering potential real-time monitoring. Additional advancements also exist with quantitative MECT where the total volume delivered could be measured, margins defined, and gradients determined.

SUN 22

IMPROVING SBRT AND PROTON THERAPY WITH LOCAL HYPERTHERMIA TO SENSITIZE HYPOXIC AND RESISTANT CELLS

Robert J. Griffin[1], Ashish Ranjan[2], Azemat Jamshidi-Parsian[1], Ruud Dings[1], Cristina Munteanu[2], Salahuddin Ahmad[3], Terence Herman[3]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]Oklahoma State University, Stillwater, OK, USA, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Stereotactic body radiotherapy (SBRT, 1 to 5 fractions of 12-24 Gy each) or proton therapy in a variety of dose regimens have become major treatment approaches in radiation oncology. However, these modalities are also faced with limited application sites due to side effects of large dose/fraction and many anatomical sites having tolerance limits well below the total dose needed to ensure tumor control. Hypoxic regions of the tumors being treated may exacerbate this difference between tolerance and curability- especially at the higher doses/fraction used clinically at present. We know from previous work that hyperthermia can effectively inhibit DNA damage repair and increase X-ray radiation-induced cell killing but little attention has been given to its potential at SBRT dose levels or with proton therapy and what effect it may have on hypoxic cells that would otherwise survive and lead to recurrence or metastasis. Our recent work demonstrates that in both hypoxic and aerobic environments, tumor and endothelial cell survival can be significantly impacted when moderate hyperthermia is added to 12- 15 Gy SBRT or 6-8 Gy proton dosing. Importantly, establishing the dose reduction factor (DRF) obtainable with thermal medicine may therefore be a realistic route to expanding the number and location of solid tumor sites that can be reliably treated with these modalities, improving control and overall patient outcomes. We found that hypoxic endothelial cells are 3.0-fold more resistant than aerobic cells to 12 Gy X-rays and higher, while hypoxic tumor cells are 2-2.5 more resistant above 12 Gy X-rays. We also observed that radiation-induced cell killing increases by 3-10 fold in hypoxic or aerobic conditions, respectively, when 42°C was applied for 1 h after 12-Gy X-rays. The net result is that hypoxic tumor or endothelial cells treated with hyperthermia become as sensitive as cells growing in normal oxygenation, suggesting that tumor control may be more ensured when SBRT is prescribed along with local tumor hyperthermia. Our preliminary results using protons at the University of Oklahoma proton therapy center suggest a similar potential with the addition of local tumor hyperthermia after a dose of 6-8 Gy using protons. Ultimately, a range of thermal therapy approaches using the improved technology now available (focused ultrasound among others) could reduce and/or potentiate the SBRT or proton dose needed for tumor control. We are currently assessing the effects of combined SBRT and protons on DNA damage repair pathways and stress factors such as HIF1alpha to elaborate on the mechanisms at play in the improved therapeutic results observed.

SUN 23

CONCURRENT THERMAL ABLATION AND INTERSTITIAL PHOTODYNAMIC THERAPY FOR CONTROLLING LOCALLY ADVANCED CANCER

Gal Shafirstein, Emily Oakley, Sasheen Hamilton, Michael Habitzruther, Joseph Spernyak, Lawrence Tworek, Alan Hutson, David Bellnier

Roswell Park Cancer Institute, Buffalo, NY, USA

Background: There is no effective therapy for patients with refractory locally advanced head and neck cancer (HNSCC). About 40% of patients with HNSCC fail the standard therapies of radiation therapy, chemotherapy and surgery, and only about 16% will respond to the newest immunotherapies. Interstitial photodynamic therapy (I-PDT) has shown promise in controlling these tumors. However, the technical challenge of delivering a therapeutic light dose in a large tumor volume, combined with the heterogeneity of photosensitizer (PS) and oxygen distribution, could pose a significant barrier to the use of I-PDT as a monotherapy. We have shown that concurrent thermal ablation and I-PDT has the potential to control locally advanced tumors in an animal model.

Methods: We treated large (10-12 mm dia.) locally advanced SCCVII squamous cell carcinomas in C3H mice. Finite element image-based computer modelling was utilized for treatment planning and analysis. Mice were injected with intravenous porfimer sodium (Photofrin™, Pf) 24 hours before light treatment. Two 2-cm long cylindrical diffusing fibers were used as light sources for I-PDT and heat source for laser thermal therapy, each delivering 150 mW/cm 630-nm light. Temperature distribution changes in the mice during treatments were measured with magnetic resonance thermometry (MRT). Viability staining was used to assess the extent of thermal ablation in excised tumor tissues. Kaplan-Meier analysis and log-rank (Mantel-Cox) statistical test was utilized to compare tumor growth delay between groups that received thermal ablation during I-PDT to those treated with thermal ablation alone. Tumor response was also evaluated using histopathology.

Results: Tumor growth delay (time to event) was significantly longer ($p=0.0012$) for animals treated with thermal ablation and I-PDT than for animals that received thermal ablation alone. The MRT-measured maximum temperature of $52 \pm 3^{\circ}C$ was the same in both groups. The calculated dose volume histograms of fluence rates were 70.4 mW/cm^2 and 3.1 mW/cm^2 for 50% and 100% of the tumor volume, respectively.

Discussion: Successful photodynamic induced ablation requires sufficient levels of Pf, oxygen and light. The MRT measurements showed that the temperature increase was not dependent on the Pf levels. The computer simulations assumed that blood was the main chromophore. The significant improvement in time to event for the group treated with I-PDT and thermal ablation, in comparison to thermal ablation alone, suggests that thermal ablation did not impede the photodynamic reaction.

Conclusions: Concurrent thermal ablation and I-PDT has the potential to improve local control of locally advanced cancer. More work is required to understand the mechanism of this new therapy.

SUN 24

PRUSSIAN BLUE NANOPARTICLE-BASED PHOTOTHERMAL THERAPY COMBINED WITH CHECKPOINT INHIBITION FOR PHOTOTHERMAL IMMUNOTHERAPY OF NEUROBLASTOMA

Juliana Cano-Mejia[1,2], Rachel Burga[2,3], Elizabeth Sweeney[2], John Fisher[1,2], Catherine Bollard[2,3], Anthony Sandler[2], Conrad Russell Cruz[2,3], Rohan Fernandes[2]

[1]University of Maryland, College Park/MD, USA, [2]Children's National Medical Center, Washington/DC, USA, [3]The George Washington University, Washington/DC, USA

Neuroblastoma is the third most common pediatric cancer, and the most common extracranial solid tumor in children, accounting for 15% of cancer-related deaths in this age group. Despite improvements in diagnosis and surgical techniques, neuroblastoma remains a challenging cancer to treat due to its ability to metastasize and become resistant to conventional therapies. We therefore engineered a next-generation therapy called "photothermal immunotherapy," which combines Prussian blue nanoparticle (PBNP)-based photothermal therapy (PTT) with anti-CTLA-4 checkpoint inhibition for treating neuroblastoma. PTT functions as a rapid and minimally invasive method for reducing tumor burden using near infrared (NIR) light-absorbing nanoparticles and a low power NIR laser. Combining PTT with the immune checkpoint inhibitor, anti-CTLA-4, reverses immunosuppression, elicits an antitumor response, and confers immunological memory. Therapeutic efficiency was tested in a syngeneic mouse model of neuroblastoma wherein the mice were intratumorally injected with PBNPs for PTT, and CTLA-4 was administered every 3 days. We found that photothermal therapy using intratumorally administered PBNPs in a mouse neuroblastoma model elicits a rapid reduction of tumor burden and growth rate, but the response is incomplete and the tumors recur. However, PBNP- combined with anti-CTLA-4 based photothermal immunotherapy results in 55% survival at 100 days. Additionally, immune response studies show that PTT elicits an infiltration of T-cells and lymphocytes to the tumor area, an immune response that is complemented by the addition of anti-CTLA-4. Depletion studies show that CD8+ and CD4+ T cells are crucial in eliciting the presented results. Finally, the photothermal immunotherapy-treated mice that survived long-term exhibited protection against neuroblastoma tumor rechallenge, suggesting the development of immunity against these tumors. Ongoing studies have built upon these findings and demonstrated the efficacy of photothermal immunotherapy in a metachranous tumor model, where treating one tumor results in complete eradication of a distal tumor. Studies where PTT is used as a "tumor vaccine" have shown a complete remission of tumor cells, elucidating the strong anti-tumor and immunological memory effect of our treatment. These results illustrate the potential of photothermal immunotherapy as a novel combination therapy for the treatment of cancer in patients with high-risk neuroblastoma due to the significantly higher tumor regression, long-term survival, and immune memory elicited by our therapy.

SUN 25

CO-DELIVERY OF NANOPARTICULATED NVP BEZ-235 DECREASES CELL PROLIFERATION OF IRREVERSIBLE ELECTROPORATION TREATED XENOGRAFT

Li Tian[1], Yang Qiao[1], Saisree Ravi[2], Ashley Chang[4], Thomas Rogers[3], Marites Melancon[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Rice University, Houston, TX, USA, [3]Mississippi State University, Starkville, MS, USA, [4]McGovern Medical School, Houston, TX, USA

Introduction

Irreversible electroporation (IRE) is an emerging, minimally invasive tumor ablation technique that has the advantage of not being affected by heat sink effect and the ability of ablation in close vicinity of major blood vessels. One noted major limitation of IRE is local recurrence at the original ablated site. We hypothesize that by combining IRE with a chemotherapeutic drug would prevent recurrence. NVP BEZ-235 (BEZ) is a dual PI3K/mTOR inhibitor that has shown promise for treating advanced solid malignancies, including inhibiting hepatocellular carcinoma growth. However, clinical trials revealed low bioavailability and high toxicity due to high dose oral administration over a long period of time. In this study, we formulated a nanoparticle-loaded BEZ (NP-BEZ) and studied its antitumor effect in combination with IRE.

Methods

IRE was performed using ECM 830 (BTX Harvard Apparatus) at various field strengths. BEZ was loaded into liposome (NP-BEZ) by hydration-sonication method. The in vitro and in vivo efficacy was tested against Hep3B cells and in nude mice bearing Hep3B xenografts, respectively. Mice were treated with a single dose of IRE at 2500 V/cm for 99 pulses. NP-BEZ (100μg of BEZ), or combination of the two (IRE+NP-BEZ). Three days post treatment, mice were euthanized and tumors were collected for histology. H&E staining was used to quantify the percent necrosis, while Ki-67 was used for cell proliferation.

Results

At the highest field strength (2500 V/cm), approximately 10% of cells still survive with IRE. Cells electroporated at 250 V/cm increased cell viability (110%) as compared to the untreated group (100 %). The hydrodynamic volume of NP-BEZ ranged from 100-500nm. Maximum drug loading was achieved at 2.7mg/mL of BEZ. Electroporation disrupted nanoparticle's integrity even at the lowest tested field strength (xx), and release BEZ from the nanoparticle. Combination of IRE and NP-BEZ significantly decreased cell viability in vitro ($p<0.05$). H&E staining suggested similar % necrosis between IRE and IRE + NP-BEZ groups. However, ki67 staining showed that IRE+NP-BEZ significantly decreased cell proliferation than IRE treatment alone (one way ANOVA followed by Holm-Sidak, $p<0.1$).

Conclusion.

Incomplete electroporation increases the viability of surviving cells. Co-delivery of NP-BEZ with IRE enhances the anti-tumoral efficacy of BEZ or IRE when used alone. Thus, NP-BEZ in combination with IRE potentially ensures complete eradication of any surviving cells left after IRE.

SUN 26

LUMINESCENCE NANOTHERMOMETERS FOR PHOTOTHERMAL THERAPY

Carlos Jacinto[1], Daniel Jaque[2]

[1]Instituto de Física, Universidade Federal de Alagoas, Maceió-AL, 57072-900, Brazil, [2]Departamento de Física, Universidad Autonoma de Madrid, Madrid, Spain

Over the last few years, the scientific community has invested a lot of effort to develop highly sensitive fluorescence nanomaterials for the most diverse applications such as nanothermometry, bio-imaging, display, biolable, etc. In fact, the battle against cancer is continuously bringing new challenges and difficulties that can only be overcome if faced from a multidisciplinary standpoint, taking advantage of the synergies between very different but complementary research areas such as biology, medicine, physics, chemistry, and mathematics. Among the different ongoing multidisciplinary research lines focusing on cancer and many other diseases, great attention is being paid to the development of new materials and techniques that would improve diagnoses and therapy. Nanotechnology is playing a central role in the development of such materials and techniques. In particular, during the last few years, the refinement of nanofabrication processes has led to the appearance of a large variety of nanosized materials having pre-tailored properties with potential application as biocompatible markers, drug deliverers and therapeutic agents. A few materials possess both features of luminescence and heating when upon optical excitation and a very important information is that cellular events are marked basically by changes in temperature. In this talk, we will present results about optical nanothermometry with multifunctional materials for photothermal therapies. We will also discuss the tailoring of rare-earth doped nanomaterials for improvement of their functionalities such as for optimal thermal sensitivity and others [1-5]. For example, the potential use of active-core/active-shell lanthanides-doped nanoparticles as subcutaneous thermal probes has been evaluated. These temperature nanoprobes operate in the infrared transparency window of biological tissues, enabling deep temperature sensing into animal bodies thanks to the temperature dependence of their emission spectra that leads to a ratiometric temperature readout. The ability of active-core/active-shell lanthanides-doped nanoparticles for unveiling fundamental tissue properties in *in vivo* conditions was demonstrated by subcutaneous thermal relaxation monitoring through the injected core/shell nanoparticles. The reported results evidence the potential of infrared luminescence nanothermometry as a diagnosis tool at the small animal level [1,2].

References:

[1] E.C. Ximendes et al., Nanoscale, 8 (2016) 3057.
[2] E.C. Ximendes et al., Nano Letters, 16 (2016) 1695.
[3] E. C. Ximendes et al., Applied Physics Letters, 108 (2016).
[4] I. Villa et al., Nano Res, 8 (2015) 649.
[5] E. Carrasco et al., Advanced Functional Materials, 25 (2015) 615.

SUN 27

MAGNETONANOTHERMOMETRY: PRESENT STATUS AND FUTURE PERSPECTIVES

Paulo De Morais

Anhui University, Hefei, Anhui, China

The present status of remote magnetonanothermometry will be presented in this talk. Emphasis will be given on the use of magnetization and magnetic susceptibility data collected from magnetic nanoparticulated material systems. Discussion regarding both the theoretical model construction to describe the collected magnetic data and the inverse calculation approach used to extract the temperature from them will be presented. It will be shown that accuracy nowadays in temperature measurements in the range of a few mili-Kelvin emerges while using the first order Langevin function to describe the recorded experimental data. The new avenue represented by remote magnetonanothermometry is expected to support future safer protocols for the hyperthermia therapy as well as for the thermal assisted drug delivery technology. Moreover, the approach of remote magnetonanothermometry should potentially impact basic science in the near future as well while providing a robust thermodynamic tool for noninvasive investigation of cell metabolism.

SUN 28

MRI THERMOMETRY FOR PHOTOTHERMAL THERAPY

R. Jason Stafford

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Laser ablation aims to coagulate a localized tissue volume as conformally as possible. Modern clinical systems utilize compact, high power, solid state laser sources which incorporate cooled applicators in order treat larger volumes of tissue. These systems operate in the near infrared part of the spectrum and therefore are synergistic emerging nanophotonic applications which provide a wealth of opportunity to provide more conformal and tumor specific targeted approaches to therapy.

MRI is a unique modality for providing guidance of these rapid, high-temperature approaches to laser ablation owing to its inherent temperature sensitivity integrated with exquisite soft tissue anatomy and functional imaging capabilities making it useful for planning, targeting, monitoring and verifying therapy delivery in a "closed-loop" fashion. MR temperature imaging data can be integrated with physical models of bioheat transfer and biological models of tissue damage so that it can play a significant role in increasing the safety and efficacy of these rapid ablation procedures by offering a mechanism monitor and control both high tissue temperatures at the probe interface and nearby critical structures, as well as aid in prediction of lesion development, particle activation or drug delivery.

Here we provide an overview of MRI guidance of laser ablation procedures with examples provided in brain, prostate, liver and bone as well as a brief discussion of some of the current challenges associated with application of this technique in various anatomical locations as well as the potentially complimentary role of high performance computing and simulation may have on planning, monitoring and verification when this unique image-feedback modality is incorporated into treatment.

SUN 29

IN VIVO FLUORESCENCE IMAGING PREDICTS DRUG UPTAKE FOR TEMPERATURE SENSITIVE LIPOSOMAL DOXORUBICIN

Anjan Motamarry, Christian Rossman, Dieter Haemmerich

Medical University of South Carolina, SC, USA

Background/Purpose:

Thermosensitive liposomal doxorubicin (TSL-Dox) is a promising nanoparticle drug delivery system that rapidly releases the contained drug in response to hyperthermia (>40 °C). Combined with localized heating, TSL-Dox allow highly localized delivery (~10-30x local dose compared to unencapsulated Dox). The goal of this study was to demonstrate ability to image drug delivery in real-time, and quantify the effect of heating duration on drug delivery.

Methods:

Nude mice carrying subcutaneous tumors (lewis lung carcinoma) were anesthetized and injected with TSL-DOX at a dose of 2mg/kg. Localized hyperthermia was induced by heating tumors for either 15 or 30 min by a custom-designed hyperthermia probe (~2 mm diameter), heated to 50 °C, and placed on the skin above the tumors. In vivo fluorescence imaging (excitation 485 nm, emission 610 nm) was performed before, during, and for 15 min following hyperthermia. After imaging, tumors were extracted and drug uptake quantified by fluorometry.

Results:

Local drug uptake could be visualized in real-time during hyperthermia, and fluorescence intensity correlated with amount of drug delivered to the tumor. Fluorescence increased by ~2.4 times when hyperthermia was increased from 15 to 30 min, demonstrating the effect of heating duration on drug uptake. Tumor drug concentration was 28.9+/-10.3 ug/g after 30 min hyperthermia, with undetectable drug amounts in control tumors not exposed to hyperthermia.

Conclusions:

In vivo fluorescence imaging may allow real-time monitoring of local drug delivery, and is predictive of delivered dose. Modulating the duration of hyperthermia allows control of locally delivered dose.

SUN 30

MAGNETIC HYPERTHERMIA IS MORE EFFICIENT THAN EXOGENOUS HEATING TO KILL NEUROBLASTOMA CELLS

Beatriz Sanz[1,2], M. Pilar Calatayud[1], Teobaldo E. Torres[1,4], Mónica L. Fanarraga[5], M. Ricardo Ibarra[1,3], Gerardo F. Goya[1,3]

[1]Instituto de Nanociencia de Aragón (INA), Universidad de Zaragoza, Zaragoza, Spain, [2]nB nanoScale Biomagnetics S.L., Zaragoza, Spain, [3]Departamento de Física de la Materia Condensada, Facultad de Ciencias, Universidad de Zaragoza, Zaragoza, Spain, [4]Laboratorio de Microscopias Avanzadas (LMA), Universidad de Zaragoza, Zaragoza, Spain, [5]Grupo de Nanomedicina-IDIVAL, Universidad de Cantabria, Santander, Spain

To consider Magnetic hyperthermia (MHT) as a standalone therapy it should achieve the maximum therapeutic effect with the minimum concentration of heating agent. The main advantage of this approach relates to the treatment of solid, inaccessible human tumors, by increasing the local temperature up to apoptotic levels, with minimal side effects on the surrounding healthy tissue. Since MHT generates heat at the intracellular space, a key question prosed many years ago was whether intracellular heat release could imply local apoptotic mechanisms that could be more efficient than exogenous heating (EHT). We have addressed this question by systematic comparison of MHT and EHT experiments with the same conditions and target temperatures. To this aim, human neuroblastoma SH-SY5Y cells were co-cultivated with magnetic nanoparticles (MNPs) and exposed to both external heat source and alternating magnetic field (AMF), in the form of dense pellets to mimic the micro-tumor environment. The effect of both heating sources was studied following the cell viability at the same target temperatures. We found that MHT was able to induce a decrement in cell viability that is larger than the corresponding EHT for the same target temperatures. In terms of temperature efficiency, MHT requires an average temperature that is 6°C lower than that required with EHT to produce a similar cytotoxic effect. In addition to the biological effects, the analysis from electron microscopy images of the cells after the EHT and MHT treatments showed morphological evidences of a higher level of cell damage when MHT was applied. These differences were associated to the intracellular action of the magnetic nanoparticles, triggered by the local release of heat by the external magnetic fields.

SUN 31

MAGNETIC HYPERTHERMIA AND MR IMAGING USING G4 PAMAM DENDRIMER COATED FE_3O_4 NANOPARTICLES

Marzieh Salimi[1,3], Saeed Sarkar[1], Reza Saber[2], Alimohamad Alizadeh[3], Hamid Delavari[4]

[1]Department of medical physics and Biomedical Engineering, Tehran university of medical sciences,, Tehran, Iran, [2]Department of modern technologies, Tehran university of medical sciences, Tehran, Iran, [3]Cancer institute, Emam Khomeini hospital, Tehran university of medical sciences, Tehran, Iran, [4]Department of Materials Engineering, Tarbiat Modares University, Tehran, Iran

Introduction:

Recently, hyperthermia has been increasingly applied in the cancer treatment since it has favourable advantages compared with other treatments including chemotherapy and radiotherapy. Iron oxide magnetic nanoparticles are used in magnetic bioseperation, clinical diagnosis and therapy including MRI and magnetic hyperthermia thanks to their very low toxicity and good biocompatibility. The polyamidoamine (PAMAM) dendrimer coated iron oxide magnetic nanoparticles(MNPs) have internal cavities makes them suitable for application in multidisciplinary cancer treatments. In this study, we assessed efficiency of G4 PAMAM coated Fe_3O_4 NPs(PAMAM@Fe_3O_4) in magnetic hyperthermia and MR imaging.

Method and materials:

Fe_3O_4 MNPs were synthesized by coprecipitation of Fe^{3+} and Fe^{2+} solution followed by surface modification with PAMAM dendrimers. The morphology and properties of obtained nanoparticles were characterized by XRD, FT-IR, TEM and DLS. The PAMAM@Fe_3O_4 NPs displayed relatively high magneto-temperature response which could be applied to hyperthermia therapy. In vivo and in vitro toxicity was assessed as well as hemolysis. The relaxivity values (r_1, r_2) were estimated using a linear fit to R_1 and R_2 versus nanoparticles concentration curves, respectively.

Results

The size of nanoparticles was approximately 10nm and the result of DLS shown 108nm hydrodynamic size. The temperature rising of NP samples measured in two frequency of 200 and 300kHz and intensity of 12kA/m. The introduced SAR increased by increasing frequency and NPs concentration and the outcomes revealed that these MNPs could be promising materials for local hyperthermia. The toxicity of PAMAM@Fe_3O_4 NPs was negligible, the renal and hepatic factors in blood as well as blood proteins did not change significantly in selected NPs concentrations used in chronic and acute toxicity in bulb-c mice. The highest amount of Hemolysis was only 8% in at NPs concentration of 1 mg/ml. Longitudinal and transverse relativities were 4.17 $s^{-1}mM^{-1}$ and 139.12 $s^{-1}mM^{-1}$, respectively.

Discussion

There are some studies focused on PAMAM@Fe_3O_4 NPs as an MRI contrast agent or a vehicle for drug delivery. Considering to suitable magnetization properties of these NPs, we decided to investigate them in magnetic hyperthermia. For clinical use, NPs must be toxic as low as possible. Our results shown that PAMAM@Fe_3O_4 NPs were very low toxic in cancer and normal cell lines and this is due to dendrimer coating of NPs and PEGylation. Because of dendrimers superior properties in MRI and drug delivery, they can be suitable candidate to consider as an appropriate coating for magnetite NPs using in magnetic hyperthermia.

SUN 32

CHEMOTHERAPY AND HYPERTHERMIA FOR LOCALIZED SOFT TISSUE SARCOMA : UP-DATE WITH LONG-TERM FOLLOW-UP

Rolf Issels, Lars Lindner

Klinikum Grosshadern- University of Munich, Munich, Germany

Background

Chemotherapy for patients with localized soft tissue sarcoma (STS) is not currently viewed as standard practice, due to the lack of survival benefit. The preliminary report of our phase 3 study demonstrated that adding regional hyperthermia to neoadjuvant chemotherapy improved local progression-free survival as the primary endpoint of patients with high-risk STS. According to study protocol, we performed a final analysis of outcome including overall survival with long-term follow-up.

Methods

We randomly assigned adult patients with non-metastatic, high-risk (deep, ≥5cm, grade 2-3) STS to receive either pre- and postoperative doxorubicin + ifosfamide + etoposide chemotherapy alone, or this regimen + regional hyperthermia. Patients were stratified according to site (extremity vs. non-extremity) and presentation of tumor (primary vs. recurrent vs. prior surgery).

Results

Of the 341 patients randomly assigned, 329 (94%) were eligible and started study treatment. Compared with the neoadjuvant chemotherapy-alone group, the addition of regional hyperthermia improved objective response rate (12.9% vs. 29.8%; P=0.002), prolonged local progression-free survival (29.2 months vs. 67.3 months; hazard ratio (HR) 0.65; log-rank P=0.002), disease-free survival (17.4 months vs. 33.3 months; HR 0.71; log-rank P=0.013), and overall survival (6.2 years vs. 15.4 years; HR 0.73;log-rank P=0.037). Hyperthermia-related adverse events were rare and without signs of late toxicity.

Conclusions

After a median follow-up of 11 years, the addition of regional hyperthermia to neoadjuvant chemotherapy improved clinical outcome which translated into a significant overall survival benefit. These findings strongly support the use of regional hyperthermia in this setting for patients with high-risk STS.

SUN 33

RESULTS OF RANDOMIZED STUDIES ON HYPERTHERMIA IN ONCOLOGY

O.K. Kurpeshev[1], J. van der Zee[2], A.V. Orlova[1]

[1]A. Tsyb Medical Radiological Research Center, Obninsk, Russia, [2]Erasmus MC Cancer Institute, Rotterdam, The Netherlands

In experimental in vitro and in vivo studies it was shown that hyperthermia (HT) is a strong radio- and chemosensitizing agent. Already in the early years of clinical application of hyperthermia, the first randomized trials were performed, at that time mainly on superficially located tumours of variable origin. More recent trials also include patients receiving their primary treatment after cancer diagnosis.

We have analysed the results of 55 randomized trials published between 1980 and 2017, including total 5099 patients. Trials were conducted in Asia (33), Europe (16), North America (5) and Australia (1). In some of these trials more than one comparison between the no HT and + HT arm could be made thanks to inclusion of more than one tumour type, or more than two study arms. The results of 9 trials on cervical were only available from a meta-analysis, and results of 5 trials in breast cancer were combined in one study. Altogether, 48 comparisons between results of no HT and +HT treatments could be made. In the vast majority of these studies, hyperthermia was applied locally with techniques using electromagnetic radiation.

Hyperthermia was added to radiotherapy (27), chemotherapy (11) or radiation plus chemotherapy (10) . A significant improvement by hyperthermia in any of the endpoints (response, palliative effect, complete response, local tumor control, disease free or overall survival) has been demonstrated in 35 of these 48 comparisons. In addition, in 6 comparisons the difference, although not significant, was larger than 10% with the better results in the +HT arm. A beneficial effect of hyperthermia was found in a large variety of tumour types: cancer of the bladder, breast, head and neck, uterine cervix, brain, esophagus, stomach, rectum, lung, and malignant melanoma and soft tissue sarcoma. Significant differences were found in 19/27 (70%) studies adding HT to RT, in 9/11 (82%) of the studies adding HT to chemotherapy, and in 7/10 (70%) studies adding HT to RT plus chemotherapy.

These results indicate that hyperthermia is a universal and effective modifier of radiotherapy and/or chemotherapy in malignant tumours.

SUN 34

REGIONAL HYPERTHERMIA FOR TREATMENT OF PEDIATRIC OVARIAN GERM CELL TUMORS

Ruediger Wessalowski[1], Gabriele Calaminus[2], Eunike Velleuer[1], Oliver Mils[1], Stefan Schönberger[2], Dominik T. Schneider[3], Rotem Lanzman[4], Eugen Ruckhäberle[5], Ivo Leuschner[6], Ulrich Göbel[7]

[1]Heinrich-Heine-University, Medical Faculty, Clinic for Pediatric Oncology, Hematology and Clinical Immunology, Duesseldorf, Germany, [2]University Children's Hospital, Department of Pediatric Hematology and Oncology, Bonn, Germany, [3]Pediatric Clinic, Municipal Hospital, Dortmund, Germany, [4]Heinrich-Heine-University, Medical Faculty, Institute of Diagnostic Radiology, Duesseldorf, Germany, [5]Heinrich-Heine-University, Medical Faculty, Department of Gynecology and Obstetrics, Duesseldorf, Germany, [6]University of Kiel, Pediatric Pathology, Kiel, Germany, [7]Heinrich-Heine-University, Medical Faculty, Pediatric Surveillance Unit (ESPED), Duesseldorf, Germany

Background: Girls with advanced (FIGO stage IV) or recurrent pediatric ovarian germ cell tumors after repeated and incomplete resection have an unfavorable prognosis. This also applies for patients who were treated according to the MAKEI therapy-optimization clinical trials conducted by the Society for Pediatric Oncology and Hematology (GPOH), so that in such situations additional regional hyperthermia (RHT) has been used in order to facilitate the tumor resection and to improve the prognosis. With effect from 2004, this is done within the scope of the Hyper-PEI protocol, each patient with primary treatment failure serving as its own control.

Study design: The outcomes presented here are taken from registry data base of relapsed or refractory germ cell tumors of the ovary for the purpose of a phase-II clinical investigation.

Methods: In the Hyper-PEI protocol, regional hyperthermia (41-43°C for 60 minutes, days 1+4) is carried out in parallel with PEI-chemotherapy (cisplatin 40 mg/m², days 1+4, etoposide 100 mg/m², days 1–4 and ifosfamide 1800 mg/m², days 1–4). According to response the patients received 4-6 treatment courses with time intervals of approximately 21 days. On suspicion of residual tumor the possibility of a complete surgical tumor resection (provided as 2nd-look operation) was investigated after the 3rd or 4th course.

Patients: From 20 December 1995 to 11 December 2014 a total of 22 girls/young women at 8;5-24;8 years of age (median:16;2 years) with recurrent or primary refractory ovarian germ cell tumors were treated according to the Hyper-PEI-protocol in the context of our interdisciplinary tumor board. The histological examination yielded different, mostly mixed germ cell tumors with following quantitative dominated subtypes: Yolk sac tumors (n=12), teratomas (n=6), embryonal carcinomas (n=3), and choriocarcinoma (n=1). In addition, in six tumors a malignant transformation was found.

Results: In 15/22 patients with a measurable tumor in diagnostic imaging and increased levels of tumor markers before RHT clinical treatment response was assessed: CR (n=4); PR (n=4); SD (n=6); PD (n=1). After 3-4 Hyper-PEI courses a 2nd-look operation was performed in 13/22 patients: R0 (n=9), R1 (n=3); R2 (n=1). Overall survival in this patient population with an unfavorable prognosis was 71% (95% CI 46-86). The median follow-up of surviving patients is 55 months (range 18–248).

Conclusion: A multi-modal therapy including regional hyperthermia according to the Hyper-PEI-protocol has led to long-term remission in the majority of patients with advanced refractory or recurrent ovarian germ cell tumors.

Funding: Deutsche Krebshilfe eV, Bonn, Elterninitiative Kinderkrebsklinik Düsseldorf eV

SUN 35

A SYSTEMATIC REVIEW AND META-ANALYSIS OF HYPERTHERMIA AND RADIOTHERAPY IN MANAGEMENT OF LOCALLY RECURRENT BREAST CANCERS

Niloy Datta[1], Emsad Puric[1], Dirk Klingbiel[2], Silvia Ordóñez[1], Stephan Bodis[1]

[1]Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland, [2]Swiss Group for Clinical Cancer Research (SAKK), Coordinating Centre, Bern, Switzerland

Purpose: A systematic review and meta-analysis was conducted to evaluate the outcome of hyperthermia (HT) and radiotherapy (RT) in locally recurrent breast cancers (LRBCs).

Material and methods: 708 abstracts were screened from eight databases according to the PRISMA guidelines. Single-arm and two-arm studies, treating LRBCs with HT and RT but without surgery (for local recurrence) or concurrent chemotherapy were considered. The evaluated endpoint was complete response (CR).

Results: Thirty-one full text articles, pertaining to 34 studies were shortlisted for the meta-analysis. Eight were two-arm (randomized, n = 5; nonrandomized, n = 3) while 26 were single-arm studies. 627 patients were enrolled in two-arm and 1483 in single-arm studies. Patients were subjected to a median of 7.5 HT sessions and an average temperature of 42.5°C was attained. Mean RT dose was 38.2 Gy (range: 26-60 Gy) and delivered mostly following HT. In the two-arm studies, a CR of 60.2% was achieved with RT+HT versus 38.1% with RT alone (odds ratio = 2.64, 95%CI: 1.66-4.18, $p<0.0001$). Risk ratio and risk difference were 1.57 (95%CI: 1.25 - 1.96, $p<0.0001$) and 0.22 (95%CI: 0.11 - 0.33, $p<0.0001$) respectively. In 26 single-arm studies, RT+HT attained a CR of 63.4% (event rate = 0.62, 95%CI: 0.57 - 0.66). Moreover, 779 patients had been previously irradiated (696 from single-arm and 83 from two-arm studies). A CR of 66.6% (event rate = 0.64, 95%CI: 0.58 - 0.70) was achieved with HT and re-irradiation (mean $\pm$ SD dose: 36.7Gy $\pm$ 7.7). Mean acute and late grade III/IV toxicities with RT+HT were 14.4% and 5.2% respectively.

Conclusions: Thermoradiotherapy (HTRT) enhances the likelihood of CR rates in LRBCs over RT alone by 22% with minimal acute and late morbidities. For even those previously irradiated, re-irradiation with HT provides a loco-regional control in two-thirds of the patients. HTRT could therefore be considered as an effective and safe palliative treatment option for LRBCs.

SUN 36

NOVEL PHOTO-INDUCED CHEMOTHERAPY DELIVERY MATRIX FOR SUPPORT OF ABDOMINAL ORGANS FOLLOWING CYTOREDUCTIVE SURGERY

Hale Arca, Nicole Levi

Department of Plastic and Reconstructive Surgery, Wake Forest University Health Sciences, Winston-Salem, NC, USA

Surgery is often the main treatment for colorectal cancer that has disseminated throughout the abdomen. After surgical revision, it is often standard treatment for the organs to be supported by polypropylene meshes. The limitations of the meshes are that they are not biodegradable and provide suitable hydrophobic porous scaffolds for residual cancer cells to grow.

A biodegradable elastomeric polyester, poly (1,8-octanediol co-citric acid) (POC) has been previously investigated for its potential in artificial tissue replacements. In the current work, POC has been synthesized by chemically coupling 1,8-octanediol to citric acid by polycondensation reactions to form a cross-linked mesh network that can be used as a drug carrier mesh. We report for the first time the development of a POC-based drug delivery film that can achieve enhanced drug release from the mesh by incorporation of heat generating nanoparticles (NPs). This new material provides a powerful dual impact by controlled drug release and providing implantable mechanical support of the abdominal organs during healing. The drug delivery mesh will kill residual cancer cells by drug release and gradually decompose to minimize inflammation that occurs with the current non-degradable meshes.

non-toxic monomers, a relatively simple synthesis that can be carried out under mild conditions without addition of toxic catalysts or crosslinking reagents (making it a good candidate for drug delivery and cost-effective scale-up), controllable mechanical and biodegradation properties non-toxic monomers, a relatively simple synthesis that can be carried out under mild conditions without addition of toxic catalysts or crosslinking reagents (making it a good candidate for drug delivery and cost-effective scale-up), controllable mechanical and biodegradation properties

Donor–acceptor conjugated polymer nanoparticles based on poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b’] dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) were prepared using Pluronic F127 as a stabilizing agent. PCPDTBSe is the thermal component of the formulation that absorbs near infrared (NIR) light then emits heat to release drug and kill cancer cells. The biocompatible and biodegradable drug carriers allow low-power NIR laser activation of NPs to increase temperature up to 50°C and the subsequent heat induction promotes the release of the drug *in vitro*. In addition, repeatable heating cycles of the NPs further increases the drug release. Encapsulating NPs into a polymer carrier will help to release the drug by creating heat. Thus, this polymer-based combination therapy can be useful in the future for clinical applications to replace polypropylene meshes and has potential for prolonged drug release as the polymer decomposes.

SUN 37

RADIATION THERAPY PLUS EXTERNAL THERMAL THERAPY RESULTS IN MODEST TOXICITIES WITH THE PROMISE OF INCREASED EFFICACY: A SINGLE INSTITUTIONAL EXPERIENCE

Jason Molitoris[1], JW Snider[1], Tejan Diwanji[1], Arpit Chhabra[1], Travis Dobbin[1], Valerie Smith[1], Andrew Cox[1], Shifeng Chen[2], Mariana Guerrero[2], Zeljko Vujaskovic[2]

[1]Dept of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, USA, [2]Dept of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA

Background: Hyperthermia has a well-documented ability to increase the effectiveness of radiation (RT) and advances in technology are allowing for increased availability of External Thermal Therapy (ETT). While ETT increases tumor response for superficial tumors, concern is warranted for RT associated toxicity to surrounding normal tissues. Our goal is the report on the acute and chronic toxicities along with overall survival (OS) and local control (LC) from our ~4 year institutional experience.

Methods: We retrospectively reviewed all patients treated at our institution who received ETT concurrently with RT of at least a BED(10) equivalent to 30Gy and 10 fractions (03/2013 – 12/2016). Patient characteristics including age, gender, race, primary disease site, histology, RT dose, RT technique, ETT temperature, and ETT duration. Outcomes evaluated were acute and late toxicities as well as LC and OS.

Results: Sixty patients received ETT/RT to 65 treatment sites. The most common malignancies were breast cancer (33%), soft tissue sarcomas (28%), and skin (15%). Seventy-two percent were treated for a recurrent tumor and 52% were undergoing reirradiation. The median RT dose 50Gy (range, 24 – 70Gy); the median ETT treatment number and prescribed treatment time were 10 (range, 2-23) and 60mins (range, 45 – 60mins), respectively. Target tumor temperature was 40-42C with applicator bolus temperature of 39-40C. Median follow up was 8.3 months. Of the 65 treatments, acute grade 2 or higher toxicities occurred in 30 (46%) and included: grade 2 dermatitis in 16 (25%), grade 3 dermatitis in 9 (14%), grade 2+ pain in 15 (23%). Two patients required treatment break and 1 patient discontinued treatment early. All but 2 (8%) of the grade 2 or higher dermatitis reactions resolved. In total, there were 4 chronic grade 3 toxicities: chronic lower extremity lymphedema (n=2), skin ulceration (n=1) and pneumonitis (n=1). Median OS was 21.6 months (95% CI 13.8 - 29.3) and 43.2% (95% CI 34.1 – 52.3) at 2 years. LC was 51.4% (95% CI 42.5 – 60.3%) at 2 years, median not reached. Median LC in cases of reirradiation was 12.7 months (95% CI 7.5 – 18.0).

Conclusions: Late grade 3 toxicity was observed in 4 (6.6%) patients without grade 4 or 5 toxicity. Concurrent ETT/RT represents a generally well-tolerated combination with the potential to increase the oncologic efficacy of treatment in selected patients.

SUN 38

STATUS OF CURRENT RESOURCES AND EXPERIENCES WITH NATURALLY OCCURRING CANCER IN COMPANION ANIMALS: BIOLOGY, IMMUNOLOGY AND EXPERIMENTAL THERAPEUTICS.

Rodney Page

Flint Animal Cancer Center, Colorado State University, Fort Collins, CO, USA

Spontaneously developing cancers in companion animals have been considered as a relevant system to interrogate the etiology, evolution and treatment of human cancers for over 50 years. All modalities of therapeutic interventions have been investigated ranging from physical interventions such as radiation and hyperthermia to gene therapy and targeted small molecules. A national infrastructure currently exists to conduct rigorous multi-institutional clinical trials that establish a more informed decision about extension into human trials. The business case for integrating companion animal trials into the drug discovery process is theoretically compelling although solid examples have not yet been collected into a body of work sufficient to change the paradigm. In order to advance the comparative oncology discipline a 2015 National Academy of Science - Academy of Medicine Workshop identified scientific, education and policy gaps that limit full understanding and implementation of companion animal cancer research. Recent advances have evolved rapidly. Examples of current efforts that will be discussed include: 1) Cross-species drug sensitivity mathematical modeling facilitates more rapid drug development, 2) A canine cancer genome atlas will be available within the next year to appropriately focus patient enrollment in targeted drug trials, and 3) Defining the immune landscape of companion animal cancers, quantifying mutational density and MHC-epitope characterization of canine cancers for immunotherapeutics development. Such changes have formed the basis of recent dedicated NCI funding to support canine-specific clinical investigations. Equally important are public awareness and education campaigns to expand canine patient enrolment in funded trials and regulatory policy issues to better understand how to integrate clinical trial data from companion animals into human drug candidate assessments. The future application of comparative oncology will provide a better prediction of novel therapeutics and combination therapeutics. The powerful impact of thermal modifications of biologic, physiologic and medical outcomes will be an interesting and important aspect to continue exploring with an improved understanding of the companion animal cancer model.

SUN 39

AN HISTORICAL PERSPECTIVE ON THE VALUE OF COMPANION CANINE CANCERS IN EXPERIMENTAL THERAPEUTICS TRIALS- ADVANTAGE FROM THE DOG'S AND HUMAN'S POINT OF VIEW

Mark Dewhirst

Duke University, Durham, NC, USA

I was fortunate in my career to cross paths with Edward Gillette, an early pioneer in the field of comparative oncology. After working for him as a research assistant while I was still in veterinary school, I had the great fortune of having him as my PhD advisor. At the time, he was just starting to build the comparative oncology program at Colorado State University, but his vision was far-reaching and prescient. Who could have guessed that 40 years after his initial foray into development and conduct of experimental therapeutics trials, funded by NIH, that today, the companion dog with cancer stands to be the best model for human cancer?

I will provide an overview that highlights the 40-year history of comparative oncology, in the mold set forth by Dr. Gillette. This is a paradigm that benefits the pet with cancer as well as impacting the development of new therapies for humans with cancer. As I see it now, the work that we did set the stage for much more sophisticated clinical trials that are emerging today. The sequencing of the canine genome and emergence of interest in immunotherapy and targeted agents sets the stage for the canine model to be the bell-weather of success vs. failure of newer therapeutics.

SUN 40

HYPO-FRACTIONATED RADIATION, MAGNETIC NANOPARTICLE HYPERTHERMIA AND VIRAL IMMUNOTHERAPY TREATMENT OF SPONTANEOUS CANINE TUMORS

P. Jack Hoopes[1], Karen Moodie[1], Margaret Crary-Burney[1], Alicia Petryk[4], James Petryk[1], Shawntel Sechrist[3], David Gladsione[1], Ashish Rajan[5], Robert Wagner[1], Alicea Bursey[1], Nichole Steinmetz[2], Steven Fiering[1]

[1]Dartmouth College, Hanover, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]St. Johnsbury Animal Hospital, St. Johnsbury, VT, USA, [4]University of Bridgeport, Bridgeport, CT, USA, [5]Oklahoma State University, Stillwater, OK, USA

Abstract

It has recently been shown that cancer treatments such as radiation and hyperthermia, which have conventionally been viewed to have modest immune based anti-cancer effects, may, if used appropriately, stimulate a significant and potentially effective local and systemic anti-cancer immune effect (abscopal effect) and improved prognosis. Using spontaneous canine cancers (3 oral melanoma, 3 oral amelioblastomas and 2 carcinomas), we have shown that hypofractionated radiation (6 x 6 Gy) and/or magnetic nanoparticle hyperthermia (2 x 43°C / 45 minutes) and/or immunogenic plant virus (2 x 200 μg) are capable of delivering a highly effect cancer treatment, that includes an immunogenic component. Two tumors received all three therapeutic modalities, one tumor received radiation and hyperthermia, two tumors received radiation and virus and three treatments included only mNP hyperthermia. The treatment regimen is conducted over a 14-day period. All patients tolerated the treatments without complication and have had local and distant tumor responses that significantly exceed responses observed following conventional therapy (surgery and/or radiation). Result suggests that both hypofractionated radiation and hyperthermia have effective immune responses that are enhanced by the intratumoral viral treatment. Molecular data from these tumors suggest HSP 70/90, calreticulin and CD47 are targets that can exploited to enhance the local and systemic (abscopal effect) immune potential of radiation and hyperthermia cancer treatment.

SUN 41

VALIDATION OF PROCASPASE-3 AS A PREFERENTIAL THERAPEUTIC TARGET FOR TREATMENT OF BRAIN CANCER THROUGH THE INCLUSION OF PET DOGS AS A COMPARATIVE TUMOR MODEL

Lisa Schlein[1], Edward Roy[1], Stephane Lezmi[4], Jayme Looper[3], Michael Podell[1], Peter Dickinson[2], Paul Hergenrother[1], Timothy Fan[1]

[1]University of Illinois, Urbana, USA, [2]University of California, Davis, USA, [3]Louisania State University, Baton Rouge, USA, [4]Ipsen Pharmaceuticals, Paris, France

Conventional glioma models for studying experimental therapies include xenogeneic and syngeneic transplant models conducted in mice. While xenogeneic transplant models may provide information pertaining to the sensitivity of human glioma cell lines to specific therapeutics, tumor-host interactions, especially immunobiologic responses, are poorly recapitulated in comparison to what occurs in people who develop glioma. Although syngeneic transplant murine models more accurately represents tumor-host responses than xenogeneic systems, the process of tumor initiation, promotion, and progression in any transplant model remains highly artificial, and likely underestimates the complexity for how gliomas naturally develop. In order to expedite the translation of novel and effective therapeutics to people diagnosed with malignant glioma, testing promising experimental compounds in highly relevant tumor models, in addition to conventional murine systems, should be considered.

Besides people, the domesticated dog is another large mammal that develops primary brain tumors spontaneously. The incidence of brain tumors in the canine species has been reported to be 3% of all tumors diagnosed annually and include anaplastic astrocytomas and glioblastoma multiforme subtypes. The development of malignant gliomas occurs more frequently in geriatric dogs and in specific breeds including Boston terriers, Boxers, and English bulldogs. Several studies demonstrate that malignant gliomas in dogs share similar genetic and histologic features as found in human patients. Additionally, the clinical presentation, treatment options, and prognosis of malignant gliomas in dogs are similar to people; suggesting that pet dogs diagnosed with spontaneously-arising gliomas may serve as excellent comparative and predictive tumor models for evaluating novel treatment strategies ultimately destined for people diagnosed with malignant gliomas.

PAC-1 is a novel, blood-brain barrier penetrant, pro-apoptotic small molecule activator of procaspase-3 (PC3), with orphan drug status for the treatment of human glioblastoma multiforme. Through the conductance of research with canine brain tumor tissues and clinical trials in pet dogs diagnosed with brain cancer, a substantive amount of scientific and clinical evidence exists for the rational combination of PAC-1 with conventional therapeutics including ionizing radiation and temozolomide therapies for improving therapeutic effects. Procaspase-3 is overexpressed in the majority of canine brain cancers and its expression correlates with increasing histologic grade. Therapeutically, PAC-1 combined with conventional treatments is well tolerated and produces objective tumor responses in dogs with glioma and meningioma. Collectively, these findings highlight the potential value of expediting novel drug development through the inclusion of pet dogs with naturally-occurring cancers.

SUN 42

IMAGE-GUIDED CATHETER-BASED ULTRASOUND THERMAL ABLATION OF TUMORS IN GENETICALLY ENGINEERED ONCOGENIC PIGS

E. Clif Burdette[1], Goutam Ghoshal[1], Emery Williams[1], Paul Neubauer[1], Lance Frith[1], Patrick Roady[2], Laurie Rund[2], Larry Schook[2]

[1]Acoustic MedSystems, Inc., Savoy, IL, USA, [2]University of Illinois, Urbana-Champaign, Urbana, IL, USA

Background

One of the serious challenges faced in development of technologies for accurate and effective delivery of ablative therapies to solid organ malignancies is the lack of larger animal models which can simulate the size and scale aspects of the physical environment and the clinical workflow characteristics encountered while treating a human patient. Tumor mimics have been the only model available to examine technical aspects of minimally invasive treatment delivery. Thus far, no animal model has been reported that can truly simulate size or scale of tumors comparable to a human patient, which are suitable for device technical evaluation. We propose to assess the treatment efficacy of 3D spatially-registered real-time image-guided needle/catheter based ultrasound (CBUS) thermal therapy in an induced tumor grown in genetically engineered oncogenic pigs, specifically soft tissue sarcomas of the extremity and retroperitoneal regions, both clinically relevant sites closely simulating human disease.

Methods

A transgenic 'oncopig' line encoding a Cre recombinase inducible transgene encoding $KRAS^{G12D}$ and $TP53^{R17H}$, a commonly mutated oncogene and tumor suppressor, respectively, in human cancers was created. Treatment of cells derived from these oncopigs with adenoviral vector encoding Cre (AdCre) led to $KRAS^{G12D}$ and $TP53^{R17H}$ expression, which rendered the cells transformed in culture and tumorigenic when engrafted into immunocompromised mice. Finally, injection of AdCre directly into these oncopigs led to the rapid and reproducible development of soft tissue sarcomas in the muscle. Ultrasound imaging was used to monitor the growth of these tumors. Once the tumor reached approximately 2cm by 3cm, it was treated with catheter based therapeutic ultrasound energy for thermal therapy. Sectored tubular transducers were used to precisely deliver thermal energy to the treatment region. Ultrasound image guidance combined with 3D EM tracking were used to place the applicator in the target region.

Results

The tumors were successfully grown in the muscle within two weeks of injecting the AdCre virus into the oncopigs. Skin incision less than 1cm length was sufficient to provide for insertion of catheter under image-guided ultrasound for ablating the muscle tumors. The tumors were treated for 6-9 minutes at 7 Watts acoustic power. Thermocouples inserted into the tumors showed temperature range of 55-65 C during the treatment. Histopathology analysis showed complete ablation of the tumor using single applicator configuration.

Conclusion

The results suggest catheter-based therapeutic ultrasound can be used to perform fast volumetric ablation of the tumors. The tracked ultrasound image guidance is important to guide and precisely place the catheter at the target region.

SUN 43

IMMUNOBIOLOGY OF LARGE HEAT SHOCK PROTEIN AND ITS BINDING RECEPTOR IN DISEASE PATHOGENESIS AND THERAPEUTIC APPLICATIONS

Xiangyang Wang[1], John Subjeck[2]

[1]Virginia Commonwealth University, Richmond, VA, USA, [2]Roswell Park Cancer Institute, Buffalo, NY, USA

Large heat shock proteins (HSPs) and molecular chaperones are known to regulate an adaptive immune response at least partially through superior capacity in shuttling antigenic polypeptides and facilitating cross-presentation by antigen-presenting cells. This forms an immunological basis for using its chaperoning activity to develop recombinant heat shock vaccines to generate an antigen/tumor-targeting cytotoxic T lymphocyte (CTL) response for therapeutic benefits. The successful preclinical studies has led to a phase I clinical trial in patients with metastatic melanoma. We recently engineered a chimeric heat shock protein by incorporating a pathogen-derived 'danger' signal into to HSP-based vaccine platform to further strengthen immune co-stimulation that is crucial for functional activation of antigen-presenting cells and T-cell priming. This second generation HSP-based immunostimulatory agent (i.e., Flagrp170), when used to reprogram the tumor microenvironment, results in mobilization of CTLs and induction of a systemic immune response capable of destroying treated local tumors as well as distant lesions. Furthermore, this Flagrp170-initiated immune reprogramming highly sensitizes established tumors to immune checkpoint PD-1 inhibitor for a significantly improved treatment outcome. During the study of large HSP-binding receptor on antigen-presenting cells, we identified scavenger receptor A (SRA), an innate pattern recognition receptor primarily expressed on myeloid cells, as a previously unrecognized immune suppressor. Our work also reveal that SRA facilitates tumor re-growth after ionizing radiation by promoting tumor re-vascularization, which not only elucidates a profound impact of tumor response to cancer therapy by an interplay of cancer cells with the host cells, but also indicates a complexity of the action of this HSP-binding receptor in tumor biology and immunology. In addition to cancer, we will discuss the potential function of SRA in other immune pathologies, such as autoimmune disorders. A better understanding of large HSP and its receptor in immune modulation may provide new opportunities to develop novel strategies for effective treatment of cancer and inflammatory diseases.

SUN 44

MILD HYPERTHERMIA IMPROVES PERFUSION AND ANTIMICROBIAL EFFICACY IN MOUSE MODEL OF STAPHYLOCOCCUS AUREUS ABSCESS

Ashish Ranjan, Rachel Wardlow, Jerry Malayer, Kaustuv Sahoo

Oklahoma State University, Stillwater, Oklahoma, USA

Systemic treatment of chronic wounds is challenging, and requires a combination of antimicrobials to be used for long duration with limited specificity and often-poor delivery. This incurs adverse side effects and can require aversive surgical treatments and limb amputations. To improve antimicrobial therapy and enable non-invasive treatment of soft-tissue wounds, the objective of this study was to investigate an innovative combination of antimicrobial chemotherapy with high intensity focused ultrasound (HIFU) mild hyperthermia (40-42°C) for wound therapy. *Staphylococcus aureus* was established in mice flank by sub-cutaneous (sc) injection of 2 x10^6 CFU. Mild HIFU hyperthermia was initiated once the abscess reached a volume of 25-50 mm^3. Briefly, once the average mild hyperthermia temperature in circular region of interest reached, a broad spectrum antimicrobial (ciprofloxacin, 10 mg/kg) and perfusion marker (Evans Blue, 40mg/kg body weight) was administered intravenously via tail vein, and 4h later CFU and mean abscess perfusion was determined. HIFU increased abscess perfusion by ~2.5-fold, resulting in improved antimicrobial efficacy to decrease average survival of *S. aureus* biofilms by ~15% *vs*. those seen with Ciprofloxacin or HIFU alone. Our in vivo data suggest that HIFU can improve antimicrobial treatment responses against deep-seated bacteria in abscess wounds via increase in blood flow, vessel permeability and perfusion.

SUN 45

LIDOCAINE-INDUCED POTENTIATION OF THERMAL DAMAGE IN KERATINOCYTE, FIBROBLAST, AND BASAL CELL CARCINOMA CELL LINES

Martin Purschke, Adam Raff, Carina Thomas, Rox Anderson

Massachusetts General Hospital / Harvard Medical School, Boston, MA, USA

Lidocaine is a local anesthetic, which blocks transmembrane sodium channel permeability and thereby disables depolarization of neurons and inhibits painful sensation. Lidocaine induces the synthesis of heat shock proteins and has been shown to sensitize cells to hyperthermia resulting in an increased cell killing of several tumor cell lines. Our hypothesis is that more rapidly dividing cells, such as cancer cells, are more susceptible to lidocaine-hyperthermia combined treatment compared to resting cells. The goal of this study was to investigate the effect of lidocaine on thermal damage using an *in vitro* model with normal skin cell lines and a skin cancer cell line. We used human keratinocyte and fibroblast as well as murine basal cell carcinoma cell lines at different cell cycle stages. Cells were seeded in multiwell plates and pre-incubated with lidocaine 20 min prior heating. Cell viability was assessed 24 hours later using an MTT assay.

The results of this study showed that lidocaine causes a dose-dependent thermal hypersensitivity in all tested cell lines. Exponential cell cycle active human keratinocytes and fibroblasts showed a similar reduction of cell survival at 44°C, which was significantly reduced when pre-incubated with low concentrations of lidocaine (0.1 and 0.2%). Non-dividing confluent cells were more resistant to the combined lidocaine hyperthermia treatment. The murine basal cell carcinoma cell line showed the highest viability loss for the hyperthermia treatment alone as well as for the combined treatment with Lidocaine concentrations as low as 0.05%. Cell cycle experiments confirmed enhanced thermal sensitization for the combined treatment in dividing cells, whereas confluent resting cells showed increased resistance and viability.

In summary, this study suggests that lidocaine potentiates thermal injury to both epidermal and dermal cells as well as in the tested cancer cell line. The synergistic effect of the combined treatment is cell cycle dependent. The increased effect in dividing cells compare to resting cells could be used in a new interesting approach to selectively treat fast dividing cancer cells, while sparing the normal surrounding tissue. Further investigation may provide a new therapeutic method for treatment certain neoplasms.

SUN 46

SENSITIZATION OF THEMORADIATION WITH CISPLATIN AND SMALL MOLECULES (PARP1- AND DNAPKCS INHIBITORS) TO IMPROVE CERVICAL CANCER TREATMENT

Vidhula Ahire[1,2], Arlene Oei[1,4], Caspar van Leeuwen[2], Hans Rodermond[1,2], Lukas Stalpers[2], Przemek Krawczyk[3], Johannes Crezee[2], Petra Kok[2], Nicolaas Franken[1,2]

[1]Laboratory for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental Molecular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [3]Dept. of Cell Biology and Histology, Amsterdam, The Netherlands, [4]The Johns Hopkins University School of Medicine, Baltimore, United States Minor Outlying Islands

In The Netherlands the 5 year survival rate for cervical cancer is 65% and has only marginally improved in the last 25 years despite more effective combined radiotherapy (RT) with cisplatin or RT with hyperthermia (HT) for patients who for medical reasons cannot be treated with cisplatin. More effective treatment strategies are urgently needed. Repair of DNA damage is an important cause of resistance to RT or cisplatin treatment in cancer cells. Targeting DNA repair mechanisms offers the possibility to sensitize tumour cells to cytotoxic treatments. Earlier, we showed that HT yields a tumor selective downregulation of the DNA repair protein BRCA2, one of the key proteins of homologous recombination (HR) repair. HT combined with further DNA repair inhibition by PARP1-inhibition or DNAPKcs inhibition causes a tumor selective enhancement of RT and cisplatin, both in vitro and in animals.

Methods: Cervical carcinoma cells and experimental tumors were treated with hyperthermia (1h 42°C), X-ray, PARP1-inhibitors, DNAPKcs inhibitor and cisplatin. Patient cervical cancer biopsies were ex vivo treated with hyperthermia only. Clonogenic survival assays and H2AX stainings (DNA-DSB) and western blot experiments were carried out.

Results: Combined treatments resulted in increased DNA-DSB as compared to radiation alone. Western blots show that hyperthermia decreased BRCA2 levels. In clonogenic survival experiments it is shown that cisplatin, PARP1- and/or DNAPKcs inhibition significantly enhanced the combined hyperthermia/radiation treatment.

Conclusion: Adding PARP1-inhibitor, DNAPk inhibitor or cisplatin significantly improves the effectiveness of thermoradiation treatment. Our findings provide new insights for patients who are suffering cervical cancer, indicating that they would benefit from a treatment including hyperthermia.

Financial support from Dutch Cancer Foundation (grants: UVA2012-5540 and UVA2015-7820).

SUN 47

HISTOLOGICAL EVALUATION OF CELLULAR CHANGES IN HEALTHY BONE AFTER MRI GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND: AN ACUTE AND CHRONIC STUDY IN PIGS

Karolina Piorkowska[1], Gino R. Somers[2,3], James Drake[1,4], Adam C Waspe[1,6]

[1]Centre for Image Guided Innovation and Therapeutic Intervention, The Hospital for Sick Children, Toronto, Canada, [2]Department of Pathology, The Hospital for Sick Children, Toronto, Canada, [3]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada, [4]Department of Neurosurgery, The Hospital for Sick Children, Toronto, Canada, [5]Department of Medical Imaging, University of Toronto, Toronto, Canada

Magnetic resonance guided high intensity focused ultrasound (MRgHIFU) is used clinically for treatment of painful osteoid osteomas and bone metastases. MRgHIFU heats tumour tissue and surrounding healthy bone to temperatures that cause cellular necrosis. This study hypothesizes that healthy bone tissue can heal and revascularize following ablation with MRgHIFU. Acute (n=6) or chronic (n=11) ~30kg Yorkshire pigs were treated with 53±12 Watts acoustic of HIFU for 20 seconds on the femur. Acute targets included the diaphysis (n=17) or metaphysis growth plate (n=3). Chronic targets (n=11) were at the diaphysis. MRI thermometry during treatment and post-treatment gadolinium-enhanced MRI imaging (T1-gad) evaluated HIFU affect. Acute animals were sacrificed immediately while chronic animals continued for 14 days prior to imaging and sacrifice. Internal control bone was collected for target comparison. Bones were immersion fixed, decalcified in 14% EDTA, embedded in paraffin and stained with hematoxylin and eosin (H&E) and trichrome and elastin staining for histological evaluation. Staining was assessed using four criteria: acute haemorrhage (AH), vasodilatation (VD), serous fluid extravasation (SFE) and fat necrosis (FN). The former two were scored on a four-tiered system (0=none, 1=present in 1x100 power field, 2=present in 2x100 power fields, 3=present in ≥3x100 power fields), whereas the latter two were scored as either absent (0) or present (1). Statistical analysis was performed using the Student's two-tailed t-test for comparison of mean scores and the Fisher exact test for tabulated non-parametric data. At acute target sites, MR thermometry indicated heating sufficient for cellular necrosis; treatment group maximum = 66±9°C compared to control bone at body temperature 35±1°C. T1-gad indicated loss of vascularity at the target site compared to control. Histologically, the changes were most marked in the subcortical region of bone, regardless of dose, target site or target depth. In treatment sites, the scores indicated that AH=1.75, VD=1.9, SFE=19 and FN=16 was significantly more pronounced than in control sites; AH=0.58, VD=0.75, SFE=1, and FN=0 (all $p<0.0003$). At chronic target sites, MR thermometry indicated sufficient heating for cellular necrosis; treatment group maximum= 85±5°C compared to control bone at body temperature 36±1°C. T1-gad of chronic animals also showed post-treatment loss of vascularity at the target site. After ~14 days survival, T1-gad showed vasculature in the target site. Histology for chronic bones is pending. This study describes distinct acute changes in the bone after HIFU treatment and the healing that occurs in healthy bone and vasculature following HIFU ablation.

SUN 48

MULTI-ENERGY COMPUTED TOMOGRAPHY (MECT) IMAGING OF ENDOVASCULAR ABLATION: THERMOEMBOLIZATION IN AN EX-VIVO PORCINE KIDNEY MODEL

Rick Layman, Chunxiao Guo, Samuel Fahrenholtz, Dodge Baluya, Erik Cressman

MD Anderson Cancer Center, Houston, TX, USA

Introduction

Thermoembolization is a new minimally invasive technique combining hyperthermia from an exothermic reaction with ischemia and a local pH change. The hydrolysis of the electrophile dichloroacetyl chloride (DCACl) yields approximately twice the energy of acid/base neutralization. Upon delivery via catheter, DCACl reacts with water or other nucleophiles to release heat energy. While blocking blood flow, it also forms a substantial amount of acid locally to further enhance the endovascular ablative effect. Additionally, dichloroacetate (DCA) is produced in situ with anti-tumor properties.

Real-time monitoring of thermoembolic procedures will be necessary to assure safe and effective delivery. Tracking the procedure through imaging is challenging since these reagents often have little intrinsic contrast. Further, the intrinsic reactivity of DCACl precludes the use of conventional contrast solutions. Improvements in computed tomography (CT) techniques have enabled exceptional contrast sensitivity such that materials similar to the surrounding native tissue can be differentiated. We demonstrate here the ability of MECT to clearly visualize the hydrolysis product of DCACl from native kidney tissue;

Methods

Fresh ex-vivo porcine kidneys were catheterized in the main renal artery and infused within 30 seconds with 4M DCACl in mineral oil with thermal probes at one pole and in the interpolar region. MECT of the treated tissues used a state-of-the-art dual source CT scanner. Acquisitions were performed as follows: Tube A 80 kV, 545 mA; Tube B 140 kV with a tin filter, 233 mA, pitch 0.6 and 0.6x128 collimation. Images were reconstructed at 0.5x0.25mm with iterative reconstruction (I41f, strength 2). Software processing was done with the energy window set to 40 keV and thresholding to differentiate DCA and normal kidney tissue. Gross pathology of the treatment areas were obtained to evaluate the ablation zone.

Results

Thermal probes indicated temperature increases from 10-22°C rising abruptly within seconds after injections were started. On visual inspection, tissues were initially mottled in appearance but over several hours evolved to confluent areas of coagulation. The distribution of DCA with MECT is clearly demonstrated in this study. The advanced acquisition techniques enhance contrast while post-processing provided further improvements. The complete ablation zone and margin are visualized and confirmed by gross pathology of the specimens.

Conclusion

MECT acquisition and post-processing provides definitive visualization necessary for thermoembolization procedures. The results of this study suggest that real-time monitoring can be achieved with MECT. Exciting future opportunities include quantitative metrics (volume, gradient distribution) to further improve monitoring and assess outcomes.

SUN 49

SUPERFICIAL HYPERTHERMIA TREATMENT PLANNING FOR RECTANGULAR WAVEGUIDES WITH CUSTOM CONFORMAL WATERBOLUS

Dario Rodrigues[1], Mark Hurwitz[1], Randolph Sinahon[2], Lyndsey Sbarro[2], Paul Stauffer[1]

[1]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [2]Department of Biomedical Engineering, Drexel University, Philadelphia, PA, USA

Background: In the United States, the most often used applicator for superficial hyperthermia treatments is the 915MHz rectangular waveguide. For large disease, the MA-120 waveguide is used with an aperture of $18\times24cm^2$. Applicator position and power level (P) are generally considered the only parameters the operator can use to adjust the heating pattern to accommodate variable size, shape, and depth of tumors spreading across a contoured tissue surface. The use of an adaptable conformal waterbolus provides extra treatment variables to enable fine-tuning of the heating pattern to patient disease.

Methods: We used a multiphysics software that couples electromagnetic, thermal, and fluid dynamics physics to simulate heating patterns from rectangular microwave (MW) waveguide applicators and custom-fit waterboluses in numerical models of superficial tumors with varying thickness (1-2cm). The tumor models were embodied in a contoured anatomical model of the human chest with multiple layers: 1.5mm skin, 3-15mm fat, 1cm muscle with interspersed ribs, and 8cm lung tissue. Temperature distributions were calculated using a parametric analysis spanning practical ranges for waterbolus parameters: +/-8cm lateral size relative to waveguide aperture; 6-46mm waterbolus thickness (h); and 38-43°C water temperature (Tb). The temperature goal for the different tumor targets was 41-45°C. To accommodate thermoregulation, we incorporated a blood perfusion model that accounts for up to four-fold increase as temperature reaches 45°C.

Results: For a $14\times20\times1.65cm^3$ tumor target surrounded by 15mm fat and using Tb=42°C, the 41°C contour includes 98% of the target (h=13-33mm, P=175W), but it decreases to 82% with a thinner waterbolus (h=6-26mm, P=125W) or 84% with a thicker waterbolus (h=26-46mm, P=150W). Size and location of the temperature peaks under the applicator varied as a function of waterbolus lateral size and thickness. Changing Tb from 38°C to 43°C provided adjustment of peak heating depth from 8mm to 2mm below the skin. Introduction of the thermoregulation model was essential for realistic simulation of MW input power (110-180W).

Conclusions: Multiphysics modeling can accurately simulate heating of complex applicator-tissue treatment configurations. The use of conformal waterboluses allows the therapist to customize heating patterns within the 41-45°C therapeutic range for each patient. By varying waterbolus thickness and/or temperature, heating patterns can be adjusted cyclically during treatment to shift hot spot locations and thus homogenize thermal dose delivered over a 60min treatment. These strategies are being used for superficial hyperthermia treatments at Thomas Jefferson University and they increase patient comfort as well as quality of thermal dose delivery.

SUN 50

COMPOSITE SCAFFOLDS FOR THERMAL ABLATION OF METASTATIC CANCER CELLS

Navid Manuchehrabadi, Francisco Pelaez, Priyatanu Roy, Harishankar Natesan, Heather Fong, Kevin Zeng, Emilian Racila, John Bischof, Samira Azarin

University of Minnesota, Minneapolis, Minnesota, USA

Focal therapies have shown promise in the treatment of various types of localized tumors, but they have not been successfully applied to disseminated tumor cells. Here we demonstrate a new approach to capture and treat metastatic disease in localized scaffolds with a non-invasive heating approach. Microporous polymeric biomaterials have been shown to attract metastasizing breast cancer cells *in vivo* early in tumor progression. In order to enhance the therapeutic potential, scaffolds were modified such that non-invasive local hyperthermia could be applied to disseminating cells by collecting them at a specific site in the body. Metal disks were incorporated into polycaprolactone scaffolds to generate heat through electromagnetic induction by an oscillating magnetic field within a radiofrequency coil. Alternating electromagnetic fields can inductively generate heat through an electrically conductive material (e.g. aluminium or copper metal disks) by eddy currents. The frequency of current used depends on the object size, material type and the penetration depth. Furthermore, the high frequency leads to a skin effect; the alternative current is forced to the surface of the metal. This, in turn, leads to an increased resistance of the metal, ultimately resulting in a greatly increased heating effect. Physically the efficacy is a function of the metal thickness d over the skin depth of increasing rapidly up to /d=4. Skin depth of aluminium and copper at frequency of 360 kHz, is about 110 μm and 135μm, respectively, suggesting metal disks size of d ≥ 0.5 mm are needed for efficient heating. Using experimental data and a finite element analysis in COMSOL® 5.2a, we predict a specific absorption rate of 160 W/g Al at (f, H) = (360kHz, 15kA/m). When implanted subcutaneously in mice, the scaffolds were biocompatible and became properly integrated within the host tissue. *Ex vivo* characterization of heat transfer dynamics within the tissue-laden biomaterial was performed through a combination of mathematical modelling, using measured thermal properties (k= 0.493 ± 0.058 W/m.K; Cp= 3.59 ± 0.14 J/g.K; = 1.06 ± 0.08 g/mL), and experimental measurements. Inductive heating of tissue-laden composite scaffolds resulted in a temperature increase from 37 to 52 °C, which was sufficient to cause an 85% reduction in metabolic activity of the tissue, as determined using a WST-1 viability assay. As the ultimate goal we want to show that the combination of capturing metastatic cells and easily destroying them early in disease progression can dramatically improve the treatment of metastatic disease.

SUN 51

AIR POCKETS IN THE URINARY BLADDER REDUCE THERMAL DOSE DURING RADIOFREQUENCY HYPERTHERMIA TREATMENT

Gerben Schooneveldt, Petra Kok, Debby Geijsen, Akke Bakker, Jean de la Rosette, Maarten Hulshof, Theo de Reijke, Hans Crezee

Academisch Medisch Centrum, Amsterdam, The Netherlands

Purpose

Hyperthermia is used as a (neo)adjuvant treatment modality in the treatment of both muscle invasive and non-muscle invasive bladder cancer. In the latter case, hyperthermia is combined with intravesical chemotherapy. During instillation, some air is often inserted into the bladder which remains present during treatment. This air pocket can shield part of the bladder from the radiofrequency (RF) radiation used to heat the bladder when using loco-regional hyperthermia, but may also reduce heat transfer out of the bladder. This study investigates the relative contribution of these opposing effects.

Materials & methods

We analysed fifteen NMIBC patients treated at our institute with mitomycin C (40 mg in 40 ml) plus hyperthermia (60 min). Loco-regional hyperthermia was delivered using our hyperthermia device with four 70 MHz antennas around the pelvis. A CT scan was made after treatment and a physician delineated the bladder on the CT scan. On the same scan, the amount of air present in the bladder was delineated. Using our in-house developed hyperthermia treatment planning system, we simulated the treatment using the clinically applied device settings. We did this once with the actual values for air, and once assuming the same volume was filled with urine. For three patients we simulated an air layer inside the bladder gradually increasing in thickness (0.25 to 1.50 cm of air), to study the effect of varying amounts of air within the same patient.

Results

The patients had on average 4.2 ml (range 0.8 – 10.1 ml) air in the bladder. The bladder volume as delineated by the physician (including air pocket and bladder wall), was on average 253 ml (range 93 – 452 ml). In most cases, the simulated temperature in the entire bladder was lower when air was present in the bladder; the effect size differed from $T \sim -0.1$ to -1.2 °C. The gradually increasing amount of air resulted in lower temperatures with small amounts of air, then reverting to rising temperatures for larger amounts of air.

Conclusion

The effect of an air pocket in the bladder during bladder hyperthermia treatment varies strongly between patients. Generally, this leads to lower temperatures in the bladder, potentially affecting treatment quality, and suggesting that care need be taken to minimise the size of air pockets during hyperthermia treatments. Larger amounts of air may increase temperature in the bladder but will lead to reduced contact between part of the bladder wall and therapeutic agent.

SUN 52

PRECLINICAL SURVIVAL STUDY DEMONSTRATING SAFE AND EFFECTIVE HEATING OF IN-VIVO PORCINE PANCREAS WITH NOVEL MULTI-APPLICATOR COIL INDUCTIVE THERMAL TREATMENT SYSTEM (TTX)

Pierre Floriano[1], Randall Jones[2], Yong Pang[2], William Riehle[2], Paul Stauffer[3], Kelly Lechtenberg[4], Teresa Schieber[4], Robin Schroeder[4], Charles Anderson[1]

[1]NeoTherma Oncology, Wichita, KS, USA, [2]ScanMed, Omaha, NE, USA, [3]Thomas Jefferson University, Philadelphia, PA, USA, [4]Midwestern Veterinary Services, Inc., Oakland, NE, USA

Background

Pancreatic cancer patients are faced with dismal odds and little improvement in survival and quality of life using conventional therapies. Thermal treatment has been shown in clinical trials to increase the effectiveness of radiation and chemotherapy in an array of tumors. But effective therapeutic hyperthermia (HT) of deep tissues has proven difficult to achieve safely. A novel radio-frequency (RF) inductively coupled TTx was evaluated in a pre-clinical pilot study for its ability to non-invasively, safely heat the pancreas of Yucatan mini-pigs (YMP) to a target range of 39.5°C-43°C. Surgically implanted thermal probes were used to monitor treatment and blood was drawn for standard liver, kidney, CBC and chemistry panels to assess pig health and organ damage.

Methods

Four healthy YMP (~53kg each) were anesthetized for probe placement and heat treatment. RFHT treatment was performed in three animals while one served as a sham control. Probes were placed on the skin and in subcutaneous (SQ) tissue, between right and left medial liver lobes, between pancreas and duodenum, at the periphery of the right kidney and in the rectum. The RFHT procedure consisted of a ramp-up period at high power followed by 60 minute 'hold' time at lower power once the deep tissue target temperature was achieved. The procedure was repeated four times with >48 hours between surgeries to allow recovery. Blood was collected before, after and 24hrs post-treatment and 3-lead ECGs were taken every 15 min. Three days after the final thermal treatment, the YMP were euthanized, necropsied and histopathologically examined.

Results

The system produced a rapid temperature ramp in all three heated pigs, achieving peri-pancreas temperatures of 39.5°C as fast as 7 min, and 41°C in 21 min, though variability was seen in heating rate and baseline organ temperatures between animals. The pancreas target temperature was safely maintained for the desired 60 min during treatments with skin and SQ tissues kept below the specified limit (<44°C). No organ damage was indicated by blood work, necropsy or histology results.

Conclusions

In this YMP model, rapid, controlled and safe deep tissue heating was demonstrated with cool surface temperatures using a novel air-coupled multi-applicator coil inductive TTx. Based on these successful results, the sponsor is integrating the TTx with magnetic resonance imaging to provide real-time non-invasive thermal monitoring to be combined with advanced treatment planning. These efforts will culminate with initiation of a first-in-human feasibility study in pancreatic cancer patients in 2017.

SUN 53

MANAGEMENT OF LOCALIZED CANCER USING SLEEVED DUAL SLOT ANTENNA MICROWAVE ABLATION TECNIQUE

Ephraim Nwoye, Z. Ayo Ibitoye, Moses Aweda

University of Lagos, Nigeria, Lagos, Nigeria

Cancer as global burden with increasing incidence is a second and among third cause of death in developed and developing economies respectively. Surgery, radiotherapy, chemotherapy, hormonal therapy and immunotherapy are the major management options. Thermal therapy is currently gaining attention as an alternative. Radiofrequency, laser, high intensity focused ultrasound, cryo and microwave ablations are forms of thermal ablation. Microwave ablation (MWA) exhibits faster heating of large targets, induction of higher temperatures within tissues, less susceptibility to perivascular heat sinks and short treatment duration makes it more suitable for the treatment of liver, lung, breast, renal and adrenal malignancies. Microwave antenna (applicator) is the most important part of MWA system. Many antennae such as dipole, monopole, single slot, dual slot, triaxial and choked have been designed mostly for liver ablation. These antennae have shortcomings especially high power reflection coefficient, low power dissipation and heat elongation on the antenna feedline (comet effect). In this research Dual Slot Antenna with a floating metallic sleeve was designed to create large ablation volume and spare adjacent tissues which are not directly involved in volume of interest. Aspect ratio, ablation diameter and ablation length of the antennae were determined from their applications on in vitro bovine liver, muscle, lung, heart, liver, lung and breast. Finite element method (FEM) was used to design and simulate the antenna geometry. It is also used to study microwave energy, necrosis, and temperature distributions in these tissues. The positions of the sleeve and the lengths were varied as well as the slot sizes to achieve optimally low reflection coefficient at operating frequency of 2.45 GHz. The best optimized design produced reflection coefficient of -25.2 dB, ablation length of 42.2 mm, ablation diameter 35.2 mm with aspect ratio of 0.83. Bovine liver, muscle, lung, heart and breast samples were ablated at different input powers and durations. Simulation results indicate greater reduction in refection coefficient and backward heating with sleeved antenna than monopole, single slot and dual slot antennae in all the tissues. Ablation diameter and aspect ratio also increased with this new antenna. *In vitro* experimentation established that sleeved antenna is capable of localizing microwave energy in tissues than the existing antennae. There were no significant differences in the simulation and experimental results of the sleeved antenna. The study demonstrated that inclusion of floating metallic sleeve on dual slot antenna reduced backward heating along antenna shaft as well as increasing aspect ratio.

Keywords: Antenna, Design, optimization, Cancer Tumour, Comsol Multiphysics, Tissues, Microwave Ablation, Modeling, heat therapy, Slot with sleeve

SUN 54

DESIGNED AND EXPERIMENTAL VALIDATION OF A SLEEVED ANTENNA FOR MICROWAVE ABLATION

Ayo Ibitoye, Ephraim Nwoye, Adebayo Aweda

College of Medicine, University of Lagos, Lagos, Nigeria

Microwave ablation technique has been reported to be a promising option in the treatment of liver diseases. It exhibits ability to heat tissue to a higher temperature, heat large tumor volume with less dependent on thermal conduction and less susceptibility to heat sinks without the need of a grounding pad when compared with radiofrequency ablation. Microwave antenna plays important roles in electromagnetic energy delivery during ablation of tissues. Monopole, triaxial, single slot, dual slot and helical antennas have been proposed for the efficient delivery of microwave power into biological tissues. Antenna geometries such as slot size, slot position, slot number and abutted end have been found to affect microwave distributions in the ablated tissue. Detrimental backward heating and small tumor ablation size are the shortcomings attributed to most of these antennas. Microwave ablation a form of thermal therapy has been mostly focused on the treatment of liver diseases with paucity of information on its application to other tissues. The aim of this study is to develop a suitable antenna for microwave ablation of different tissues in the field of tumor management. COMSOL Multiphysics version 4.4 (Stockholm, Sweden), which is based on finite element methods (FEM), was used to design and simulate monopole and dual slot with sleeve antennas. Power, specific absorption rate (SAR), temperature and necrosis distributions in the selected tissues were determined using these antennas. Monopole and dual slot with sleeve antennas were designed, simulated, constructed and applied in this study based on a semi-rigid coaxial cable. Ex vivo experiments were performed on liver, lung, muscle and heart of bovine obtained from a public animal slaughter house. The microwave energy was delivered using a 2.45 GHz solid-state microwave generator at 40 W for 3, 5 and 10 min. Aspect ratio, ablation length and ablation diameter were also determined on ablated tissues and compared with simulated results. The dual slot antenna with sleeve produces localised microwave energy better than the monopole antenna in all ablated tissues using simulation and experimental validation methods. There were significant differences in ablation diameter and aspect ratio between the sleeve antenna and monopole antenna. Additionally, there were no significant differences between the simulation and experimental results. This study demonstrated that the dual slot antenna with sleeve produced larger ablation zones and higher sphericity index in ex vivo bovine tissues with minimal backward heating when compared with the monopole antenna.

SUN 55

FOCUSING WITH MICROWAVE HYPERTHERMIA ARRAY APPLICATORS: FREQUENCY MATTERS

Hana Dobsicek Trefna[1], Björn Martinsson[1], Julia Ravanis[1], Martin Torstensson[1], Petra Kok[2], Mikael Persson[1]

[1]Chalmers University of Technology, Gothenburg, Sweden, [2]AMC Medical Centre, Amsterdam, The Netherlands

Introduction

Addition of hyperthermia to radiotherapy has been shown beneficial in management of many types of cancer. In our work, we aim to develop microwave system for deep hyperthermia that is capable of modifying the focus size according to tumor position and volume. This is achieved by selection and alternation of operating frequency of the antennas in addition to amplitude and phase optimization. In this paper we quantitatively compare the focusing in realistic tumors in the head obtained with our UWB antenna applicator operating at different frequencies.

Methods

Two optimization algorithms, generalized Eigenvalue Problem Algorithm and the Gradient based Problem of Moments, were implemented to find the most appropriate frequency or set of frequencies for treatment of specific tumors in head. In particular, three realistic tumors located in tongue, nasal region and skull base were considered in this simulation study.

A head applicator, the larger of two exchangeable applicators developed at our institute for heat delivery in the head and neck region was applied. The applicator consists of 16 self-grounded bow-tie antennas arranged in two elliptical rings and operates in frequency range of 400 - 900 MHz. Each antenna is placed inside a conical enclosure and cooled separately by circulated distilled water. To guarantee transport of EM energy and patient skin cooling, an additional water bolus layer is used to fill the space between the antennas and the patient with water.

Results

In nasal case, the lowest HTQ, of 0.66 was obtained for frequencies around 600 MHz, while the HTQ for 400 MHz and 900 MHz reached values 0.79 and 0.98, respectively. The results for tongue tumor case are similar. The best HTQ achieved in tumor located in skull base, 3.39 was obtained at the lowest applicable frequency, 400 MHz. Since such a high HTQ is not satisfactory and it only degrade with higher frequencies, it is obvious that he applicator should operate at even lower frequencies to effectively heat the tumors in such a challenging location.

Conclusion

The frequency analysis reported here endorses the use of UWB system, as the most appropriate results for each tumor case were achieved at different frequencies. Both optimization methods exhibit similar performance in terms of HTQ and tumor coverage for single frequency solutions.

POS 1

HEAT-TARGETED DRUG DELIVERY USING THE COMBAT BRS DEVICE FOR TREATING BLADDER CANCER

Thomas Longo, Steven Brousell, Joseph Fantony, Mark Dewhirst, Paolo Maccarini, Ivan Spasojevic, Brant Inman

Duke University, Durham,NC, USA

Introduction/Objective: Mild bladder hyperthermia (~43°C) can be used to improve intravesical drug delivery, to trigger payload release from systemically-administered thermally-sensitive liposomes, and to elicit immune responses. In this study we assess a novel conductive bladder heater, the Combat BRS device, in a live porcine bladder model to assess its ability to function as a heat-targeted drug delivery platform for use in bladder cancer.

Methods: Twelve 60 kg female swine were anesthestized and catheterized with a 3-way 16 F catheter. A multidimensional and multiparametric thermal monitoring system (fiberoptic microprobes, semiconductor germanium thermistors, custom designed/fabricated thermistor strips, and infrared cameras) was surgically implanted for high resolution 3D bladder temperature mapping. The Combat BRS device was used to heat the bladders to a target ~43°C for 2 hours. Pigs received intravesical mitomycin C (MMC, 2 mg/mL), systemic thermally-sensitive liposomes containing doxorubicin (Dox), or both. Pharmacokinetic testing was done by measuring MMC and Dox levels in blood and tissues (bladder, lymph nodes, liver, kidney, spleen, heart, and lung) with an Agilent 1200 series liquid chromatography and Applied Biosciences API 5500 QTrap electrospray tandem-mass spectrometry. Data acquisition and quantification was performed by Analyst 1.6.2 software.

Results: Heat mapping demonstrated consistent intravesical temperatures of 42.9°C (±0.14) and a temperature gradient of 1.5°C across the detrusor, resulting in full thickness bladder heating >41°C (Dox drug release occurs at 41°C). Adjacent organ and core body temperature increased modestly, well below safety thresholds. Mean bladder tissue MMC level was 0.9 μM. Mean tissue Dox level was 117.2 μM in the bladder and 6.7 μM in the heart, a 17-fold difference. Liver, kidney, spleen, lung, and LN tissue all contained significantly lower Dox levels than the bladder.

Conclusions: The Combat BRS device effectively heated the entire bladder wall to acceptable target temperatures and with excellent temperature safety parameters. Combat BRS was able to effectively trigger the release of Dox from systemically-administered thermally-sensitive liposomes, resulting in bladder Dox levels far exceeding levels required for anti-neoplastic effects, while concurrently minimizing unwanted drug delivery to other organ sites. Heat-targeted drug delivery has the potential to make systemic chemotherapy much more effective while also dramatically improving safety.

POS 2

MODELING THE ELECTRICAL-THERMAL PERFORMANCE OF INTERNALLY COOLED WET (ICW) ELECTRODES FOR RF ABLATION

Macarena Trujillo, Jose Bon, Enrique Berjano

Universidad Politécnica de Valencia, Valencia, Spain

Introduction:

Internally cooled wet (ICW) electrodes which combine saline infusion and internal cooling of the electrode are used as a competent alternative to internally cooled (IC) or wet electrodes in radiofrequency ablation (RFA). Experimental studies have shown that ICW electrodes produce greater coagulation zones than IC and wet electrodes separately. However, there is no information about the relationship between ICW electrodes performance and the electrical, thermal and tissue response they provoke in the tissue. The aim of this study is to assess the effect of the main phenomena associated with the use of an ICW electrode in RFA: rehydration, thermal convection and increase in electrical conductivity, and propose how they can be introduced in a theoretical model formulation.

Methods:

We build an in vivo computer model for a 12-minute RF hepatic ablation using an ICW electrode (17G, 3 cm tip) by an impedance-control pulsing protocol with a constant current of 1.5 A. Moreover, we build an IC electrode computer model to compare with the ICW results modeling.

Results:

We obtained that rehydration which implies the use of an ICW affects mainly to the coagulation zone size, the increase in electrical conductivity to the delay of the roll-off time, and the thermal convection has no effect. A continuous saline infusion can produce total absence of roll-off time and differences of 50% for the coagulation zone volume comparing with IC. The computer results agree those results obtained in experimental studies.

Conclusions:

The rehydration phenomena and the increase in electrical conductivity produced by the use of an ICW are the main responsible for the absence of roll-off and a greater coagulation zone volume than the obtained with IC electrodes. The modeling of both phenomena is hence essential for an accurate modeling of ICW electrodes.

POS 3

HYPERTHERMIA COMBINED WITH HYDROGEL PROMOTED APOPTOSIS VIA VARIOUS BIOLOGICAL MECHANISMS IN SKIN AND PROSTATE CANCER CELL LINES COMPARISON WITH NORMAL CELL LINES

Bihter Yavuz[1,2], Gülengül Duman[1], Onur Cem Namli[1], Berrin Erdag[2]

[1]Yeditepe University, Istanbul, Turkey, [2]TUBITAK MAM, Gebze/ Kocaeli, Turkey

Hyperthermia is a therapeutic procedure of heat application on body tissues in the range of 40-44°C, which plays an important role in cancer treatment. This technique aims to improve the results of conventional treatment strategies such as chemotherapy and/or radiotherapy. It induces apoptosis or necrosis via various mechanisms and influences tumour blood flow, oxygen and nutrient supply in vivo conditions.

This study aimed to address the pathways of hyperthermia induced cell death with and without hydrogel system on selected cancer cell lines, *humanepidermoid carcinoma* (A431) and *prostate adenocarcinoma* (PC-3) compared to normal skin, *primary epidermal keratinocytes* (HACAT) and *normal human prostate epithelial* (PNT1A).

The different temperature ranges, 41-44°C, examined separately and combined with pluronic hydrogel (F127) on normal and cancer cell lines at different time intervals; 1 to 30 minutes respectively. Heat applied on to the cell culture with the help of heat probe, which is newly designed, and hydrogel system. Cell viability and proliferation examined with WST-1 assay. Annexin-V FITC and propidium iodide assay analysed with flow cytometry for the detection of apoptosis and necrosis at single cell level. To examine the cellular and molecular mechanisms of apoptosis promoting under combination treatment of hyperthermia with hydrogel, cell lysates analysed with western blot and for further tumour formation after heat shock colony formation assay was performed.

The results obtained from WST-1 assay that cells were exposed to 41 °C for 15 minutes and 43 °C for 15 minutes showed a significant cell death on cancer cell line compared to the normal cell line as a control group. The cell destruction ability of hydrogel (F127) with heat is 2-fold higher than alone hyperthermia at the 41 °C and 43 °C temperature (single shot treatment, 15 min). The results have also indicated that cells go apoptosis by different pathways depends to cell line under hyperthermic treatment. As a conclusion, the hydrogel heat system significantly increases the cell death by apoptosis of both A431 and PC-3 cell lines besides heat itself and it has slightly effect on normal cell lines; HACAT and PNT1A.

POS 4

OBSERVATION OF LIPID CRYSTALLIZATION IN HUMAN FAT CELLS

Like Zeng, George Frangineas

ZELTIQ Aesthetics, Inc, Pleasanton, CA, USA

Cryolipolysis is a novel non-invasive technique for localized fat reduction that employs controlled, selective extraction of heat from fat cells while sparing injury to skin and other structures. The proposed mechanism of cryolipolysis includes intracellular lipid crystallization (i.e., lipid-ice formation) that contributes to the immediate fat cell death or delayed apoptosis. This lipid-ice formation is believed to initiate a prolonged inflammatory panniculitis, phagocytic process, and eventually lead to a gradual fat cell clearance. Lipids in the liquid state are not birefringent while solid lipid-ice crystals exhibit strong birefringence, which is detectable under polarized microscopy. This work utilized a polarized microscope equipped with a cryostage to study the lipid crystallization process in freshly harvested human fat cells. The fat cells were placed into the cryostage and cooled to a predetermined temperature set point and duration. The lipids were found to supercool at temperatures below their thermodynamic melting points. We observed that the crystallization was characterized by many nucleation processes and these nuclei slowly grew into crystals (lipid-ice). In order to quantify the lipid crystallization process, the birefringent intensity pattern of the lipid-ice was recorded and analyzed. Our results showed that the intensity was dependent upon both the temperature set point and duration. Specifically, a colder temperature or longer duration resulted in greater birefringent signal intensity. Further, our intensity-time analysis suggested a maximal birefringent intensity for a given temperature set point, implying that there exists a maximal fraction of lipids that can form lipid-ice at a given temperature set point. The results observed in this study further elucidate the cryolipolysis mechanism of action, eventually leading to optimization of the fat reduction treatment parameters.

POS 5

INTRAABDOMINAL TEMPERATURE CHANGES BY APPLICATION OF RADIOFREQUENCY DEVICE (REMISSION1°C)

Hyung Joon Han[1], Tae-Jin Song[1], Won-Jin Park[2]

[1]Korea University Ansan Hospital, Ansan/Gyeonggi-di, Republic of Korea, [2]WonJin Aesthetic Surgery Clinic, Seoul/Seoul, Republic of Korea

Introductions Exposure of biological subjects to electromagnetic fields with a radiofrequency is directly correlated with temperature elevation. In order to evaluate the ability of radiofrequency device (**REMISSION1°c**) to increase and sustain temperature in swine models, hypothesizing that exact changes of intraabdominal temperatures near organs were demonstrated.

Method This study was performed under a protocol approved by Institutional Animal Care & Use Committee of Korea University. Three female Yorkshire swine were prepared for experimentation. We checked the intraabdominal temperature in right upper quadrant near liver, left upper quadrant near stomach, mid abdomen around small bowels, subcutaneously layer on mid abdomen, and lower abdomen near urinary bladder. Radiofrequency device monopolar applicator 150Ø were applied on the abdomen with backside electrode plate, which was operated during 60 minutes.

Results The mean baseline intraabdominal temperature was 36.4±1.1 °C and 60 minutes was 39.4±2.8 °C after radiofrequency device application. There was a uniform tendency of temperature elevations during operation of that device during 60 minutes operation of radiofrequency device. After removal of applicator of the device, intraabdominal temperature reduction was uniform during 30 minutes from 39.6±3.13 to 38.5±2.0 °C.

Conclusions The results obtained in the current study demonstrated the ability of radiofrequency device to provide a hyperthermia in the intraabdominal cavity near stomach, liver, small bowels, and urinary bladder.

POS 6

ROLE OF HIF-1AIN THE RESPONSE OF TUMORS TO THE COMBINATION OF HYPERTHERMIA AND RADIATION *IN VIVO*

Wonwoo Kim[1], Mi-Sook Kim[1,2]

[1]*Radiation Non-clinic Center, Korea Institute of Radiological & Medical Sciences, Seoul, Republic of Korea,*
[2]*Department of Radiation Oncology, Korea Institute of Radiological & Medical Sciences, Seoul, Republic of Korea*

Background: Mild temperature hyperthermia (MTH) increases blood flow and oxygenation in tumors. On the other hand, high-dose irradiation such as stereotactic body radiotherapy (SBRT) or stereotactic radiation surgery (SRS) damages blood vessels, decreases blood flow and increases hypoxia in tumors, thereby it upregulates hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor, which promote tumor recurrence and metastasis after radiotherapy. The purpose of the present study was to reveal whether MTH decreases the radiation-induced upregulation of HIF-1 and VEGF, thereby it enhances the efficacy of high-dose radiation against tumors.

Methods: FSaII fibrosarcoma grown subcutaneous in the leg of C3H mice were used. Tumors were irradiated with 15 Gy using ^{60}Co irradiator and heated at 41 with an Oncothermia heating unit. The blood perfusion and hypoxia were determined with Hoechst 33342 and pimonidazole, respectively. The expression levels of HIF-1 and VEGF in tumor sections were determined with immunhistochemical method. Apoptosis of tumor cells was assessed with terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) staining and tumor growth was determined.

Results: MTH at 41 for 30 min increased blood perfusion and decreased hypoxia whereas 15 Gy irradiation decreased blood perfusion and increased hypoxia in FSaII tumors. The irradiation markedly increased the expression HIF-1 and VEGF in the tumors in 3 days and MTH applied immediately after tumor irradiation significantly prevented the radiation-induced upregulation of HIF-1 and VEGF. MTH significantly increased the effects of radiation to induce apoptosis and suppress tumor growth.

Conclusion: MTH inhibits the radiation-induced upregulation of HIF-1 and VEGF, thereby it enhances the response of tumor to high-dose irradiation. MTH may effectively enhance the efficacy of SBRT or SRS.

POS 7

MAGNETIC NANOSTRUCTURES OVERLAID WITH GOLD FOR APPLICATIONS IN COMPUTED TOMOGRAPHY AND MAGNETOHYPERTHERMIA

Elis Regina Siqueira, Breno Coelho, Marcelo Souza, Paulo César Morais, Ricardo Azevedo, Alicia Ombredane

University of Brasilia, Brasília, Distrito Federal, Brazil

Introduction: Nanotechnology offers nowadays a huge variety of tools for innovation in therapy and theranostic and it is viewed with great interest in the field of Oncology. This forefront of the medical field has continuously demanding for development of high precision and non-invasive diagnosis approaches and improved therapy protocols. Herein we report on the successful development of a multifunctional nanomaterial system for cancer therapy (magnetohyperthermia) and theranostic (micro-CT), which is based on magnetic iron oxide nanostructures overlaid with nanometer-sized Gold thickness. While keeping the magnetic properties of the inner core the as-developed nanomaterial exploits the rich surface chemistry of Gold for further bio-functionalization, aiming biological site specificity. Methodology: iron oxide-based magnetic nanoparticles were synthesized via co-precipitation of Iron ions in alkaline medium, following Gold surface-dressing using sodium borohydride ($NaBH_4$) as reducing agent of Au^{3+} (from $HAuCl_4$). Characterization of the core-shell magnetic nanostructure was performed using X-ray diffraction (XRD), transmission electron microscopy (TEM), dynamic light scattering (DLS), magnetic resonance (MR), magnetic hyperthermia, and micro-CT. Moreover, cytotoxicity assays were conducted with keratinocyte and fibroblast cell lines using colloidal suspensions of the as-produced magnetic core-shell structures. Results: XRD data confirm both maghemite and Gold phases. TEM micrographs showed diameter varying in the 14-17 nm range. DLS was used to track the hydrodynamic diameter, polidispersity (below 0.30) and zeta potential for six months, indicating no parameter change while keeping the colloidal suspension at 25° C. Peak position and linewidth observed in the MR spectra confirmed successful production of iron oxide-based nanostructures. Time dependent AC-field heating curves indicated acceptable temperature increase while performing magnetic hyperthermia. Assessed Hounsfield Unit values were high enough for application in micro-CT. Cytotoxicity assays showed biocompatibility even after 72 hours of incubation with the colloidal suspension. Conclusions: our findings confirm phase, morphology, colloidal stability, magnetic properties and biocompatibility of the as-produced core-shell nanomaterial while tests involving AC-field heating and micro-CT demonstrated very promising application of the maghemite-Gold/ core-shell nanomaterial in magnetohyperthermia and as contrast agent.

POS 8

SENSITIVITY ANALYSIS FOR MODELING RF ABLATION USING COMPLEX FINITE ELEMENT METHOD

Juan Monsalvo, Manuel Garcia, Harry Millwater, Yusheng Feng

The University of Texas at San Antonio, San Antonio, Texas 78249, USA

In radiofrequency ablation (RFA) for cancer treatment, the temperature is sensitive to various parameters as well as boundary conditions. It is important to determine how each model parameter affects the temperature distribution over the region of interest. The analysis results could in turn control the tolerance of parameter variations with respect to the effectiveness of treatment outcome. Usually, the sensitivity analysis with respect to computational domain and boundary conditions is very challenging. In this talk, we present an alternative method for sensitivity analysis using complex finite element method (a.k.a, ZFEM), which is more accurate and robust compared to other numerical methods. The RFA is modeled by coupling Bioheat Transfer and Joule Heating Equations. The sensitivity analysis for temperature field is conducted with respect to all material property parameters and boundary conditions. The major advantage of ZFEM is its capability to provide a comprehensive sensitivity results of all model parameters and boundary conditions due the complex nature of this numerical method, in which regular derivatives can be calculated efficiently. Numerical experiments demonstrate that ZFEM is not only comprehensive but also accurate in comparing finite difference and regular finite element methods. Results show that RFA procedure is very sensitive to the electric field and temperature boundary conditions. Moreover, the thermal and electrical conductivities in the healthy tissue domain are the most sensitive parameters.

POS 9

SEMI-GREEN SYNTHESIS AND CHARACTERIZATION OF SUPERPARAMAGNETIC FE_3O_4-MNPS WITH AQUEOUS EXTRACTS FROM C. VERUM AND NATURAL EXTRACT FROM V. PLANIFOLIA.

A.L. Ramírez-Núñez[1], J. Santoyo-Salazar[1], L.F. Jiménez-García[2], B. Sanz[3], G.F. Goya-Rossetti[3]

[1]CINVESTAV-IPN, México, Mexico, [2]UNAM, México, Mexico, [3]Instituto de Nanociencia de Aragón (INA), Universidad de Zaragoza, España, Spain

Recently biosynthetic methods employing either biological entities or plant extracts have emerged as an easy, fast and economical alternative to chemical and physical síntesis procedures for the production of safer nanomaterials for human use. An eco-friendly semi-green method was used in order to obtain magnetite magnetic nanoparticles (Fe_3O_4-MNPs). Biomolecules from aqueous extracts can act as capping and reducing agents wich effectively replace toxic chemical reductans. Plant extracts with a rich mixture of active biological phytochemicals (i.e. tannins, saponnins, flavonoids, carbohydrates) control and shape the growing nanoparticles. The green synthesis of Fe_3O_4-MNPs with aqueous extracts represent a major advantage in the synthesis of MNPs for biomedical usage, due to their efficient drug delivery carriers for specific cancer diseases. In order to explore the diversity of biomolecules in the obtention of Fe_3O_4-MNPs, in this work an aqueous extract from *Cinnamomun verum* and *Vanilla planifolia* (natural pods and synthetic extract) were used during the synthesis of magnetite. The Fe_3O_4 MNPs were identified by XRD as having the spatial group *Fd3m* inverse spinel FCC structure, a= 8.355 Å in synthetic vanilla and a=8.362 Å in vanilla pods extract *(V. planifolia),* and a=8.366 Å in *C. verum*. IR peaks at 576 cm^{-1} correspond to Fe-O bonding formation; vibrational peaks at 576-1641 and 3415 cm^{-1} suggest phenol molecules involved in bio-reduction process. XRD and HRTEM diffraction patterns overlap with the corresponding Fe_3O_4 peaks (220),(311),(400),(511),(440). The *d* spacing 2.4 Å in *V. planifolia* and 2.7 Å in *C. verum* match the main diffraction plane 35° (311). The particle size calculated by Scherrer´s equation (t=Kl/b cos) in *V. planifolia* was 12 nm and 14 nm in *C. verum*. AFM-MFM data show a monodomain arrangement of 2-3 nm in *V. planifolia* and 5-6 nm in *C. verum*. VSM data indicate that magnetization increases rather using *C. verum* extract (64.89 emu/g) than *V. planifolia* (46.6 emu/g). The SPA values suggest that vanilla pods extract has an advantageous performance during Fe_3O4-MNPs synthesis showing also heating capability (64.51 W/g). The bio-synthesis of Fe_3O_4 MNPs obtained by aqueous plant extracts are commensurable to those obtained by a chemical method with a better performance than synthetic extracts.

POS 10

UPTAKE AND RETENTION OF ANTIBODY CONJUGATED FERRITE NANOPARTICLES – A STUDY USING XENOGRAFT MODELS OF HER2 POSITIVE BREAST CANCER.

Preethi Korangath, James Barnett, Anirudh Sharma, Jacqueline Stewart, Elizabeth Henderson, Shu-han Yu, Sri Kamal Kandala, Rajeev Hatwar, Mohammed Hedayati, Brian Simons, Saraswati Sukumar, Robert Ivkov

Johns Hopkins University, Baltimore, MD, USA

Background: Nanoparticle-based cancer therapy and drug delivery has advanced significantly in recent years, providing new opportunities. Yet, significant deficiencies in knowledge remain. Results of clinical trials often fail to recapitulate preclinical experiences, implying that model-specific features, which do not accurately reflect clinical realities. It has been recognized for some time that the unique properties of nanoparticles lead to interactions with components of host immune systems; but, less understood is how these interactions affect uptake and distribution in tumours, In this study, we sought to address this using HER2 cancer as a model.

Methods: Aqueous suspensions of 80-nm diameter starch-coated ferrite particles, Plain (BNF-plain), Herceptin-conjugated (BNF-HER), and Isotype control antibody-conjugated (BNF-IgG) were injected intravenously into mice bearing orthotopic HCC1954 (HER2+) and MDAMB231 (HER2-) xenografts. We also used xenografts of MCF7, MCF7-HER2, and BT474 having varied HER2 protein expression. Tumours were implanted into athymic nude or NOD-SCID Gamma (NSG) female mice. When the tumour volume reaches 150-200mm^3, they were divided into cohorts of five individuals bearing two tumours. Mice were sacrificed 24 hours post injection to collect tumours and liver. We compared the nanoparticle content and distribution among the tumours and between the two models using histopathology and inductively-coupled plasma mass spectrometry (ICP-MS).

Results: Mice injected with either BNF-HER or BNF-IgG nanoparticles had higher accumulated iron in tumours than either control or BNF-plain injected mice. Measured iron accumulation in tumours of mice injected with BNF-plain was only slightly higher than in control mice. Mice injected with antibody-labelled nanoparticles demonstrated significantly lower iron accumulation in their livers than BNF-plain injected mice. Comparing between nude and NSG models, more iron was measured in tumours harvested from NSG mice than from nude mice. No statistically significant difference of iron accumulation was found between BNF-HER and BNF-IgG groups indicating non-specific uptake. Further, no statistically-significant positive correlation between the HER2 status and BNF-HER uptake was determined, implicating interactions with other components of the tumor microenvironment dominate an active transport process. Immunohistochemical analysis of tumours showed that the particles are associated with IBA-1 positive (macrophages/monocytes) cells.

Conclusion: These results demonstrate that antibody-conjugated nanoparticles are taken up by tumour-associated immune cells, and that the host immune plays a role to determine tumour-targeting of nanoparticles. The evidence gathered implicates these processes as dominant over cancer cell-specific nanoparticle-antibody binding. A passive uptake mechanism is unsupported by our evidence demonstrating the lack of significant iron accumulation in tumours harvested from mice injected with BNF-plain nanoparticles.

POS 11

PHOTODYNAMIC THERAPY CAN CURE NATURAL CUTANEOUS HEMANGIOSARCOMA IN DOGS

Martha Rocha, Carolina Lucci, João Paulo Longo, Luis Muehlmann, Ricardo Azevedo

University of Brasilia, Brasilia, DF, Brazil

Cutaneous hemangiosarcoma is a malignant highly metastatic neoplasia that arises from the endothelial cells. This type of tumor frequently occurs in dogs and can appear anywhere on the skin, but is most commonly present on the ventral abdomen and inguinal regions, or other areas of skin that are sparsely haired and light in color. The most effective treatment will require a wide surgical excision of the tumor, along with some of the normal skin tissue surrounding it. This study aimed to treat natural occurrence cutaneous hemangiosarcoma in dogs using photodynamic therapy (PDT) with aluminum-chloride-phthalocyanine nanoemulsion (AlClPht-nano) as photosensitizer. Five dogs were used, all with histopathological diagnosis of cutaneous hemangiosarcoma of natural occurrence. Animals were anesthetized to keep immobile. AlClPht-nano (40 μM) was injected intra and peritumoral. After 15 minutes, the masses were irradiated by a LED (658-662 wave length, 80 mW potency) for 25 minutes (Fluency = 120J/cm^2). Animals were reevaluated 7 days after the treatment. The number of sections was based on the observation of the lesion, and PDT sections were repeated every 7 days until the mass could not be macroscopically seen anymore. On this occasion, an excisional biopsy of the area was taken and forwarded to histopathology analysis. Before each PDT application and the excisional biopsy, blood was collected from each animal for hematological analysis (complete blood count and liver and kidney function). During the treatment, macroscopically it could be observed inflammation and necrosis on the tumoral mass area. The number of PDT sections varied from 2 to 4, mostly depending on the size of the initial mass, and by the end of the treatment a total remission of the neoplasia was observed in all cases. Microscopically analysis of the excisional biopsy showed only necrosis and hemorrhage, and no cancer cells. The patients did not show any alteration on their blood parameters that could be related to the PDT. In conclusion, PDT with AlClPht-nano is a safe and effective treatment for cutaneous hemangiosarcoma in dogs.

POS 12

PROCESSING AND PHYSICAL PROPERTIES OF GD-DTPA COMPLEX-FUNCTIONALIZED MAGNETIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

Sandra Irene Eguía Eguía[1], Octavio Fuentes Ramírez[1], Lorenzo Gildo Ortíz[1], Patricia Maldonando Altamirano[2], Jorge Ricardo Aguilar Hernández[2], Jaime Santoyo Salazar[3]

[1]Doctorado en Nanociencias y Nanotecnología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Zacatenco, Ciudad de México, Mexico, [2]Escuela Superior de Física y Matemáticas, Instituto Politécnico Nacional, Ciudad de México, Mexico, [3]Departamento de Física, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Zacatenco, Ciudad de México, Mexico

Nowdays, the development of functionalized nanoparticles has an important growth, because of their future possibilities and applications in cancer treatment. Functionalized magnetite nanoparticles can be used as magnetic domains core with an organic bicompatible shell to add complex systems. In this work, Magnetite (Fe_3O_4) nanoparticles have been funtionalizated with gadolinium (Gd) and diethylenetriaminepentaacetic acid (DTPA) to add optical properties and biocompatibility, respectively. Fe_3O_4 nanoparticles have been synthesized with different batches, via co-precipitation at 80°C from ferrous Fe^{2+} and ferric Fe^{3+} ions, under an inert atmosphere. In one of the batches, during the synthesis, 3-amino-1-propanol was used as a reducing agent and stabilizer. In the other synthesis, the magnetite nanoparticles were aminated through silanization, using 3-aminopropyltriethoxysilane (APTES), as linker. The amine-magnetite nanoparticles enable the covalent conjugation of a paramagnetic gadolinium complex Gd- (DTPA). The surface of these nanoparticles was functionalized with DTPA via carbodiimide chemistry; where the DTPA acts as complexing agent for the introduction of gadolinioum ions on the surface of the nanomaterial. Morphology, particle size, structure and magnetic properties of the as-prepared nanocomposites were charcaterized using X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), Raman Spectroscopy, Transmission Electron Microscopy (TEM), Vibrating Sample Magnetometer (VSM), Fhotoluminiscence and Magnetic Force Microscopy (MFM) to define their physical properties in the synthesis and their application as contrast agents and hyperthermia.

POS 13

MULTIPLE INJECTIONS OF MAGNETIC IRON OXIDE NANOPARTICLES IN MICE: TOXICITY STUDY

Monica Pereira Garcia, Vanessa Carvalho Moreiraa, Mariana Marzullo Pedreirab, Jaqueline Rodrigues Silva, Ricardo Bentes Azevedo

University of Brasilia, Brasília,DF, Brazil

Introduction: Magnetic iron oxide nanoparticles coated with meso-2,3-dimercaptosuccinic acid (DMSA-MNPs) constitute an innovative and promising approach for delivering cell-specific heat and as potential platforms to provide both imaging, as contrast agents in nuclear magnetic resonance images, and therapy, like in hyperthermia. Biocompatibility and toxicity of these nanoparticles must be analyzed mainly when multiples injections are necessary. **Methods**: Using hematological and serum biochemical analysis, as well as cell toxicity assay in bone marrow and peritoneal macrophages we studied the biocompatibility and toxicity of DMSA-MNPs after multiple injections in mice. Mice received four applications of 100 μL of DMSA–MNPs (1,95 g/L) suspension through the tail vein, every 15 days. After that they stayed 45 days without any application. **Results**: Hematological and serum biochemical results support that DMSA-MNPs were biocompatibility while preserving both hepatic and renal normal activity once no statistically significant difference were showed in the erythrogram and leukocyte counts, as well as for liver and kidney enzymes and serum iron of experimental animals compared with the control group. Moreover, DMSA-MNPs had no toxic effects on bone marrow and peritoneal macrophages, as evidenced by Flow Cytometry using Annexin V-FITC/Propidium Iodide assay. The number of living cells in the bone marrow was greater than 13% compared to the number of living cells in the control group. The type of death was predominantly by apoptosis, representing 99.86% of dead cells, while necrosis was only 0.14%. In peritoneal macrophages was also observed an increase in the percentage of living cells. Difference between the groups was not significant since the percentage of living cells in the control group was 96.55% whereas the experimental group was 96.92%. The predominant cell death pathway was apoptosis in both groups. **Discussion**: After administration of substances nanostructured, it was possible to observe significant variation in leukocyte populations representing a mild and temporary inflammation that occurs in a time and dose dependent. Here, leukocyte counts did not change. Liver injury is the most common manifestation of drug toxicity and accounts for more than 50% of cases of acute liver failure. Here, we observed only a slight decrease in the values of gamma-glutamyl transferase, what is not indicative of liver disease. Despite the multiple applications, no increase in serum iron levels was found what could cause damage to cell membranes, proteins and DNA. **Conclusion**: Our results showed that multiple injections of DMSA-MNPs are biocompatible and not toxicity, supporting their application as promising nanomaterial platform for biomedical use.

POS 14

ANTI-TUMOR EFFECT OF HYPERTHERMIA IN COMBINATION WITH THE EXTRACT OF FERMENTED SOYBEAN

Kimiko Yoshimizu[1], Tohru Takahaashi[2], Takeo Hasegawa[3], Itsuo Yamamoto[4], Haeun Cho[5]

[1]Garden Clinic nakamachi, Tokyo, Japan, [2]Kansai Medical University, Hirakata, Osaka, Japan, [3]Louis Pasteur Center for Medical Research, Kyoto, Japan, [4]Kyouei Hyperthermia Co, Ltd, Iwaki, Japan, [5]University of Minnesota, Minneapolis, MN, USA

Introduction. Mild heating of tumors or local heating at fever range temperatures has been known to enhance anti-tumor immunity. The intestinal microbiota profile and intestinal immunity is closely related to the systemic immunity. The extracts of fermented soybeans (FS) improves the intestinal microbiota composition, thereby they increase the intestinal immunity. The purpose of the present study was to elucidate whether anti-tumor immunity can be enhanced by the combination of tumor heating and FS treatment.

Methods. Lewis lung carcinoma grown s.c. in the legs of C57BL/6 were heated at 41-42°C for 20 min 5 times at 2 days interval using capacitive application of 8 MHz RF. The FS used was the end product of 5-repeated fermentations of soybeans. The tumor bearing mice were orally administered with FS at 10 ml/kg/day. The host mice survival, tumor growth rate, lung metastases, immune cells in spleens, blood cytokines and intestinal immune lymphocyte were assessed.

Results. The combination of tumor hyperthermia and SF was far more effective than either of them alone in suppressing tumor growth, reducing lung metastases and prolonging host survival. Tumor heating markedly increased the NK cell activity in the spleen but the FS treatment caused no visible changes in NK activity. However the combination of tumor heating and FS treatment markedly increased the NK cells activity and CTL cell activity in the spleens and CD4mRNA levels in small intestine. FS treatment markedly increased the IL-6 level in blood of the tumor-bearing mice. FS treatment significantly increased the mRNA for CD4 and IFN-r in small intestines. The combination of tumor heating and FS treatment significantly increased the intestinal INF-mRNA.

Conclusions. Mild hyperthermia of tumor alone and SF treatment alone induced considerable degree of anti-tumor immune response in tumor-bearing mice, and the combination of the two modalities evoked marked anti-tumor immunity.

POS 15

EFFECTS OF VARIATIONS IN BLOOD PERFUSION AND ANATOMY ON MODELLED TEMPERATURE DISTRIBUTION DURING WIRA HYPERTHERMIA

Michael Jackson[1,2], Victoria Timchenko[2], Zain Khan[2], Olivia Ng[2]

[1]Prince of Wales Hospital, Randwick, NSW, Australia, [2]University of New South Wales, Kensington, NSW, Australia

In combined treatments such as hyperthermia and radiotherapy, temperature control is crucial to provide an optimum and safe heat dose, and at the same time to avoid overheating of normal tissues, thus minimizing the risk of skin burns and other side effects. Computational modelling can provide the means for treatment planning by predicting the values of temperatures inside the tissues which cannot be assessed in-vivo.

A computational model of coupled radiation and heat transfer was developed to calculate the temperatures in superficial tissues during radiative heating by a water-filtered infrared-A (wIRA) irradiator. This irradiator is equipped with a thermographically controlled system consisting of an infrared camera and a computer-controlled feedback system. Our computational model allows us to simulate real-time control of the wIRA radiation unit by switching the heating on and off in a defined range of maximum skin temperature (42°C – 43°C).

This model takes into account the volumetric heat generation due to absorbed radiation, transient heat conduction, blood perfusion and metabolic heat generation. Three dimensional simulations were undertaken to analyse the effects of the blood perfusion in the skin tissues on the temperature distribution. Scar tissue has been shown to affect heat transfer and therefore different sizes of surgical scar and different levels of baseline tumour perfusion compared to normal tissue were investigated.

It was shown that changes in perfusion and variations in anatomy within the treated volume lead to temperature inhomogeneity on the skin surface and in the deeper tissues.

POS 16

ARRHENIUS KINETIC ANALYSIS OF DYNAMIC MR SIGNAL CHANGES IN A PROTEIN COAGULATION PHANTOM

Chris MacLellan[1], Ken-Pin Hwang[1], R. Jason Stafford[1,2]

[1]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas, USA

Introduction: Several MR parameters exhibit abrupt nonlinear changes in their temperature dependence that have been associated with irreversible changes in tissue state. In this work, a technique is investigated for estimating the Arrhenius kinetic parameters that characterize these changes using Magnetic Resonance Temperature Imaging (MRTI) monitoring. The feasibility of this technique is evaluated in a protein coagulation phantom where a nonlinearity or breakpoint in the temperature dependence of the T1-weighted signal serves as the effect of interest. The recovered parameters are compared to literature values and the area of coagulation identified on post-treatment imaging.

Methods: A protein coagulation phantom was created using 1:1 mixture of egg white and distilled water combined with 1.5% agarose. Thermal lesions (N=11) were created using a water-cooled diffusing laser fiber (980nm; 7-15W; 3-13 minutes) while MRTI was acquired using a multi-echo spoiled gradient echo technique on a 3T clinical MR scanner. A breakpoint in the T1-weighted signal was identified at approximately 60°C on a pixel by pixel basis by applying a 4 parameter bilinear fit to each temperature vs. signal curve. The temperature histories before and after each breakpoint were classified as non-coagulated or coagulated, respectively. These classifications were used in a coupled Arrhenius thermal dose-logistic model to find the maximum likelihood kinetic parameters that define the occurrence of the breakpoint. The recovered parameters were compared with independent measurements of the coagulation of egg white. 6 additional ablations were performed in an identical phantom where the region of post-treatment T1 change was segmented and found to reflect the region of visual coagulation. The region predicted by the maximum likelihood parameters was quantitatively compared to the segmented region using the Dice Similarity Coefficient (DSC) and Mean Distance to Agreement (MDA).

Results: The activation energy recovered from the breakpoint analysis was 405 kJ/mol and was contained within the range of literature values (248-439 kJ/mol). The DSC and MDA between the model predicted region and the segmented area of post-treatment change in T1 were 0.83 and 0.92 mm, respectively.

Conclusion: An objective methodology was applied for identifying breakpoints observed during MRTI monitoring and an optimal set of kinetic parameters was found that characterized the breakpoints. These parameters are consistent with literature values and agree with other observed alterations in phantom state (visual coagulation and T1 change). Further investigation using multi-parametric monitoring will allow examination of whether these and other nonlinear changes provide unique information compared to traditional post-treatment indicators of thermal damage.

POS 17

MAGNETIC HYPERTHERMIA CONTROLLED RELEASE OF DOXORUBYCIN FROM MAGNETIC FOLATE-TARGETED LIPOSOMES

Emilio Ramos Cintra, Marcilia Viana Pavam Gonçalves, Relton Romeis Oliveira, Thais Leite Nascimento, Andris Figueiroa Bakuzis, Eliana Martins Lima

Universidade Federal de Goias, Goiania,GO, Brazil

Current treatments using anticancer drugs are associated with poor specificity, high toxicity and incidence of adverse effects. Encapsulation and tumor targeting of these agents in nanostructured systems is a widely used strategy to overcome such drawbacks. Among the drugs used for cancer treatment, doxorubicin (DXR) is highlighted as the choice treatment for several tumors. However, high toxicity, especially cardiotoxicity, and low penetration into solid tumors still limit its clinical use and efficacy. Due to the extensive blood flow and vascular permeability of tumors, nanostructured drug delivery systems such as liposomes are able to transport drugs into the tumor region. Liposomes can reach the tumor passively or may have their surface modified by ligands that are rapidly taken up by the targeted tissues. In the case of tumors overexpressing folate receptors, the attachment of molecules with high affinity for folate receptors on the liposome surface may lead to the active uptake of these structures.

In this work we co-encapsulated dextran coated magnetic nanoparticles (DMN) and DXR in folate-targeted liposomes. Our choice was motivated by the fact that superparamagnetic iron oxide magnetic nanoparticles with chemically modified surface have been used *in vivo* for several applications such as contrast agent in image resonance, immunoassays, hyperthermia, drug release and cell separation. These particles can be controlled using an external magnetic field. Thus, it is possible to position and monitor the localization of the particles following administration with the application of an external AC magnetic field. This technique allows an increase in temperature of tumor cells from 41 to 46°C without damaging neighboring tissues. We prepared magnetic liposomes by the lipid film hydration technique. Liposomes containing DMN were prepared by hydrating the lipid film with magnetic fluid. DXR was encapsulated into magnetic liposomes by pH gradient. Free drug and non-encapsulated DMN were separated from the loaded vesicles by size exclusion chromatography. Drug encapsulation efficiency (EE%) was determined by spectrophotometry. Magnetic nanoparticles EE% was determined using the vibrating sample magnetometer (VSM) technique. Doxorubicin EE% in liposomes containing magnetic nanoparticles was 85% for a lipid:drug molar ratio of 10:1 when 64 mM phosphatidylcholine was used. We demonstrated that a high amount of DXR can be co-encapsulated with magnetic nanoparticles within liposomes, employing a simple technique, which opens perspectives for a clinical therapeutic use for the newly developed liposome-based nanocarrier.

POS 18

THERMOCHROMIC PAINT FORMULATION AND PHANTOM TO OPTIMIZE THERAPEUTIC ULTRASOUND EXPOSURES FOR BONE CANCER THERAPY

Ayele H Negussie[1], Navid Farr[1], Ari Partanen[1,2], Li Piin Sung[3], Avinash Eranki[4], Andrew S Mikhail[1], Brad J Wood[1]

[1]Center for Interventional Oncology Radioloy and Imaging Sciences, CC, NIC, NIH, 9000 Rockville PIke, Bethesda, MD, USA, [2]Clinical Science MR Therapy, Philips,, Andover, Massachusetts, USA, [3]National Institute of Standards and Technology, Gaithersburg, MD, USA, [4]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Health System, Washinton, DC, USA

Introduction: Materials that change color in response to temperature changes (thermochromism) have unique importance for analytical, industrial, and medical applications as, e.g., a safety indicator in thermally sensitive systems and on reporting thermal history. High intensity focused ultrasound (HIFU) enables highly localized, non-invasive thermal ablation of certain tumors. However, a challenge of hepatic tumor HIFU requires transmission of sufficient therapeutic energy through the ribcage, while minimizing heat damage to bone, or symptoms of bone heating. Development and validation of models and tools to better inform pre-treatment planning is highly desirable to optimize HIFU application. Controlled experiments that display temperatures and have materials with similar geometries to human bone are required.

Herein, we report on a thermochromic paint that does not change its color below human body temperature and gradually and irreversibly changes color between 35 and 65, as a thermal reporter.

Methods: Temperature-indicating paint containing thermochromic ink was formulated. The paint has the property of gradually but permanently changing color with increasing temperature. Using 3D-printed bone-mimicking phantoms (BMP), four thin coatings of paint were applied with 30 minutes between each coating to allow for the paint to dry. Then, each painted BMP was immersed in a hot water bath (temperature ranging from 35-65°C at 5°C intervals) for 30s and the resulting color density was measured using Spectro-Guide (BYK, Columbia, MD). For HIFU experiments, the painted BMP was embedded in soft tissue-mimicking phantom and submerged in 40 °C deionized and degassed water. HIFU exposures were applied using a pre-clinical HIFU system, targeting locations 1cm or 2cm behind the bone phantom at two acoustic power levels (20 and 30W) for 30 or 60s in continuous wave mode.

Results: For all painted BMPs the color density increased with increasing temperature, exhibiting sharp change in color density at around 65 °C, near the instant cell death threshold. Qualitative assessment of achieved maximum temperature was obtained by evaluation of color change post-HIFU. Both the magnitude and the spatial extent of color change corresponded with the HIFU exposure parameters. The color density increased with higher energy HIFU exposures, and the area of color change increased with longer HIFU exposure times.

Conclusion: A thermochromic paint formulation that gradually and irreversibly changes color upon temperature elevation was developed and used in the characterization of ablative HIFU bone cancer applications. This may be useful in characterization, risk mitigation, and optimization of intercostal HIFU sonication methods and numerical models.

POS 19

METAL FOAM BASED REWARMING OF VITRIFIED TISSUES SYSTEMS

Navid Manuchehrabadi[1], Meng Shi[2], Aiden Carley Clopton[1], Jinbin Qui[2], Feng Xu[2], Tian Jian Lu[2], John Bischof[1]

[1]University of Minnesota, Minneapolis, Minnesota, USA, [2]Xi'an Jiaotong University, Xian Shi, Shaanxi Sheng, China

Tissues have been successfully vitrified by loading high molarity (6–8.4 M) cryoprotective agents (CPAs) such as VS55, DP6 and even glycerol at critical cooling rates of 2.5, 40 and 85 °C/min respectively. However, successful rewarming from the vitrified state remains challenging with standard convective methods as it requires critical warming rates (CWR) of 55, 185 and $3.2x10^4$ °C/min respectively to avoid devitrifiation. Furthermore, the warming rates must be spatially uniform to avoid thermal stresses ≥ yield stress (3.2 MPa), which can crack the tissue. By achieving faster yet sufficiently uniform warming rates, CPA concentration can be reduced thereby reducing chemical toxicity and allowing more tissues to be preserved and stored by vitrification. Here we present a new method of ultra-rapid rewarming of vitrified biomaterial by inductively warming metal foams embedded in vitrified samples utilizing radiofrequency (RF) fields. In inductive heating, eddy currents heat the metal foams, but not the other material by means of non-contact electromagnetic induction. This yields the benefits of rapid heating and easy manipulation. The frequency of current used depends on the object size, material type and the penetration depth. Here we tested copper foamdue to its high electrical and thermal conductivity. Skin depth of copper is calculated at 360kHz, the frequency of operation, to be 109 μm. This means that the foam should be at least 450 μm to ensure maximum efficacy. Copper foams (1.8 mL) with different porosities of .89, .94 and .97 at RF setting of (360kHz, 20 kA/m) were deployed directly into a cryovial filled with VS55 (8.4 M). Controlled cooling to the vitrified state was achieved at rates ≥10°C/min. Once vitrified, standard convective warming was compared directly to RF rewarming. RF warming rates up to 2000 °C/min and specific absorption rates (SAR) ≥ 100 W/g Cu were experimentally measured. This compares to only 100 °C/min, which is < CWR of DP6 and glycerol, by convective thawing in 37°C water bath. Computational modeling suggests that tissues up to 4 mm thick can be warmed by this approach without cracking. The ultra-rapid rewarming has the advantage of faster rewarming than traditional methods, however, it is only applicable to tissues with thin and simple geomtries such as arteries, heart valves or skin.. In the future we will study the biological (*i.e.*, viability) limits of this technology; by finding the lowest possible concentrations of CPA that still allow vitrification prior to deploying ultra-rapid warming technology.

POS 20

COMBINING DOXORUBICIN AND HYPERTHERMIA INCREASES CYTOTOXICITY IN HCT116 CELLS.

Sanem Ozayral, Anirudh Sharma, Robert Ivkov

Johns Hopkins University School of Medicine, Maryland, USA

Background: Studies have shown that combining doxorubicin with hyperthermia has better outcomes in the clinic for many gastrointestinal cancer patients. Doxorubicin, a common chemotherapy agent, induces cell death via DNA intercalation, production of reactive oxygen species or cell cycle arrest. Hyperthermia, exposing tumors to elevated temperatures, could induce cell death by denaturing proteins. Enhanced cytotoxicity can be achieved by this combination even at low doses of the chemotherapeutic agent. Therefore side effects of doxorubicin such as cardiotoxicity can be reduced. Chemo resistant cell lines become more sensitive to the treatment when doxorubicin is combined with hyperthermia. It has been shown that combination treatments are more effective, however it has not been broadly studied how the sequence of the treatments affects cytotoxicity. Here we report the results comparing relative toxicity of simultaneous or sequential hyperthermia and doxorubicin treatments on colorectal cancer cells in tissue culture.

Methods: Human colorectal cancer cell line (HCT116) were grown in McCoy's 5A media and treated with water bath hyperthermia by exposing cells to temperatures ranging from 41°C - 45°C for 60 minutes. HCT116 cells were treated with different doses of doxorubicin ranging from 0.1-1.25 μg/ml for 90 minutes. Three different combination treatments were carried out: 1) treated with doxorubicin followed by water bath hyperthermia 2) treated with water bath hyperthermia and then exposed to doxorubicin 3) doxorubicin and water bath hyperthermia simultaneously. In all, treatment times were 90 minutes for doxorubicin and 60 minutes for water bath hyperthermia. Clonogenic survival assays were used to evaluate the cytotoxicity.

Results: Single-modality exposure with water bath hyperthermia or doxorubicin demonstrated dose-dependent toxicity reducing single cell surviving fractions to 0.01% and 15±10% at the highest doses of heat or doxorubicin, respectively. Single cell surviving fractions were measured 47±2% or 29±5% with water bath hyperthermia at 42°C or 0.5μg/ml doxorubicin, respectively. For sequential exposure with hyperthermia and doxorubicin, surviving fractions were comparable regardless of the sequence and reduced to 7±2%. However, simultaneous exposure was consistently more toxic than either sequential exposures, producing single cell surviving fractions measured to be 1.5±0.7%, a ten-fold reduction over single agent exposure at the same doses.

Conclusion: Chemotherapy combined with hyperthermia exposure always increases cytotoxicity compared to single agent exposure but the combination is most effective when the treatments are carried out simultaneously.

POS 21

COMBINED MAGNETIC HYPERTHERMIA AND IONIZING RADIATION INDUCES AN ABSCOPAL EFFECT

Jacqueline Stewart, Mikko Helenius, Anilchandra Attaluri, Elliot Mackrell, Anusha Badathala, Monica Garcia, Viviana Barquet, Sai Gargi, Preethi Korangath, Robert Ivkov

Johns Hopkins University, Baltimore, MD, USA

Background: Demonstrations of abscopal effects following radiation therapy (RT) of solid tumors have recently garnered significant attention. Focal heat therapy (HT) combined with RT offers additional potential to induce immune-mediated abscopal effects, as cellular damage resulting from HT increases the release of heat shock proteins in the tumor microenvironment potentially stimulating a downstream cascade of immune responses. Magnetic hyperthermia (MHT) can be used to produce localized heat inside the tumor. Magnetic iron oxide nanoparticles (MIONs) can generate intense heat when exposed to alternating magnetic fields (AMFs). We aim to determine the relationship between tumor burden (volume) and therapy (MHT+RT) to elicit, and to identify the tumor-associated cell populations involved in an abscopal response in a mouse cancer model.

Methods: Murine colorectal cancer (CRC) cells, CT26, were used. Sensitivity of the cells to RT, HT, and RT+HT was characterized with clonogenic cell survival assay . Immune-competent Balb/c male mice bearing two bilateral subcutaneous CT26 tumors in the thigh were used for *in vivo* studies. One of the tumors designated 'focal' received treatment, whereas the other, 'distal', did not. Mice were randomly divided into four cohorts – control, RT, MHT, and MHT+RT. Analysis of archival data from prior studies was used to determine target tumor volume at time of treatment. RT and MHT doses were study-design variables. Both tumors were monitored for response to treatment with caliper measurements. Flow cytometry was used to analyze tumor cell populations.

Results: CT26 cells demonstrate dose dependent response to both RT and HT, but significant sensitivity to RT+MHT at relatively mild doses of 2 Gy and 42°C (30 min). Abscopal response to RT was most pronounced when primary tumor volume ranged between 0.16-0.26 cm^3 at time of treatment.

Conclusions: Studies are ongoing, and preliminary data suggest that an abscopal response is variable, and depends on tumor burden at time of treatment for both RT and RT+MHT. Conversely, MHT alone demonstrated no measurable abscopal effect. Results obtained from flow cytometry and other assays will be presented.

POS 22

3D PRINTED TISSUE-MIMICKING THERMOCHROMIC PHANTOM OF THE LUMBAR SPINE FOR PRE-CLINICAL TESTING OF MRGFUS ABLATIONS OF THE FACET JOINT AND MEDIAL BRANCH NERVE

Hari Trivedi, Derrick Gillan, Matthew Adams, Aaron Losey, Chris Diederich, Eugene Ozhinsky, Matthew Bucknor, Viola Rieke

University of California, San Francisco, San Francisco, USA

Background

Current therapies for lumbar facet arthropathy are invasive and often require repeat treatments. There is strong evidence that MR-guided focused ultrasound (MRgFUS) could be a safe and effective non-invasive method of facet joint ablation, however it is not yet FDA approved largely due to a lack of pre-clinical data. The goal of this project is to develop a thermochromic tissue-mimicking phantom of the lumbar spine to investigate the feasibility of MRgFUS ablation of the facet joint and medial branch nerve.

Methods

A 3D model of the lumbar spine was segmented from a de-identified CT scan. Multiple 3D-printed materials including TangoBlack, VeroWhite, ABS plastic (Stratasys, Israel), and gypsum (3D Systems, CA, USA) were tested for speed of sound and linear sound attenuation coefficient using a through-transmission technique. A thermochromic tissue-mimicking phantom (TTMP) designed to change color as a function of temperature (from 40 - 64°C) was created and the 3D-printed spine was embedded within. Multiple high energy sonications ranging from 1800 – 2700 J were targeted to the facet joints and medial branch nerve location using an ExAblate MRgFUS system (Insightec, Israel) connected to a 3T MR scanner (GE). Temperature was monitored using a standard proton resonant frequency shift technique. The phantom was dissected and the sonication targets were assessed for color change as compared to the expected region of ablation on MR-thermometry. The spinal canal and neural foramina were carefully examined to detect any unexpected heat deposition.

Results

The calculated sound attenuation coefficients were 131.6, 44.7, 134.1, and 271.4 Np/m-MHz and speeds of sound were 1974.3, 2435.8, 1982.7, and 2122.4 m/s for TangoBlack, VeroWhite, ABS plastic, and gypsum respectively. Of these, gypsum was nearest to published values for cortical bone and was therefore used to 3D-print the lumbar spine. Following sonication, dissection of the TTMP revealed good concordance between the regions of color change within the phantom and expected areas of ablation. No heat deposition was observed in critical areas including the spinal canal and nerve roots.

Conclusion

An anatomic model of the human lumbar spine was successfully 3D-printed using gypsum and embedded within a thermochromic tissue-mimicking phantom. Ablated regions in the phantom correlated well to expected ablations based on MR-thermometry. No near or far-field heat deposition was detected in non-targeted areas. These findings demonstrate the utility of an anatomic spine phantom in developing ideal sonication trajectories and energies for facet joint and medial branch nerve ablations.

POS 23

TISSUE FRACTIONATION USING MICROSECOND-LONG HIFU PULSES ON A CLINICAL MR-HIFU SYSTEM

Avinash Eranki[1,2], Navid Farr[2], Ari Partanen[3], Karun V.Sharma[1], Christoper T.Rossi[1], AeRang Kim[1], David Woods[2], Pavel Yarmolenko[1], Peter C.W.Kim[1], Bradford J.Wood[2]

[1]Childrens National Health System, Washington, DC, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]Philips, Andover, MA, USA

INTRODUCTION

High intensity focused ultrasound (HIFU) is a technique that can noninvasively heat and necrose a targeted site with minimal or no damage to intervening tissues. Recently, HIFU methods have been used to mechanically disrupt tissues at the focus. These techniques use sonication pulses with low duty cycles (<5%) and high acoustic pressures. In this experimental work, we study the effect of hundreds of microsecond-long HIFU pulses on *ex vivo* porcine liver using a clinical magnetic resonance imaging (MRI) - guided HIFU (MR-HIFU) system.

METHODS & MATERIALS

Acoustic power, number of cycles/pulse, pulse repetition frequency (PRF), and total sonication time were each varied while keeping other sonication parameters constant. Each porcine liver tissue sample was sonicated in a 3×3 grid pattern with 1 mm spacing. Temperature and thermal dose were also quantified at the focal region using MRI. Sonicated lesions were histologically analysed using H&E for lesion structure.

RESULTS & CONCLUSION

Our results systematically demonstrated the ability to produce three distinct types of physical lesions in *ex vivo* liver tissue: i. solid-thermal, ii. paste-like, and iii. vacuolated. Sonication parameters at PRF greater than 20 Hz resulted in collateral tissue damage beyond the focal region characterized by whitened tissue, even though the tissue was intact in H&E staining. Significant differences in temperature and thermal dose were observed between the parameter set with total sonication time of 1630.8 seconds and all other parameter sets. There were additional significant differences between the sonication parameter sets with PRF of 60 Hz compared to other parameters sets. The lesions created using this regime of HIFU produced several partially lysed cells. In tumors, this may release tumor-specific antigens into the cytoplasm and potentially attracting a strong anti-tumor response. A clinical MR-HIFU system was utilized to generate reproducible mechanically fractionated lesions as well as to produce distinct lesion types and thermal bioeffects in *ex vivo* liver tissues. These results could guide future immunological studies involving HIFU due to the ability to produce varying lesion types, which may or may not attract favourable anti-tumor immune response. Furthermore, these results may inform and guide clinical translation and the selection of requisite sonication parameters to produce spatially precise lesions in different tissues using a clinical MR-HIFU system.

POS 24

THE LINEAR-QUADRATIC FORMULA TO MODEL HYPERTHERMIC RADIOSENSITIZATION OF CARCINOMA CELLS *IN VITRO*

Taylor Ibelli, Anilchandra Attaluri, Budri Abubaker-Sharif, Haoming Zhou, Madhav Seshadri, Monica Garcia, Robert Ivkov

Johns Hopkins University, Baltimore, Maryland, USA

Biological modelling of radiotherapy and hyperthermia combination therapies may help to predict cellular dose-responses in various cancer cell lines. The linear-quadratic (LQ) formula, $\frac{S_d}{S_0} = e^{-(\alpha d+\beta d^2)}$ models the radiosensitization of cell lines based on clonogenic survival, where d is the radiation dose, S_d and S_0 are surviving fractions at dose d and d=0, respectively, and α and β are experimentally derived parameters for the linear and quadratic terms. While the α/β ratio is used to predict optimal dosages per fraction in radiotherapy alone, our goal is to investigate whether α/β parameters can be applied to predict the efficacy of multimodal combination treatments. The current study aims to evaluate the effectiveness of the LQ model, using α, β and α/β ratio as parameters, in predicting the radiosensitization of water bath (WB) hyperthermia treatments amongst pancreas (Panc01, Panc02, MiaPaca2), colon (HCT116), mammary (MDA-MB231), and prostate (LAPC4, PC3, MycCap) carcinoma cell lines. Our approach is to curve-fit clonogenic survival after all cell line treatments (radiotherapy alone, WB hyperthermia alone, and radiotherapy combined with WB hyperthermia) using a weighted least squares fitted polynomial equation. The derived α, β, and α/β ratios from the polynomial equation can be used to compare the differences in sensitivities to multimodal therapy among all carcinoma cell lines. Overall, the LQ formula may help to predict radiosensitivity to WB hyperthermia of various carcinoma cell lines and improve fractionation schedules.

POS 25

POTENTIAL PATHWAY OF HEPG2 CELLS TOWARD DEATH WITH HYPERTHERMIA AND ROS INDUCED BY MAGNETIC HYDROXYAPATITE NANOPARTICLES AND ALTERNATING MAGNETIC FIELDS

Chun Ting Yang[1,2], Keng Yuan Lee[1], Fan Qi Meng[1], Robert Ivkov[2], Feng Huei Lin[1]

[1]National Taiwan University, Taipei, Taiwan, [2]Johns Hopkins University School of Medicine, Baltimore, USA

Purpose: Hepatocellular carcinoma (HCC) is the most common cancer in the Asian and African areas and there are new cases also found in the United States. As the disease progresses, the symptoms get worse in the late stage and difficult to cure. Hyperthermia means that human body tissue is exposed to high temperatures (up to 43°C) to damage and kill cancer cells. The conventional cancer therapy such as chemotherapy and radiotherapy are usually combined with hyperthermia to increased oxygen delivery at the tumor site to cancer cells death. However, hyperthermia could not heat homogeneous and provide the enough energy in the body deep region. This study aimed to provide a MHT method to kill HepG2 cells via mHAPs as a themo-seed under Alternative Magnetic Field (AMF) induction. The mechanism of cancer cells apoptosis/death with MHT are investigated. **Methods and Materials:** HepG2 cells with mHAPs were elevated to 43 ± 0.5°C for 30 min under AMF induction to provide therapeutic temperature. mHAPs were synthesized as a themo-seed by a co-precipitation method. The molecular mechanisms and signaling pathway for killing cancer cells by MHT were analyzed using *in vitro* study. **Results:** When HepG2 cells treated by MHT, a microarray probe shows 1,532 genes were upregulated and 544 genes were downregulated at four hr. The DNA repair gene, IL-17 and apoptosis gene, FOS and JUN were downregulated and decreased gradually at sixth hr. The flow cytometry shows that MHT group may induce apoptosis or necrosis in HepG2 cells with DNA damage, but not AMF treatment. Western blot shows cancer cells receiving thermal stress to death through p-P38 signaling pathway. **Conclusions:** The research suggests a cancer therapy technology, a MHT model, to raise cure rate of the clinical treatment for Hepatocellular carcinoma (HCC) which presents no symptoms, hard to diagnose in the early stage and high death rate. This approach provides a therapeutic temperature in the tumor local area, induces DNA damage and inhibits p-P38 such that the HepG2 cancer cells were successfully killed.

POS 26

INVESTIGATING THE IMPACT OF ALTERNATING MAGNETIC FIELD EXPOSURES ON BIOFILM GROWN ON METALLIC SURFACES: IMPLICATIONS FOR TREATMENT OF PROSTHETIC JOINT INFECTION

Sumbul Shaikh, Imalka Munaweera, Yonatan Chatzinoff, Bingbing Cheng, Cecil Futch, James Howard, Seth Daly, David Greenberg, Rajiv Chopra

UT Southwestern Medical Center, Dallas, Tx, USA

Introduction

Prosthetic joint infection (PJI) is a major challenge in the field of joint arthroplasty due to the presence of bacterial biofilm on infected implants. The accepted treatment for PJI is a revision surgery and multiple weeks of antibiotics. Although effective, the treatment is expensive and negatively impacts patient quality of life. We are developing a non-invasive thermal treatment for PJI employing high frequency (>100 kHz) alternating magnetic fields (AMF). The purpose of this work is to understand how biofilm responds to AMF exposures of varying duration and power, and what components of the biofilm are impacted. Further, the effectiveness of antibiotics when combined with AMF exposures is investigated.

Methods

Biofilms were grown on stainless steel washers using organisms commonly involved in PJI. Washers with biofilm were placed in a custom-built solenoid and exposed to AMF at different powers (20 W) and exposure durations (0 - 15 mins). After exposure, washers were either sonicated to remove bacteria and perform colony counts, stained with crystal violet to evaluate biofilm matrix load, or imaged with scanning electron microscopy and confocal microscopy to acquire images of the biofilm matrix and bacteria. Finally, washers exposed to 0 or 3 minutes of AMF were incubated for 18 hours with ciprofloxacin (0, 0.125, 0.25, or 0.5 ug/ml) to study the influence of the exposures on the effectiveness of the drug.

Results

After 5 minutes of AMF exposure at 20W, >5-log reduction in bacterial count was observed. Crystal violet staining confirmed a loss of biofilm matrix within the first minute of AMF exposure. Confocal and scanning electron microscopy also confirmed removal of biofilm matrix within 1 minute of AMF exposure, and combination studies of antibiotics and AMF demonstrated a 5-log increase in the sensitivity of PAO1 to ciprofloxacin.

Conclusion

These initial studies confirm AMF exposures are bactericidal to biofilm on metal surfaces. Further, the AMF exposure appears to remove the matrix associated with the biofilm and may explain the increased sensitivity to antibiotics that was observed.

POS 27

A CASE REPORT OF RECURRED HEPATOCELLULAR CARCINOMA PATIENT TREATED WITH RADIO-FREQUENCY HYPERTHERMIA IN CONJUNCTION WITH SORAFENIB

Jee-Hye Kim[1], Jong-Hoon Lee[2], Jong-Cheon Joo[3], Jeong-Bok Lee[1], Chong-Kwan Cho[1], Hwa-Seung Yoo[1]

[1]Daejeon University, Daejeon, Republic of Korea, [2]Woosuk University, Jeonju, Republic of Korea, [3]Wonkwang University, Jeonju, Republic of Korea

Objective: The purpose of this study is to report the effects of radio-frequency hyperthermia cancer treatment in conjunction with Sorafenib on hepatocellular carcinoma patient.

Method: The patient was diagnosed with hepatocellular carcinoma at S6/7 and treated with right posterior sectionectomy. After 4 months, tumor recurrence was found at S4, 5 and 8. After transarterial chemoembolization, the patient was prescribed Sorafenib (proprietary name Nexavar) as well as proceeding with radio-frequency hyperthermia. The clinical outcomes were measured by computed tomography, laboratory findings including tumor markers (AFP, PIVKA-II), natural killer (NK) cell activity, and numeric rating scales (NRS).

Results: After the treatment, tumor size was decreased accompanying by reducing the level of tumor markers (AFP, PIVKA-II). Major clinical symptoms were improved with increasing NK cell activity. There were no adverse events based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Conclusion: This case suggests that radio-frequency hyperthermia has synergistic effect for the treatment of hepatocellular carcinoma patient in conjunction with Sorafenib.

Key words: Hepatocellular carcinoma, Radio-frequency hyperthermia, Sorafenib, -fetoprotein, PIVKA-II, Natural killer cell activity.

POS 28

MODELING AND MEASUREMENT OF HEATING PATTERNS OF A HIFU APPLICATOR: PRELIMINARY RESULTS

Raquel Martinez[1], A. Ramos[2], A. Vera[3], L. Leija[3]

[1]Department of Biomedical Engineering, Polytechnic University of Chiapas, Chiapas, Mexico, [2]Group of R&D "Systems and Ultrasonic Technologies", Institute for Physical and Information Technologies, CSIC, Madrid, Spain, [3]3Electrical Engineering Department, Bioelectronics Section, CINVESTAV-IPN, Mexico City, Mexico

Keywords — **ultrasonic heating, finite element method, heating modeling, HIFU heating, thermography**

It is well known that, in focused ultrasonic systems, the radiated beams through tissues converge around a focal point. This phenomenon produces a temperature increment over 56°C in few seconds, at the focus by the mechanical waves energy transformation into heat, due to acoustic absorption in the tissue. This can originate thermal coagulation, instantaneous cell damage or instantaneous ablation [1]–[3]. These possible effects make high-intensity focused ultrasound (HIFU) a suitable therapeutic tool for delivering localized energy to treat benign and malignant tumors in a non-invasive way without damaging surrounding tissues. A previous study reported that by adding a conical applicator, HIFU energy could be delivered more efficiently, thus notably reducing the electrical power needed to drive the device and reaching haemostasis temperatures [4], [5] which is based on ultrasound propagation FEM modelling using a 2-MHz HIFU transducer.\n\nMATERIALS AND METHODS: Acoustic field characterisation and numerical simulations in water were performed with and without the proposed applicator. Parameters such as form factor, ellipsoidal shape ratio, and Euclidean distance were used (among others. Besides, results from both, acoustic propagation modeling and ultrasonic characterization of this applicator, are necessary, previously to accurately investigate the resulting heating patterns created by this HIFU device. The aims of this work are to obtain a simulated heating pattern by means of finite element method (FEM) modeling and also to measure the applicator surface temperature with an infrared camera. First, ultrasonic propagation was performed in order to use their resulting data as inputs for the heating modeling. Then, for the experimental comparison, the ultrasonic device was driven with only 20 W during 120 s and thermographic pictures (using model Ti32, Fluke Corporation®) were taken every 15 s for the conical emitting surface. Preliminary results have shown that in both, simulated and experimental analyses, the heating concentrates around the focal point; however, thermographic images depicted a slightly larger heating area over the applicator surface, probably due to ultrasonic non-linear propagation, and some fast thermal diffusion.

[1] G. T. Haar and C. Coussios, "High intensity focused ultrasound: physical principles and devices," *Int J Hyperth.*, vol. 23, no. 2, pp. 89–104, 2007.

[2] G. ter Haar, "Therapeutic applications of ultrasound," *Prog. Biophys. Mol. Biol.*, vol. 93, no. 1–3, pp. 111–129, 2007.

[3] C. J. Diederich and K. Hynynen, "Ultrasound technology for hyperthermia," *Ultrasound Med. Biol.*, vol. 25, no. 6, pp. 871–887, 1999.

[4] R. Martínez-Valdez, A. Ramos Fernández, A. Vera Hernandez, and L. Leija Salas, "Design of a low power hybrid HIFU applicator for haemostasis based on acoustic propagation modelling.," *Int. J. Hyperthermia*, pp. 1–11, Dec. 2015.

[5] S. Vaezy, S. Vaezy, F. Starr, E. Chi, C. Cornejo, L. Crum, and R. W. Martin, "Intra-operative acoustic hemostasis of liver: production of a homogenate for effective treatment," *Ultrasonics*, vol. 43, no. 4, pp. 265–269, 2005.

MON 1

MODELING ENDOCRINE RESISTANCE IN BREAST CANCER – A SYSTEMS BIOLOGY APPROACH

Robert Clarke

Georgetown University Medical Center, Washington DC, USA

Background: 70% of newly diagnosed breast cancers express the oestrogen receptor-alpha (ER; ESR1) and most receive an endocrine therapy that inhibits ER action. These treatments are usually in the form of an antiestrogen (competitive inhibitor of ER action) or an aromatase inhibitor (blocks the production of oestrogen). Despite these therapies conferring an increase in overall survival, de novo and acquired resistance limit this benefit for many patients. More women die each year from ER+ breast cancer than from any other breast cancer subtype.

Methods: We have generated data from multiple high and low throughput platforms and used both computational and mathematical modelling to capture key features of the molecular signalling regulated by ER. More specifically, the signalling is modelled in the context of its ability to integrate, coordinate and control the function of key cellular processes.

Results: We identified a series of integrated functions that regulate and coordinate the cellular responses to the stresses induced by antiestrogen therapy or oestrogen withdrawal. For acquired resistance, key functions include adaptation of cellular metabolism, activation of the unfolded protein response (UPR), autophagy, and cellular proliferation, and suppression of apoptosis. Knowledge guided differential dependency network modelling of transcriptomic data identified key topological features of the underlying molecular signalling. Transitions among ER-driven phenotypes, reflecting the activities of a critical 'master regulator' of this integrated network, can be modelled as a form of Waddington landscape. This approach is further supported by our data showing that much of the acquired phenotype can be reversed with the use of histone deacetylase and DNA methyltransferase inhibitors. The resulting model implies that drug holidays may improve the activity of endocrine therapies.

Conclusion: A systems approach to data analysis and interpretation led to the construction of a unified hypothesis of molecular signalling and cell functions that alter in response to treatment. This unified hypothesis invokes integrated and coordinated signalling among modules that reflect autophagy, apoptosis, cell metabolism, proliferation, and UPR.

MON 2

IN SITU VACCINATION TO TREAT CANCER USING PLANT-DERIVED VIRAL LIKE NANOPARTICLES FROM COMPEA MOSAIC VIRUS

Steven Fiering[1], Patrick Lizotte[1], Mee Rie Sheen[1], Sourabh Shukla[2], Jack Hoopes[1], Nicole Steinmetz[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [2]Case Western Reserve University, Cleveland OH, USA

Immunotherapy for cancer is making impressive impacts in the clinic. One strategy very relevant to thermal medicine is *in situ* vaccination. This approach puts immunostimulatory reagents into an identified tumor to break the local immunosuppression, stimulate a local anti-tumor approach and most importantly stimulate systemic antitumor immune responses to eliminate metastatic disease. This is essentially an antitumor therapeutic vaccination, because the tumors provide the antigens and the adjuvants are the immunostimulatory reagents, thus "*in situ* vaccination". There are many immunostimulatory reagents that can be used and each has different capabilities. Here we report on plant-derived viral-like nanoparticles from Cowpea Mosaic Virus used in mouse cancer models. These particles are only composed of viral capsid proteins, have no nucleic acids and have no recognized immunostimulatory reagents. However, they are strongly immunostimulatory through unknown pathways and cause dramatic changes in the tumor microenvironment that lead to primary tumor reduction and potent resistance to metastatic tumors. The treatment is immune-mediated but response in the lungs requires different immune components than response in flank tumors of the same melanoma model. Tumor reduction or elimination occurs in many anatomic locations and with multiple tumor types and in multiple strains of inbred mice. Treatment of a primary tumor by direct intratumoral injection mediates robust rejection of a rechallenge with the same tumor. The mechanisms and pathways of immunostimulation are under investigation. In addition to the inherent immunostimulatory adjuvant properties of these nanoparticles, they are a versatile platform to which other reagents for immune modulation can be attached. This demonstration of the value of viral-like nanoparticles for treatment of cancer opens a new avenue of cancer immunotherapy.

MON 3

AMPLIFYING THE IMMUNE CONSEQUENCE OF RADIATION-INDUCED CANCER CELL DEATH TO CONTROL DISTANT TUMORS

Jason Baird[1], Marka Crittenden[1,2], Gwen Kramer[1], Shelly Bambina[1], David Friedman[1], Michael Gough[1]

[1]Earle A. Chiles Research Institute, Portland, OR, USA, [2]The Oregon Clinic, Portland, OR, USA

Background

Though radiation therapy can effectively kill cancer cells in the treatment field, regression of tumors outside the treatment field is extremely rare. Immunotherapy has the potential to amplify the consequences of local therapy to generate systemic immunity. To generate immune responses to cancer cell death, we generally aim for cross presentation of tumor-associated antigens by dendritic cells, as these cells are uniquely able to initiate new immune responses from naïve T cells. However, we demonstrate that cancer cell death induced by radiation results in phagocytosis by tumor macrophages and drives macrophage differentiation into phenotypes that suppress T cell responses.

Methods

We establish tumors in immune competent mice and use CT-guidance to deliver radiation to the tumor with minimal dose to normal tissue. We test these therapies in a range of knockout mice lacking components of the macrophage response to dying cells, along with systemically administered therapeutic antibodies, or along with immune adjuvants delivered directly to the tumor.

Results

We demonstrate that by blocking phagocytic pathways in macrophages that respond to dying cells we can overcome immune suppression, improve local control of the tumor, and generate systemic immunity. As an alternative approach, we tested a range of immune adjuvants for their ability to prevent suppressive polarization of macrophages. We found that ligands that activate the STING (STimulator of INterferon Genes) sensor in macrophages could prevent suppressive differentiation of macrophages and repolarize already differentiated tumor macrophages to pro-inflammatory phenotypes. Local administration of STING ligands to the tumor in combination with radiation therapy resulted in dramatic local tumor regression and control of distant tumors. Local tumor control included both early innate immune destruction of the tumor, and later CD8 T cell mediated control of residual disease, while distant responses were entirely dependent on CD8 T cells.

Conclusions

We propose that therapies targeting the macrophage response to cancer cell death can be provided alongside conventional approaches that improve systemic T cell function, to amplify the immune consequences of local cancer treatment and generate systemic immunity to cancer.

MON 4

LARGE RADIATION FRACTION SIZE, HYPERTHERMIA AND VIRAL –LIKE NANOPARTICLE ENHANCEMENT OF THE ABSCOPAL EFFECT IN A SPONTANEOUS CANINE ORAL MELANOMA MODEL

P. Jack Hoopes[1], Karen Moodie[1], Alicia Petryk[2], James Petryk[1], Nicole Steinmetz[4], Robert Wagner[1], Margaret Crary-Burney[1], Alicea Bursey[1], Ashish Rajan[3], Steven Fiering[1]

[1]Dartmouth, Lebanon, NH, USA, [2]University of Bridgeport, Bridgeport, CT, USA, [3]Oklahoma State University, Stillwater, OK, USA, [4]Case Western Reserve Univeristy, Cleveland, OH, USA

We and others have recently shown that cancer treatments such as radiation and hyperthermia, which were previously believed to have modest immune effects, have the potential to contribute to an effective anti-cancer immune reaction. Using spontaneous canine oral melanoma cancers, we have delivered hypofractionated radiation (6 x 6 Gy), hyperthermia (2 x 43°C / 30 minutes) and/or an immunogenic viral–like nanoparticle (4 x 200 μg local tumor treatments). Preliminary data suggests that a combination of these therapies, possibly in association with other immune modulating agents is capable of stimulating an effective anti-cancer immune reaction that positively correlates with control of both the local tumor and systemic disease.

MON 5

ELICITING IMMUNOGENIC CELL DEATH USING PRUSSIAN BLUE NANOPARTICLE-BASED PHOTOTHERMAL THERAPY AND THE IMPLICATIONS FOR CANCER THERAPY

Elizabeth E. Sweeney, Rachel A. Burga, Juliana Cano-Mejia, Rohan Fernandes

Children's National Health System, Washington, DC, USA

Immunogenic cell death (ICD) is a highly favorable cellular fate in cancer therapy as it not only decreases cancer burden, but can also stimulate an anti-tumor immune response. Therapies that elicit ICD have the clinical potential to treat primary cancer, as well as prevent recurrence and metastasis, when the resultant immunological response is robust. In other cases, when an ICD-inducing therapy generates a less potent anti-tumor response, it can be combined with other complementary immunotherapies, such as immune checkpoint inhibitors, to eradicate disease and prevent future cancers.

Nanoparticle-based photothermal therapy (PTT) has been widely used in the literature to ablate cancer cells *in vitro* and *in vivo*. While many cellular consequences of PTT have been discovered, the study of its subsequent immunological effects and implications in the context of cancer is ongoing. Here, we demonstrate the use of Prussian blue nanoparticles (PBNPs) as agents of PTT to increase cell temperatures and establish gradients of varied regimes of cell death. By varying the concentration of PBNPs used for PTT, we achieve controlled hyperthermic and ablative temperature increases that lead to primarily apoptosis or necrosis depending on temperature, both *in vitro* and *in vivo*. Moreover, we show that PTT can elicit ICD in a panel of cancer cell lines. The detection of ICD is described by various consensus guidelines and is primarily associated by secretion or expression of damage-associated molecular patterns (DAMPs) by cancer cells. We show regimes of ICD as a result of PTT, as measured by two DAMPs of interest: decreased intracellular HMGB1 and increased cell surface calreticulin. Further, we illustrate that the properties of the resultant ICD produced in PTT-treated cancer cells can be used as a prophylactic vaccine. When cancer cells are treated with PTT *in vitro* and then implanted *in vivo*, the animals' immune systems are primed to reject any subsequent tumor challenges.

These data demonstrate the powerful capability of PBNP-based PTT to not only ablate cancer cells, but generate long-lasting immunological memory against cancer recurrence and metastasis, a primary challenge in the field of cancer therapy. Future studies will further elucidate the phenomena addressed in an effort to translate the research to patients.

MON 6

COMBINATION OF FOCAL NANOPARTICLE HEAT THERAPY AND RADIOTHERAPY CREATES IMMUNOLOGICAL RESPONSE GREATER THAN ITS PARTS

Mikko Helenius[1], Jackie Stewart[1], Shu-Han Yu[1], Preethi Korangath[1], James Barnett[1], Anirudh Sharma[1], Sri Kamal Kandala[1], Charles Drake[3,4], Angelo M. De Marzo[2,3], Robert Ivkov[1]

[1]Johns Hopkins University School of Medicine, Department of Radiation Oncology, Baltimore, MD, USA, [2]Johns Hopkins University School of Medicine, Department of Pathology, Baltimore, MD, USA, [3]Johns Hopkins University School of Medicine, Department of Urology, Buchanan Brady Urological Institute, Baltimore, MD, USA, [4]Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

Background: Even with markedly enhanced diagnostic and therapeutic strategies, prostate cancer (PCa) persists as a major contributor of mortality in men. New approaches to therapy are still needed. Recent developments indicate significant systemic therapeutic enhancement can be achieved with combined focal radiation and heat therapies to enhance therapeutic effects towards secondary or distal tumors via modulation of the immune response.

Methods: To explore effects of combined heat and radiation stresses, we tested mouse PCa cell line (Myc-Cap) apoptosis and senescence in response to hyperthermia (HT) followed by radiation (RT) with clonogenic cell survival assay. Subsequently, we used the Myc-Cap cells to generate primary and distal tumors *in vivo* in male FVB mice. Tumor growth was monitored with caliper measurements, and primary tumors were injected with starch coated Bionized NanoFerrite nanoparticles (BNF-NP) when the tumor achieved a pre-determined volume for treatment. We divided the animals into therapy control cohorts (n=18), RT (12 Gy, n=12), HT (n=9), or HT+RT (n=9). Tumors measurements were recorded twice a week up to 40 days? Following therapy (12d after), we collected tumor tissues to characterize tumor-associated leucocyte (CD8, CD4, Foxp3) populations using fluorescence-activated cell sorting (FACS).

Results: *In vitro* results demonstrated increased susceptibility to combined HT+RT, consistent with previously published results. After this positive confirmation we moved to our animal model. *In vivo* results demonstrated that combinatorial therapy (HT+RT) significantly reduced both primary (treated) and distal (untreated) tumor volumes following treatment. In contrast, HT or RT alone produced less pronounced or no response in distal tumors. In addition, populations of FoxP3 expressing cells in distal tumor increased markedly with the combinatorial therapy. It was noted, however that the volume of the primary tumor size at time of treatment correlated with therapy outcome.

Conclusions: Synergy, we observed with *in vitro* studies, suggests that radiation dose could be decreased also *in* vivo. Heat therapy (HT) combined with radiation therapy (RT) produced local tumor control similar to RT alone but the combination had markedly greater effect on distal tumors (abscopal effect) than either RT or HT alone, which we hypothesize is mediated by altered immune signaling in response to tumor (primary, treated) injury. Evidence for altered immune signaling initiated by combinatorial therapy was the measured increase in FoxP3 expressing leucocytes in that cohort. Implications and future directions of this study will be discussed.

MON 7

B16 CANCER ANTIGEN RELEASE AND PRESENTATION DEPENDS ON FOCAL THERAPY CONDITIONS

Qi Shao, Stephen O'Flanagan, Jackson Raynor, Brandon Burbach, Samira Azarin, Yoji Shimizu, John Bischof

University of Minnesota, MN, USA

Minimally invasive focal therapies including hyperthermia, cryosurgery and irreversible electroporation (IRE) of local cancers have become common. Ongoing efforts to combine focal therapy with adjuvant immunotherapy to address both local and systemic cancer are beginning to show some promise. Nevertheless, the role of focal therapy in releasing endogenous antigens that can subsequently activate tumor-specific CD8 T cells to generate cytotoxic T lymphocytes (CTLs), required for a systemic immune response, is not well understood. Here, we compare three modes of focal therapy for their quantitative protein release and their abilities to activate T cells.

B16 cells, which express a known tumor antigen from tyrosinase related protein 2 (TRP-2), were collected in suspension and exposed to focal therapy conditions, i.e. heating (50°C, 30min), cryo-freezing (-80°C, 30min) and IRE (1250V/cm, 50μs, 99 pulses and 1Hz). After exposure, the total protein release was quantified by BCA assay. The lysates were also incubated with antigen presenting cells (APCs) derived from differentiated bone marrow-derived dendritic cells (DCs). Lysate-loaded APCs were then combined with purified, naive (CD44-Low) TRP-2-specific T cells that were labelled with CellTrace Violet (CTV). After 3 days, flow cytometry was used to measure the T cell activation (upregulation of CD44) and CTL proliferation (dilution of CTV). Controls included DCs incubated with the purified TRP-2 peptide and B16 lysates by repetitive thermal cycling between room temperature and liquid nitrogen (LN2).

Compared to LN2 control (protein loss=100%) protein release following IRE was 110±37% of control, cryo-freezing yielded 90±10% of control, and heating yielded only 29±16%. Using only the PBS-soluble protein of 10^5 cell equivalent lysates of the above focal therapy conditions, T cell activation and proliferation was then assessed. Activation from highest to lowest was: LN2 control, cryotherapy, IRE and heat. Interestingly, only the IRE sample generated significant insoluble protein (60% of total), which in a separate test was able to generate a robust T cell response, 2-3x higher than the LN2 control with soluble protein.

This study demonstrates that focal therapies release different amounts of protein with variable immune response. For instance, our data suggests that there is a "quality" to the released protein (e.g. solubility) to affect an immune response. Further optimization of specific focal therapy conditions that promote protein release and antigen presentation is warranted to yield predictable and robust immune responses. This information will ultimately help in designing focal therapies with adjuvant immunotherapies that can ultimately treat both local and systemic disease.

MON 8

GALECTIN-1-BASED TUMOR-TARGETING FOR PHOTOTHERMAL THERAPY

Samir Jenkins[1], Dmitry Nedosekin[1], Ruud Dings[1], Jingyi Chen[2], Robert Griffin[0]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

Anginex is an antiangiogenic, synthetic 33mer that binds to galectin-1, which is overexpressed by the tumor endothelium- a critical requirement for effective nanomedicine delivery- as well as by tumor cells themselves. In the present study, anginex was used as a targeting agent after conjugation to polydopamine-coated Au nanocages, which were selected for their photothermal conversion, biocompatibility and functionalization potential. Approximately 6 x10^4 peptides were conjugated to each particle, and targeting was confirmed by darkfield microscopy, photoacoustic microscopy, and photoacoustic flow cytometry. The peptide retained its biological activity after conjugation, as demonstrated through migration and tube formation assays, which showed similar effects from the free and nanoparticle-bound peptide. Additionally, the construct affected zebrafish development in a manner similar to inhibitors of neovascularization. In vitro, the construct resulted in 90 % cell killing following a 20 min irradiation with an 808 nm laser, while the cell viability was unaffected in the absence of laser. In vivo, anginex enabled these nanocages to specifically target tumor tissue resulting in a 3 fold increase in tumor accumulation, which was visualized by photoacoustic microscopy and confirmed with mass analysis. The particle concentration in circulation was monitored photoacoustically and the clearance was found to be biphasic, with particles still circulating after 24 h. Additionally, little outward sign of toxicity was observed in mice. These studies demonstrate the potential of anginex as a targeting agent for theranostic nanomedicines.

MON 9

MRI-GUIDED LASER ABLATION FOR SYMPTOMATIC, PERIPHERAL SOFT-TISSUE VASCULAR ANOMALIES: FEASIBILITY, SAFETY, AND EFFECTIVENESS IN THE FIRST 19 PATIENTS.

David Woodrum, Scott Thompson, Matthew Callstrom, Emily Bendel, Lori Cranston, Krzysztof Gorny, Michael McKusick

Mayo Clinic, Rochester, MN, USA

Purpose: To determine the feasibility, safety and early effectiveness of MRI-guided laser ablation for treatment of symptomatic, peripheral soft tissue vascular anomalies.

Materials and Methods: An IRB-approved retrospective review was undertaken of all patients who underwent MRI-guided laser ablation for treatment of symptomatic, peripheral soft tissue vascular anomalies (VA) during the period from January 1, 2008 to December 31, 2016. US/MRI- or MRI-guided and monitored laser ablation was performed under general anesthesia. Intraprocedural monitoring was performed with proton-resonance frequency MR thermometry.

Results: Twenty-two patients (14F/8M, age 2 to 58) with 22 VA located in the face (N=3), neck (N=1), thorax (N=6) or extremities (N=12) were treated. Needle placement was performed with US/MRI (N=8) or MRI alone (N=14). MRI-guided laser ablation for moderate to severe pain (N=18), facial swelling due to mass effect (N=3) or consumptive coagulopathy secondary to hemangioma-thrombocytopenia syndrome (N=1). The median VA diameter was 3.7 cm (range, 1.6 to 9.0 cm). VA were ablated in 1 (N=14), 2 (N=6) or 3 sessions (N=2). Repeat ablation was undertaken due to incomplete pain relief (N=3) or planned multiple stage sessions due to large size (N=2) or facial location (N=3). Median ablation time was 5.5 minutes (2 to 60 min) at an average power of 13.5 watts (7.5 to 25 W). Patients were discharged same day (N=10) or after overnight observation (N=12). At an average follow-up of 9 months (range 1 to 30 months), 16 patients with painful VA reported complete (N=14) or partial (N=5) symptomatic pain relief. The three patients with partial pain relief underwent repeat ablation with MRI-guided laser ablation (N=1) or cryoablation (N=2) with follow-up pending. The patient with hemangioma-thrombocytopenia syndrome developed normalization of coagulation parameters after three ablation sessions. There were no major complications and four minor complications.

Conclusions: MRI-guided laser ablation is feasible, safe and effective for treatment of symptomatic, peripheral soft-tissue vascular anomalies.

MON 10

REAL-TIME MONITORING OF INDOCYANINE GREEN PHOTOTHERMAL ABLATION USING PHOTOACOUSTIC IMAGING

Nicholas Benvenuto[1], Houra Taghavi[3], Trevor Mitcham[3], Erik Cressman[2], Rahul Sheth[2], Richard Bouchard[3]

[1]Sidney Kimmel Medical College, Philadelphia, PA, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Imaging Physics, Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

Introduction

Thermal ablation is a cornerstone in the management of primary and metastatic liver tumors. Conventional ablation modalities and image guidance systems are limited by 1) the inability to accurately visualize ablation zones intraprocedurally and 2) the lack of specificity for ablating tumor versus normal tissue. As a result, tumors may be incompletely treated, and/or a substantial amount of adjacent liver parenchyma may be thermally injured. Indocyanine green (ICG) is a clinically approved fluorescent molecule that has recently been shown to localize to primary and metastatic liver tumors with target-to-background ratios as high as 30:1. Moreover, ICG can generate cytotoxic hyperthermia with low power laser irradiation. Photoacoustic imaging (PAI) is a promising technique that has the potential to visualize ICG localization as well as thermal ablation in real-time. In this study, we evaluated the real-time monitoring capabilities of PAI during ICG photothermal ablation of liver phantoms.

Methods

Inclusions of 0.05, 0.1, 0.2 and 0.4 mg/mL ICG-gelatin solution were embedded in gelatin phantoms and ex vivo porcine liver. Each inclusion was irradiated via a fiberoptic catheter at a wavelength of 808-nm and laser powers of 0.5W, 1W, and 2W. Imaging and temperature measurements were recorded using a photoacoustic imaging platform (VisualSonics Vevo 2100 LAZR) and thermocouple temperature probes as gold standard. A gelatin-only inclusion was used as a negative control.

Results

Even at the lowest concentration of 0.05 mg/mL, ICG-specific temperature generation was achievable. When irradiated at 2W for two minutes, 0.05 mg/ml generated temperature increases of 49.4°C and 21.9°C in the ex vivo liver and gelatin phantom, respectively. Thermal ablation temperatures were readily achievable with higher concentrations: 0.4 mg/mL at 2W generated temperature increases of 66.2°C and 56.7°C in ex vivo liver and gelatin phantom, respectively. There was minimal (0.2-0.3°C) temperature increase within adjacent parenchyma. Photoacoustic temperature measurements were found to correlate highly with direct thermocouple temperature measurements.

Conclusion

We have demonstrated ablative temperature generation in ICG inclusions and liver phantoms. Heat generation is confined to the area of ICG localization, raising the possibility of tumor-specific thermal ablation that can be imaged in real-time with PAI.

MON 11

OPTIMIZING INFRARED HYPERTHERMIA, PHOTOBIOMODULATION, IONIZING RADIATION TECHNIQUES, AND ADJUVANT THERAPEUTICS IN THE SALVAGE OF RECURRENT STAGE IV PROSTATE CANCER.

Edward Abraham[1], Van Woo[1], Robert Griffin[2]

[1]Artesian Cancer Center, Claremore, OK, USA, [2]Radiation Oncology, UAMS, Little Rock, AR, USA

BACKGROUND: We have been optimizing an approach for treating recurrent and stage IV prostate cancer in patients with rapidly rising PSA levels and both local and distant metastatic disease. We have assessed treatment success by normalization of PSA levels and clinical improvement.

METHODS: Our approach optimizes clinically available modalities in the treatment of metastatic prostate cancer. This clinical pilot grew out of our phase I clinical investigation of administration of intravenous ATP (published in Journal Purinergic Signaling 2016). We observed optimal clinical response in patients receiving i.v. ATP followed by single fraction radiation and single fraction radionucleide targeting of bone metastases (Quadramet: samarium-153). The infrared approach we use involves broad spectrum infrared A heating with RFID thermal chip tumor temperature monitoring. Photobiomodulation utilizes discrete wavelength infrared radiation at 810 or 830 nm in low level laser therapy (LLLT) mode. Infrared hyperthermia (tumor heating between 40°C-45°C) and photobiomodulation and oral ATP prior to Quadramet targeting bone metastases and external beam radiation targeted at Prostascint scan (internal epitope PSMA binding site) soft tissue prostate tumor in the prostate bed and lymph nodes. We have monitored clinical and biochemical (PSA) response to therapy. Recurrence was indicated by a PSA doubling time of less than 6 months. Imaging techniques to assess the extent of disease include technetium-99 bone scan, NaF-18 PET CT bone scans to assess extent of bony metastases. ProstaScint scans to assess local recurrence and soft tissue and lymph node involvement. Infrared hyperthermia and thermal monitoring target both the recurrent disease and bone metastases.

RESULTS: Treatment response to fractionated radiation therapy with 180 cGy per fraction in a total dose of 7020 cGy had a time from PSA maximum to normal levels of 84 days, whereas patients with hypo-fractionated radiation therapy with 600 cGy times 3 to a total dose of 1800 cGy over 3 elapsed days had a time to normalization of PSA of 84 days. Both approaches resulted in significant improvement in quality of life and functional status but the latter required significantly less treatment time.

CONCLUSION: The combination of infrared hyperthermia, photobiomodulation with fractionated radiation therapy in the absence of any anti-androgen hormonal therapy results in PSA normalization and clinical improvement in patients with locally recurrent and stage IV (metastatic to bone) prostate cancer. This approach avoids the toxicity of chemotherapy and hormonal therapy and has been well tolerated by the patients receiving this treatment. Considerations of the mechanistic basis for this approach will be discussed.

MON 12

WATER-FILTERED INFRARED-A HYPERTHERMIA FOR SUPERFICIAL, WIDESPREAD BREAST CANCER RECURRENCES: CHANCES, LIMITATIONS, OPEN QUESTIONS

Peter Vaupel[1], Markus Notter[2]

[1]Dept. Radiation Oncology,Klinikum rechts der Isar, Munich, Germany, [2]Dept. Radiooncology, Lindenhofspital, Berne, Switzerland

Locally recurrent breast cancer after previous radiotherapy is a challenging clinical situation since initial RT considerably limits the level of re-irradiation (re-RT). Under these conditions, the combination with superficial hyperthermia (sHT) offers the possibility of achieving local control even with lower RT doses as recently shown by Notter et al. (IHJ, 2016). In this retrospective study, 73 patients with large-area, locally recurrent breast cancer (46 patients with lymphangiosis included) were treated with combined hypo-fractionated, **low-dose re-RT** (4 Gy 1x/week up to a total dose of 20 Gy), delivered 1-4 min **after thermography-controlled water-filtered infrared A hyperthermia (wIRA-HT).** Response rates in patients with macroscopic disease were 61% CR and 33% PR.

In this study, good local control of heavily pretreated, large-area breast cancer recurrences is based on a sufficiently homogeneous and most compliant heat deposition with therapeutically relevant temperatures of 39.6-40.1°C in a depth of 20 mm (invasive temperature monitoring at maximum skin temperatures of 42-43°C), the maximum radiative penetration depth of wIRA being 5 mm (10% of incident irradiance). Due to conduction, convection, and MIE-scattering (i.e.,"forward scattering"), the primary absorbed radiation energy is dissipated within the target volume. Thus, under steady conditions, the ultimately heated tissue volume (with treatment temperatures reached within 2-4 min) is much larger than the original column of absorption. Irradiances up to 150-200 mW/cm^2 were applied without generation of heat pain and thus limited patient compliance. In contrast, convent-ional, unfiltered NIR only allows irradiances $<$100 mW/cm^2 and short exposure times.

The clinical wIRA/sHT-setting (hydrosun 750) used offers a series of advantages over other techniques currently used in clinical oncology. These include: contact-free heating (e.g. of ulcerated, bleeding tumors) and treatment of irregularly shaped, widespread lesions. No patchwork technique is required for larger sizes (diameter of treatment field is 23-26 cm per applicator with approx. 7% inhomogeneity of irradiance, circular field area = 420-530 cm^2). Adaptation to larger areas can be achieved by a twin-applicator system. wIRA is independent of individual body contours. While thermal dosimetry for HT is generally performed with fiberoptic probes that sample only a small number of fixed locations, in the system applied real-time thermography is used which measures large surface temperature distributions allowing for the observation of dynamic developments during sHT sessions. Thermography also enables the instant and easily achievable protection of heat-sensitive tissue structures (e.g. scars) and can thus avoid hot spots and grade 2-4 toxicities. Because of low toxicity with this treatment schedule, wIRA-RT can be used for re-reRT-settings (e.g. in 17 patients in our study).

Limitations for wIRA-HT are diffuse, large- sized tumor lesions with depth extensions $>$20 mm. wIRA-HT is not recommended for nodular tumors with depth extensions $>$20 mm.

wIRA-sHT/re-RT is ready to be prospectively tested against standard schedules.

MON 13

EFFECTS OF VARIABLE POWER ON TISSUE ABLATION DYNAMICS DURING MAGNETIC RESONANCE GUIDED LASER-INDUCED THERMAL THERAPY

Sean Munier, Nitesh Patel, Shabbar Danish

Department of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, USA

Background: Magnetic resonance-guided laser-induced thermal therapy (MRgLITT) is a real-time MRI guided, minimally invasive procedure used to treat various intracranial pathologies. Little is known about the effects of varying power on ablation. This work seeks to evaluate the effects of variable power on the maximal estimated thermal damage during ablation and duration required to reach maximal ablation.

Methods: We used real-time ablation data from 93 patients across various intracranial pathologies. All ablations were performed using the Visualase Thermal Therapy System (Medtronic Inc., Minneapolis, MN), using a 980-nm diffusing tip diode laser. Cases were stratified into low, medium, and high power. Maximal thermal damage estimate (TDE_{max}) achieved and time to reach maximal damage (t_{max}) was measured and compared between groups. Ablation area change for cases in which an initial thermal dose was followed by a subsequent dose, with increased power, was also assessed.

Results: TDE_{max} in the high power group (284.2 ± 77.5 mm^2) was significantly greater than TDE_{max} in the medium power group (206.5 ± 53.2 mm^2) and low power group (180.5 ± 70.1 mm^2). The t_{max} of the high power group (93 ± 41 seconds) was shorter than the t_{max} of the low power group (137 ± 52 seconds). In cases where a second thermal dose was delivered at higher power, the TDE expanded an average of 51.4 mm^2 beyond the initial TDE generated by the initial ablation.

Conclusion: Increased power results in a larger TDE_{max} and faster ablation rate. In cases where an initial thermal dose does not fully ablate the target lesion, a second ablation at higher power can increase the area of ablation. Future studies are needed to examine clinical outcomes as well as the effects of previous therapies on ablation dynamics.

MON 14

A HETEROGENEOUS TISSUE MODEL FOR TREATMENT PLANNING IN LASER INDUCED THERMAL THERAPY

Drew Mitchell, Christopher MacLellan, Samuel Fahrenholtz, John Hazle, Jason Stafford, David Fuentes

The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Introduction: Magnetic resonance-guided laser-induced thermal therapy (MRgLITT) is a minimally invasive ablative procedure, which can be used to treat primary and metastatic brain tumors, radiation necrosis, and epilepsy. Clinicians heuristically use a combination of prior information and pretreatment imaging to plan the procedural approach. While this approach is acceptable in relatively homogenous tissue environments, the laser induced heat transfer is largely unpredictable near critical structures and heat sinks, such as large vasculature and the ventricles. A physics-based model simulating heterogeneous tissue properties for a priori planning magnetic resonance-guided laser induced thermal therapy (MRgLITT) procedures in treatment of focal disease in brain is presented and evaluated.

Methods: A linear superposition of analytic point source solutions to the steady state Pennes bioheat transfer equation simulates laser-induced heating in brain tissue. An approximation to the source term allows computation of heterogeneous tissue properties. Optimization of tissue-dependent optical attenuation coefficients by an interior point method trains models with 1,2,4,8, and 16 tissue labels. In N=30 MR thermometry datasets, modeling prediction accuracy is quantitatively determined by the Dice similarity coefficient (DSC) between model-predicted and measured ablation regions (T>57 degrees C).

Results: Median DSC values for homogeneous and heterogeneous tissue models were approximately 0.86, independent of number of tissue labels, as expected for lesions already modeled well by a homogeneous model. The cases in the bottom quartile, where the homogeneous model failed, spanned DSC values from 0.68 to 0.79 for a single tissue label and improved to a range from 0.76 to 0.82 when modeled with 8 tissue labels, indicating a significant improvement in the ability of this model to capture heterogeneities responsible for underperformance in predictive capability of homogeneous models.

Conclusion: This work accomplishes more accurate treatment outcome prediction by modeling up to 16 different tissue types with independent optical properties and represents another step toward commercialized MRgLITT treatment planning programs capable of improving pre-treatment planning and treatment quality. Future work will include more capable segmentation methods, such as random forest, and modeling with additional relevant physical parameters, and prediction from a transient solution of the Pennes bioheat equation.

MON 15

EXPANDING USE OF HYPERTHERMIA IN TODAY'S ONCOLOGY CLINIC: INITIAL IMPRESSIONS FROM THE THOMAS JEFFERSON THERMAL ONCOLOGY PROGRAM

Mark Hurwitz, Dario Rodrigues, Pramilla Anne, Voichita Bar-Ad, Paul Stauffer

Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

Introduction

Numerous studies have demonstrated benefit to hyperthermia combined with radiation or chemotherapy in treatment of cancer, however, hyperthermia remains an under-utilized modality in oncology. The thermal oncology program at Thomas Jefferson University was recently reinvigorated with the goal of expanding applications of oncologic thermal therapy. While development of leading edge trials is a focus of the program, expansion of current clinical indications that build on the expansive clinical literature supporting use of hyperthermia remains a priority. We assert that there are present opportunities to expand use of hyperthermia to a greater number of cancer patients as part of routine care, and present examples here in support of this hypothesis.

Methods

A new clinical hyperthermia program was initiated at Thomas Jefferson University in May, 2014; first with superficial hyperthermia and subsequently interstitial and deep regional hyperthermia, with the full range of options available since November, 2015. In the United States there is one FDA approved device for deep regional hyperthermia; however, this approval is under a humane device exemption (HDE) with a specific indication for treatment of cervical cancer with radiation when chemotherapy is contraindicated. Under FDA guidelines, expanded use of the BSD 2000 for deep regional hyperthermia of advanced disease in the pelvis was requested with supporting literature, and subsequently granted by our institutional IRB. Here we present our initial experience in successful application of hyperthermia in an expanding number of oncologic scenarios.

Results

There are a wide range of opportunities for routine use of hyperthermia in today's oncology clinic beyond the most established applications such as for recurrent chest wall disease, head and neck malignancies and cervical cancer. Examples including advanced cases of psuedomyxoma peritonei, mucosal melanoma, recurrent and primary rectal, genitourinary, and neuroendocrine tumors will be presented. The ability to effectively and safely heat pelvic malignancies with current commercially available technology will be discussed.

Conclusion

Current opportunities exist for application of hyperthermia to a wide range of cancer patients. While clinical studies are indicated to further expand indications for use of hyperthermia, existing literature coupled with the excellent safety profile of hyperthermia provide a context for greater utilization in today's oncology clinic.

MON 16

CONCURRENT PENCIL BEAM SCANNING PROTON THERAPY AND HYPERTHERMIA: INITIAL CLINICAL EXPERIENCE

James Snider, III[1], Arpit Chhabra[1], Tejan Diwanji[1], Jason Molitoris[1], Lolly Johnson[1], Mandy Clevenger[1], William Regine[2], Zeljko Vujaskovic[2]

[1]University of Maryland Medical Center-Maryland Proton Treatment Center, Baltimore, MD, USA, [2]University of Maryland School of Medicine-Maryland Proton Treatment Center, Baltimore, MD, USA

Background: The addition of hyperthermia (HT) to conventional, photon radiotherapy courses is known to increase efficacy through multiple mechanisms including radiosensitization of hypoxic cell populations and inhibition of DNA repair. HT reduces the oxygen enhancement ratio of "low" linear energy transfer (LET) radiation (e.g. photon and proton) and increases radiobiologic effect (RBE), potentially mimicking high LET particle therapy (e.g. ^{12}C ion) [Datta et al. 2014]. Naturally, both enthusiasm for improved outcomes and concerns regarding increased toxicity have arisen for this approach, yet exceedingly limited data exists to date as institutions with the capacity to deliver both proton therapy and hyperthermia are rare.

Methods: At the Maryland Proton Treatment Center, over 200 patients have been treated with pencil beam scanning proton therapy (PBSPT) since the facility's activation in early 2016. The University of Maryland Medical Center has treated 87 patients with external (ETT) or interstitial thermal therapy in the last 4 years. All treatments have been delivered on the BSD-500 microwave hyperthermia platform with the target tumor temperature of 40-42°C. Three patients have been treated with concurrent PBSPT and ETT: 2 patients postoperatively, for myxofibrosarcoma, and one, for inguinal recurrence from vulvar squamous cell carcinoma (SCC). Treatment courses were as follows: inguinal SCC (reirradiation 45Gy(RBE), 9 twice-weekly-ETT, bolus 39°C-60 min), high grade chest wall myxofibrosarcoma (reirradiation 60Gy(RBE), 5 weekly-ETT, bolus 40°C-45 min), intermediate grade shoulder myxofibrosarcoma (de novo 66Gy(RBE), 4 weekly-ETT, bolus 40°C-45 min).

Results: All patients completed their courses of proton and hyperthermia treatment without substantial acute complication or interruption. The patient treated in the de novo setting for shoulder myxofibrosarcoma experienced only grade 1 radiation dermatitis, hyperpigmentation, fatigue, and pain under treatment; post-treatment, no significant complications (follow-up 6 mo). The patient reirradiated for recurrent chest wall myxofibrosarcoma experienced grade 2 radiation dermatitis and grade 1 fatigue and hyperpigmentation under treatment; post-treatment, grade 1 joint range of motion limitation (follow-up 3 mo). The patient reirradiated for inguinal vulvar SCC recurrence experienced grade 2 radiation dermatitis and grade 1 fatigue, pain, and hyperpigmentation under treatment; post-treatment, grade 3 soft tissue necrosis requiring aggressive wound care (follow-up 6 mo). The patients with myxofibrosarcoma have currently no evidence of disease; the patient with inguinal SCC has persistent disease outside of the reirradiation field, with tumoral response in-field.

Conclusion: Concurrent PBSPT and ETT appears safe, effective, and promising. Further investigation and expansion of clinical experience is warranted amongst institutions with technical capabilities.

MON 17

IMAGE-GUIDED TARGETED DOXORUBICIN DELIVERY WITH HYPERTHERMIA TO OPTIMZE LOCO-REGIONAL CONTROL IN BREAST CANCER; STUDY DESIGN OF THE I-GO FEASIBILITY STUDY.

Josanne de Maar[1], Roel Deckers[1], Britt Suelmann[1], Manon Braat[1], Sabine Linn[2,1], Chrit Moonen[1], Elsken van der Wall[1]

[1]University Medical Center Utrecht, Utrecht, The Netherlands, [2]Netherlands Cancer Institute, Amsterdam, The Netherlands

Introduction Advances in systemic treatment led to improved overall survival in patients with metastatic breast cancer[1]. Various studies suggest that by obtaining loco-regional control, overall survival in advanced disease can further be improved[2,3].

Pre-operative chemotherapy can be used in metastatic breast cancer to make radical removal of the primary tumor feasible, while simultaneously maintaining control of already present metastatic sites. The doxorubicin and cyclophosphamide regimen (AC) is well-known both in (neo-)adjuvant setting as in treatment of metastatic breast cancer. At present, optimal local control in advanced breast cancer using adequate dosing of doxorubicin is hampered by its toxic systemic effects. Therefore we aim to increase doxorubicin deposition in the primary tumor without interfering with systemic efficacy and toxicity, by combining lyso-thermosensitive liposomal doxorubicin (LTLD, ThermoDox) with local mild hyperthermia, induced by Magnetic Resonance guided High Intensity Focused Ultrasound (MR-HIFU). When heated to 40-43°C, ThermoDox releases a very high concentration of doxorubicin locally within seconds[4-6]. In the absence of hyperthermia, ThermoDox leads to a similar biodistribution and antitumor efficacy to free doxorubicin. MR-HIFU allows for controlled heating of deep-seated tumors. The aim of our upcoming phase I study is to investigate the safety, feasibility and tolerability of the combination of MR-HIFU hyperthermia, ThermoDox and cyclophosphamide.

Methods We will perform a single-arm phase I feasibility study in 6-12 patients with de novo stage IV her2-negative breast cancer, who have not received previous chemotherapy. The study treatment consists of up to 6 cycles at 21-day intervals of ThermoDox (40mg/m^2) administered during MR-HIFU induced hyperthermia (60 minutes at 40-42 C) and cyclophosphamide (600 mg/m^2) administered afterwards. A dedicated MR-HIFU breast system (Philips Healthcare) integrated with a clinical 1.5T MRI scanner will be used for safe and controlled heating of the tumour[7]. Primary endpoints are safety, tolerability and feasibility. Secondary endpoint is efficacy, assessed by clinical and pathological response.

Results We anticipate increased tumor shrinkage due to higher local doxorubicin deposition, without compromising systemic toxicity or control of distant disease.

Conclusion We hypothesize that ThermoDox combined with MR-HIFU induced hyperthermia can safely substitute doxorubicin in the AC-regimen for metastatic breast cancer. If feasibility and tolerability are adequate, this approach could lead to loco-regional control in breast cancer without surgery.

References; [1]Sundquist, 2017, the Breast; [2]Khan 2016, Sem Rad Onc; [3]Headon, 2016, Mol Clin Oncology; [4]Kong, 2000, Cancer Res; [5]Ranjan, 2012, JCR; [6]Staruch, 2012, Int J Hyperthermia [7]Deckers, 2015, Phys Med Biol

Acknowledgements: Dutch Cancer Foundation, VoltaValo (CTMM)

MON 18

A PILOT CLINICAL STUDY ON CRYO-THERMAL THERAPY OF LIVER CANCER

Wentao Li[1], Zan Shen[2], Guangzhi Wang[1], Xinhong He[1], Lichao Xu[1], Kangwei Zhang[3], Kun He[3], Ping Liu[3], Aili Zhang[3], Guangyuan Zhang[4], Yonggang Wang[2], Shengping Wang[5], Weijun Peng[5], Lisa X. Xu[3]

[1]Department of Interventional Radiology, Fudan University Shanghai Cancer Center, shanghai, China, [2]Department of Oncology, Shanghai Jiaotong University Affiliated Sixth People's Hospital, shanghai, China, [3]School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, shanghai, China, [4]Department of Radiology, Shanghai Proton and Heavy Ion Center, shanghai, China, [5]Department of Radiology, Fudan University Shanghai Cancer Center, shanghai, China

Introduction: A novel cryo-thermal therapy was developed for tumor ablation by alternating cooling and radio frequency (RF) heating of tumor tissues. Mechanically inducing a whole-body immune response against distal metastases in animal models is considered as a promising strategy against metastatic cancer. In this study, we aimed to assess the safety and efficacy of the cryo-thermal therapy of liver cancer in clinic.

Methods: 8 patients with colorectal cancer liver metastases were included in this pilot study. Lesions ranging from 1.2 to 4.0 cm were treated with cryo-thermal ablation. First, Argon-helium knifes (Cryo-HIT™) were inserted in the target area with the distance between adjacent probes less than 15 mm. When the ice ball was 5mm beyond the boundary of the tumor, the power was reduced to maintain ice ball unchanged until 15min. After rewarmed, a cycle of RFA was performed by Umbrella Electrode (MedSphere International, Inc.). According to the preoperative planning, the power and heating time was set to maintain the temperature 50 degrees about 5mm beyond the tumor for 15min. All patients underwent standard magnetic resonance imaging of liver cancer on day 1 or 2 prior to the ablation procedure, and 1 month and 3 month after. The size and apparent diffusion coefficient (ADC) value of each lesion were compared. The blood test and immunology indexes were run for each patient before the ablation procedure, and on day 3, 1 month, 3 month and 6 month after.

Results: The ablation procedure was well tolerated in all patients without major complications or procedure-related mortality. Complete response was achieved in all treated lesions. There was no irregular or nodular enhancement observed in all lesions on 1 or 3 month follow-up. The mean ADC value showed predictable increasing following ablation from 0.90 to 1.19 to 1.25 $\times 10^{-3}$ mm^2/s. The immunology indexes in these cases with disease progression and free indicated that the effectiveness of the therapy seemed related to the patient's immune status. After the cryo-thermal tumor ablation, matured DCs and macrophages were correlated with good prognosis. Existing data suggested that further investigation of the subsets and function of T cells, MDSCs, NKs, DCs, and macrophages after the ablation would be necessary to evaluate the anti-tumor immunity induced by the cryo-thermal therapy.

Conclusion: Cryo-thermal therapy is safe and highly effective for local tumor ablation without major complications. The mechanism of anti-tumor immune response induced is investigating.

MON 19

COMPARISON OF INDUCED BIOLOGICAL EFFECTS OF MODULATED ELECTROHYPERTHERMIA TO CONVENTIONAL CAPACITIVE HYPERTHERMIA

Oliver Szasz

St. Istvan University, Biotechnics Department, Budaors, Hungary

Introduction: Capacitive coupling is a popular technical solution of hyperthermia realization in oncology. Modulated electrohyperthermia (mEHT) is an emerging new loco-regional radiofrequency (RF) method. Several technical innovations implemented in mEHT producing certain differences in its biological effects compared to the conventional hyperthermia (HT) methods. Our objective is to point the major differences of biological effects.

Methods: The mEHT method has particular basic concept among conventional hyperthermia solutions. The RF energy by mEHT selectively targets the clusters of transmembrane proteins (rafts) of the malignant cells. Heating the rafts on high temperature does not heat up the entire tumour mass to the thermal cytotoxic level, but excites special signal transduction pathways producing damage associated molecular pattern induced from the extracellular side. We measured the differences with various immunohistochemical methods, as well as by flow cytometry and Western-blot.

Results: Despite the same temperature we observed earlier definite differences in the biological response in vivo [1], and also contrary to the similar capacitive coupling the efficacy of the absorbed power observed very different in vivo. Despite the same electromagnetic phenomena of the RF current the differences between mEHT and HT are characteristic, and well-shown in vitro [2]. The mEHT was able to induce significant apoptotic cell death process in vitro and immunogenic cancer cell death in vivo in mild temperature range (≤42oC) where conventional HT did not induce significant cell destruction. Effect of HT was identical with the water-bath heating at 42oC. Compared to HT, mEHT in vitro produced significant enhancement of ROS, Caspases 3, 8 and 9, calreticulin, and extracellular HSP70 expression, as well as the E-cadherin and beta-catenin expression showed re-established adherent connections by mEHT, which was not observed by HT treatment on the same temperature. Furthermore, significant differences were observed in comparison of GeneChip heat-maps between the HT and mEHT on the same temperature both in vitro [3] and in vivo [4].

Conclusions: mEHT applies non-equilibrium, non-homogeneous membrane-heating feature to improve the effects of conventional heating by HT. It is a new kind of hyperthermia therapy extending with feasible advantages the conventional capacitive coupled HT method.

1. Andocs et.al. (2009) Strahlentherapie und Onkologie 185:120–126
2. Yang et.al. (2016) Oncotarget, doi: 10.18632/oncotarget.11444
3. Andocs et.al. (2016) Cell Death Discovery (Nature Publishing Group), 2, 16039
4. Andocs et.al (2014) Cell Stress and Chaperones 20(1):37-46

MON 20

OUTCOMES AND TOXICITY DATA OF EXTERNAL THERMAL THERAPY (ETT) CONCURRENT WITH EXTERNAL BEAM RADIATION THERAPY (EBRT) IN THE MANAGEMENT OF NON-MELANOMA SKIN CANCERS

Arpit Chhabra, James Snider, Zeljko Vujaskovic

University of Maryland Medical Center, Baltimore, MD, USA

Introduction:

Nonmelanoma skin cancers represent a very common malignant histology. The role of definitive and adjuvant external beam radiation therapy (EBRT) for management of cutaneous squamous and basal cell carcinomas has been previously well defined. Unfortunately, data on the use of concurrent external thermal therapy (ETT) with EBRT in this setting is relatively lacking. As such, we sought to report the outcomes and toxicity data in our single-institutional experience using EBRT with concurrent ETT for nonmelanoma skin cancers.

Methods:

We retrospectively reviewed our institutional experience with external thermal therapy to evaluate patients with nonmelanoma cutaneous malignancies who had received definitive or adjuvant EBRT and concurrent ETT. EBRT was delivered with either photon or electron based techniques at the physician's discretion. ETT was given over 45-60 minutes using the BSD-500 microwave hyperthermia system with a target temperature of 40-42 degrees Celsius delivered on non-consecutive days. Local relapse free was calculated from end of EBRT date to biopsy proven recurrent/refractory lesion.

Results:

Seven lesions in six patients diagnosed with nonmelanoma cutaneous malignancies were available for review. 33% were male, while 67% were female with a median age of 61 years (range: 37-93). Primary histologies were cutaneous squamous cell (n=4 lesions), basal cell (n=2 lesions) and poorly differentiated (n=1 lesion) carcinoma. EBRT was delivered with definitive intent for 6 lesions, and adjuvantly for presence of positive margins in one lesion. EBRT was delivered with photon and electron beam therapy for 4 and 3 lesions, respectively. Median EBRT dose was 60Gy (range: 48Gy-66Gy) delivered in 2-7Gy/fraction. Induction and concurrent cetuximab was utilized for one squamous cell carcinoma lesion, otherwise, no other systemic therapies were utilized neoadjuvantly or concurrently for any other lesion. Median local relapse free rate was 231 days from end of EBRT (range: 128-629 days). Acute toxicities from treatment included radiation dermatitis of grade 1 (n=2 lesions), grade 2 (n=3 lesions), and grade 3 (n=2 lesions).

Conclusion:

Primary and recurrent nonmelanoma cutaneous malignancies are a challenging histology to manage. Based on our review of treating these lesions with EBRT + ETT, our results display good local relapse free rates with acceptable toxicity profiles. This data tends to support strong consideration of using ETT concurrently with EBRT in this setting.

MON 21

TARGETABILITY OF ADULT SOFT TISSUE SARCOMAS FOR MILD HYPERTHERMIA TREATMENTS USING MAGNETIC RESONANCE IMAGING-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND

Jochen Cammin[1], Satya V.V.N. Kothapalli[2], Hong Chen[2], Ari Partanen[3], Imran Zoberi[1], Michael B. Altman[1]

[1]Washington University in St. Louis, Department of Radiation Oncology, St. Louis, MO, USA, [2]Washington University in St. Louis, Department of Biomedical Engineering, St. Louis, MO, USA, [3]Philips, Clinical Science MR Therapy, Andover, MA, USA

Background: Mild hyperthermia (MHT) in conjunction with radiation or chemotherapy (RT/CT) for the treatment of malignant tumors has been proven to be more effective than RT/CT alone. Magnetic resonance imaging-guided high-intensity focused ultrasound (MR-HIFU) is a novel modality to achieve MHT with precisely monitored thermal doses. However, the applicability of MR-HIFU for MHT treatment of various tumors, including adult soft tissue sarcomas (STS), has not been studied in detail. This retrospective study investigates HIFU targetability of extremity STS tumors in the adult patient population using a commercially available MR-HIFU system, and estimates how many MHT sonications are required to cover the total tumor volume.

Methods: A database of computed tomography (CT) images and associated radiation treatment plans of adult extremity STS patients treated in our department with external-beam radiation were retrospectively assessed for tumor accessibility with a commercial MR-HIFU therapy planning software (Sonalleve, Philips). The MHT target was taken as the gross tumor volume (GTV) defined for radiation treatment planning. Targetability was scored based on tumor location, volume, and depth, structures within and/or beyond the HIFU beam path, and the physical parameters of the Sonalleve MR-HIFU system. Published MR thermometry data (Tillander *et al*., 2016) was used to estimate the achievable heating volume for a target temperature of 41°C.

Results: 8/10 consecutive patients were determined to have HIFU-accessible STS. Imaging data sets from these 8 patients (ages 33 to 88) were analyzed. Tumor locations included lower leg, thigh, humerus, upper arm, and buttock. The mean tumor volume was 677±278 cc (range: 152–1169 cc). The number of required HIFU sonications was given by the ratio of tumor volume (minus volumes near critical structures) to the volume (100 cc) of a 44-mm diameter heating cell. The accessibility of each proposed treatment cell location was verified. The mean number of required MHT sonications was 7.25±2.7 (range: 2–8).

Conclusions: Extremity STS in adults may be treated with MHT adjuvant to RT/CT using a commercially available MR-HIFU system. Several factors, including large target volumes, and size limitations of the HIFU treatment cells will require splitting the treatment into multiple fractions. However, this can be accommodated with one or two MHT sessions per week given a typical RT course lasting five to six weeks. We are currently expanding the patient database for this study to analyze feasibility on a greater variety of patient geometries.

MON 22

NANOTECHNOLOGY IN THERMAL MEDICINE – CURRENT STATUS, FUTURE OPPORTUNITIES & NIH GRANT SUPPORT

Christina Liu

National Institutes of Health, Bethesda, MD, USA

Nanotechnology has provided the novel, paradigm shifting solutions to medical problems and cancer, in particular. To further these research goals, NCI formed a program called Alliance for Nanotechnology in Cancer in 2004 support efforts to harness the power of nanotechnology to transform the way we diagnose, treat and prevent cancer. Currently, the Alliance supports Centers of Cancer Nanotechnology Excellence, Innovative Research in Cancer Nanotechnology, and Cancer Nanotechnology Training Centers. Also, an intramural arm of the Alliance - Nanotechnology Characterization Laboratory provides a characterization support to evaluate clinically promising nanomaterials and establish their physical, pharmacological and toxicological characteristics.

During my talk, I will first briefly analyze current NIH support in the mechanistic understanding of hyperthermia in disease treatment. Next, I will discuss the nanotechnology-based development and optimization to enhance the efficacy of thermal medicine with more focus on cancer treatment. Further progress in nanotechnology-enabled thermal medicine will likely to follow two parallel tracks. First one will be with the development of new tools and techniques in the research arena while the second one associated with on-going translation to the clinical environment. We anticipate that more active-targeting delivering strategies of heat-generating nanoparticles, as well as nanoparticles themselves, will be developed and optimized for broader applications. To make the translational efforts more widespread, access to consistent GLP characterization and GMP manufacturing facilities will need to become more available. As the progress of these two tracks is dependent on each other, the second part of my talk will offer advice and recommendation of what are needed in both tracks to develop robust and clinically translatable tools to have a significant impact in thermal medicine applications. I will conclude my talk with information about the Alliance Program, NIH grant mechanisms and funding opportunities for support in thermal medicine research.

MON 23

SYNERGISTIC IMMUNO-PHOTOTHERMAL NANOTHERAPY (SYMPHONY): A NOVEL TREATMENT FOR LOCALIZED AND METASTATIC BLADDER CANCER

Steven Brousell, Yang Liu, Paolo Maccarini, Gregory Palmer, Wiguins Etienne, Yulin Zhao, Chen-Ting Lee, Xiumei Ma, Tuan Vo-Dinh, Brant Inman

Duke University, Durham, NC, USA

Introduction/Objective: We developed a novel treatment for localized and metastatic bladder cancer comprised of gold nanoparticle-based photothermal therapy and immunotherapy (SYMPHONY). We demonstrate that it effectively ablates primary tumors, destroys metastases abscopally, and induces potent anti-tumor immunity.

Methods: MB49 murine bladder cancer cells were injected into the bilateral flanks of C57BL/6 mice and grown until 100 mm^3 in size. PEG-functionalized gold nanostars, developed and manufactured by our team, were administered intravenously. A 808-nm laser (0.6 W/cm^2) was used to trigger plasmonic heat production from the gold nanostars in one flank 24 hours after injection, while the other flank was left untreated. Anti-PD-L1 antibody immunotherapy was co-administered intraperitoneally and repeated q3days. Mice were assessed for ipsilateral and contralateral tumor response and survival. Flow cytometry, multiplex cytokine profiling, and T cell receptor sequencing were used to characterize the immune response. Mice achieving a complete response were re-challenged with an additional injection of MB49 tumor cells 90 days later.

Results: Gold nanostar-mediated phototherapy alone completely ablated ipsilateral tumors in 4/5 of mice (pT0 at necropsy) but contralateral tumors grew and all 5 mice required sacrifice within 14 days. Anti-PD-L1 therapy alone slowed tumor growth in 3/5 mice, but tumors rapidly began growing again and 5/5 mice required sacrifice by 45 days. Combined treatment (i.e. SYMPHONY) ablated 5/5 ipsilateral tumors and resulted in partial (3/5) and complete responses (2/5) of untreated contralateral tumors, demonstrating a strong abscopal effect. After 90 days of follow-up, the two mice achieving a complete response with SYMPHONY were re-challenged with MB49 and neither developed a tumor over the ensuing 4 weeks indicating strong and effective immune memory. Flow cytometry showed CD4 and CD8 T cell proliferation, decreased myeloid derived suppressor cells, and increased IL2 with SYMPHONY.

Conclusions: SYMPHONY treatment resulted not only in effective ablation of primary tumors but also in immune-mediated abscopal destruction of untreated distant tumors. Strong and permanent anti-tumor immunity developed in some mice, indicating that with further optimization, SYMPHONY may be able to cure more advanced bladder cancers.

MON 24

ACTIVATING SERIAL KILLERS OF CANCER CELLS: HYPERTHERMIA AS SUPPORTING STRATEGY FOR MELANOMA IMMUNOTHERAPY

Esther Wagena[2], Stefan Kuehberger[2], Daphne Craenmehr[2], Bettina Weigelin[1,2]

[1]MD Anderson Cancer Center, Houston, TX, USA, [2]Radboud University Medical Center, Nijmegen, The Netherlands

For many cancer types, immunotherapy is an emerging first-line treatment, with the potential to reach complete regression in patient subsets. The main effector cells mediating tumor eradication are cytotoxic T lymphocytes (CTL), which kill cancer cells in a cell-contact and tumor-antigen-specific manner. But although endogenous and therapeutically applied CTL are observed to infiltrate tumors in patients, their capacity to control tumor growth is often insufficient. Thus, to overcome tumor resistance, supporting strategies are required to enhance immunotherapy. Using live-cell imaging of organotypic in vitro assays and intravital microscopy, we studied the capacity of fever-range hyperthermia to enhance CTL effector function against mouse melanoma.

Using a collagen-based 3D assay and time-lapse microscopy over up to 48 hours, we show that OVA-specific CTL effector function against B16F10/OVA melanoma cells is an inefficient process with a high failure rate. Killing is rarely completed by a single CTL contact, but requires a sequence of sublethal hits, delivered by multiple CTL ('additive cytotoxicity'). Optical reporters (perforin-mediated Ca2+ influx and nuclear envelope rupture) confirmed the induction of sublethal damage to the cellular and nuclear membranes, and allowed to visualize serial CTL hits followed by repeated recovery of the melanoma cell. To study the temperature-dependence of CTL effector dynamics, we tested a range of temperatures (<32 °C – 41.5 °C), which were applied continuously and in clinically relevant dosing schemes ranging from 1 – 3 hours per day. Enhanced killing was observed already after treatments of 38.5 °C for 1 hour on two consecutive days, while hypothermia (<32 °C) and temperatures ≥ 41.5 °C impaired CTL migration, viability and, consequently, killing capacity. The accelerated apoptosis rates were associated with stabilized CTL – tumor cell contacts and impaired recovery of melanoma cells from CTL-mediated damage.

To validate the results in the complex physiological environment of the skin, we used intravital multiphoton microscopy to visualize adoptively-transferred CTL and melanoma cells during whole-body hyperthermia in live tumors. Moderate whole-body hyperthermia (39.5 °C) applied for 1 h induced an immediate block of melanoma cell proliferation which only slowly recovered over 48 h. We further observed impaired cell motility and enhanced apoptosis rates, concurrently to a large influx of phagocytic immune cells targeting the tumor.

In summary, kinetic imaging and intravital microscopy were successfully applied to deepen our mechanistic understanding of immune cell function during fever-range hyperthermia which forms the basis for improved, rationale design of combination therapies.

MON 25

ADRENERGIC SIGNALING IMPAIRS ACTIVATION OF CD8$^+$T CELLS BY BLOCKING METABOLIC REPROGRAMMING

Guanxi Qiao, Mark Bucsek, Elizabeth Repasky, Bonnie Hylander

Roswell Park Cancer Institute, Buffalo.NY, USA

Adrenergic stress promotes tumor progression by several mechanisms. Mice housed at standard housing temperature (ST, 22°C) experience chronic adrenergic cold stress sufficient to elevate norepinephrine (NE) levels compared to mice housed at thermoneutrality (TT, 30°C) and we found that tumors grow faster at ST. We have also previously reported that the anti-tumor immune response is suppressed at ST. CD8$^+$T cells isolated from 4T1 tumors in these mice have reduced expression of markers of activation (CD69, glut-1) and effector function (IFNγ). These deficits are reversed by housing mice at TT which reduced adrenergic stress. New data from our lab shows that treating mice at ST with the -adrenergic receptor *antagonist* propranolol also reverses immunosuppression. Coincident with this effect, we see increased cell surface expression of the glucose transporter glut-1 on CD8$^+$T cells, which is critical for glycolysis. Based on the fact that T cell activation and function require up-regulation of glycolysis (i.e. "metabolic reprogramming"), **we hypothesize** that adrenergic signaling impairs the antitumor efficacy of CD8$^+$T cells by impairing metabolic reprogramming. To test this hypothesis, CD8$^+$ T cells were isolated from BALB/c mice and activated with anti-CD3/CD28 antibodies +/- the -AR *agonist* isoproterenol (ISO). Using Seahorse Extracellular Flux Analysis to compare the bioenergetics of control and ISO treated CD8$^+$T cells, we found that adrenergic signaling significantly reduced both ECAR (rate of glycolysis) and the ratio of oxidative phosphorylation/glycolytic rate (OCR/ECAR). These data support the idea that adrenergic signaling blocks metabolic reprogramming in CD8$^+$ T cells thereby inhibiting T cell activation. Current work is focused on identifying the precise intracellular pathways by which adrenergic signaling and T cell metabolism intersect.

This work was supported by grants from the New York State Department of Health Peter T. Rowley Breast Cancer Research Grant (C028252) and the Roswell Park Cancer Institute Alliance Foundation.

MON 26

THE MICROBIOME IS HIGHLY RELEVANT TO IMMUNE THERAPY. CAN THERMAL THERAPY AFFECT BOTH THE MICROBIOME AND IMMUNE THERAPY?

Joan Bull

The University of Texas McGovern School of Medicine, Houston, Texas, USA

BACKGROUND: There are effective immune therapies for advanced malignancies, including anti-checkpoint inhibitors (ACIs) and now, tumor antigen-specific adoptive cell transfer. These two types of immune therapies produce durable responses & long survivals in patients with epithelial and hematological malignancies. Unfortunately, response rates are 30% or less. Responses need to be much greater.

METHODS: ACI-induced responses can be increased by combining ACIs or by combining an ACI with chemotherapy. Yet, both maneuvers increase toxicity. The natural gut microbiome interestingly affects immunity and can enhance response to ACIs. Thermal therapy (systemic, local/regional, ablative HIFU or cryotherapy) also improves anti-tumor immunity, yet thermal therapy has not yet been clinically investigated with ACIs nor for its effect on the microbiome. While the ACIs amplify CD8+ T-cell proliferation, tumor invasion and cytotoxicity, when there are a scarcity of CD8+ T-cells in the tumor or its stroma, tumor response to ACIs is limited. Antigen-specific adoptive cell transfer, a highly complex modality, can increase the number of tumor-specific CD8+ T-cells in the tumor and tumor microenvironment.

RESULTS: Thermal therapy boosts host immune response and escalates the anti-tumor cytotoxicity of effector T-lymphocytes, and can increase ACI-induced response. Altering the intestinal microbiome also significantly increases immunity and response to the ACIs. However, not all malignancies respond to ACIs. For example, gastrointestinal (GI) cancers generally do not respond to ACIs. Yet, tumor antigen-specific adoptive cell therapy using *ex vivo* expanded tumor-infiltrating lymphocytes is a highly effective immune therapy in GI malignancies. Regrettably, antigen-specific adoptive lymphocyte transfer is limited in availability at this time.

CONCLUSION: Clearly, the immune ACIs improve survival of patients with advanced melanoma, NSCLC, Hodgkin's disease, and head & neck cancer, if there are enough CD8+ T-lymphocytes. Can thermal therapy increase the number of effector T-lymphocytes? Certainly, the addition of thermal therapy can be expected to increase the response rate of the immune ACIs by increasing the ability of cytotoxic CD8+ T-lymphocytes to enter the tumor, thus increasing tumor kill. Also, altering the gut microbiome can positively affect ACI therapy. Problematically, some cancers, such as GI neoplasms do not respond to ACIs. However, tumor antigen-specific adoptive cell transfer has been shown to give durable responses in advanced cancers of the GI tract. How thermal therapy affects antigen-specific adoptive cell therapy or the microbiome is unknown and research in these areas as well as with ACIs is warranted.

MON 27

RETHINKING SPONTANEOUS HYPOTHERMIA IN HUMAN SEPSIS.

Monique T Fonseca[1], Abner C Rodrigues[2], Luana C Cezar[1], Andre Fujita[2], Francisco G Soriano[3], Alexandre A Steiner[1]

[1]Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil, [2]Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil, [3]Medical School, University of São Paulo, São Paulo, Brazil

Although septic patients are usually febrile, a considerable portion of them develops hypothermia. This phenomenon is poorly understood and generally viewed as something dysregulated and progressive. For this reason, septic patients who become hypothermic are usually rewarmed, a practice that has probably contributed to our lack of knowledge on septic hypothermia. Here, we performed a retrospective study to characterize spontaneous hypothermia in a rare cohort of patients not subjected to active rewarming, and the results were surprising. In the study, hypothermia was defined as body temperature below 36.0°C for longer than 2 h, with at least one reading of 35.5°C or less. Data from 93 patients were extracted from the 2005-2012 database of the University of Sao Paulo Hospital (Brazil). Of these, 23% presented hypothermia at the time sepsis was diagnosed, a figure that is consistent with previous studies. However, we identified an additional group of patients (31%) who were not hypothermic initially, but developed hypothermia during the ICU stay. Hence, septic hypothermia seems to be more common than previously thought. Hypothermia was found to develop in episodes that are transient and self-limiting in 97.1% of the cases. It often occurred in multiples: the median number of hypothermic episodes per patient was 2, and the maximum number was 12. Importantly, hypothermia was rarely observed in the moments that preceded death, when multiple organ failure is presumably at its peak. Moreover, nearly half of the hypothermic episodes had onset in the absence of shock or respiratory distress, and the incidence of hypothermia was not increased by either of these conditions. Next, we evaluated whether hypothermia could be a pharmacotherapy-related epiphenomenon. A total of 113 drugs were administered to the patients, which included antipyretics, sedatives and neuroleptics, but none of the drugs was a predictor for the development of hypothermia. In conclusion, this study shows that hypothermia is a predominantly transient, self-limiting, and nonterminal phenomenon that is inherent to human sepsis. These characteristics resemble those of the regulated hypothermia shown to replace fever in animal models of severe systemic inflammation. Perhaps it is not necessary to fight off septic hypothermia with active rewarming.

Support: FAPESP, AHA & CAPES.

MON 28

THE EFFECT OF AGGREGATION OF MAGNETIC NANOPARTICLES ON PERFORMANCE OF THERANOSTIC APPLICATIONS IN MEDICINE

Ondrej Hovorka

University of Southampton, Southampton, UK

In this talk we overview the recent progress in our understanding of the effects of aggregation of magnetic nanoparticles on performance of therapeutic and diagnostic technologies (theranostics) based on magnetic particle hyperthermia for cancer therapy, magnetic particle imaging, and magnetorelaxometry for disease detection. Employing large scale computational modelling of statistical aggregates of magnetic nanoparticles typically observed in intracellular environments [1], we show that depending on the structure of aggregates the theranostic performance may become considerably degraded. We also illustrate various memory effects spanning the superparamagnetic to hysteretic thermal fluctuation regime of magnetic nanoparticle behaviour, and discuss their potential utilisation for optimising theranostic applications [2]. Understanding the effects of aggregation of magnetic nanoparticles is becoming increasingly important, as it implies that optimal theranostic designs of magnetic nanostructures need to take into consideration realistic biological environments.

References:

[1] Etheridge et al., "Accounting for biological aggregation in heating and imaging of magnetic nanoparticles", Technology 2, 214 (2014).

[2] O. Hovorka, "Thermal activation in statistical clusters of magnetic nanoparticles", Journal of Physics D: Applied Physics 50, 044004 (2017).

MON 29

LOCAL VS GLOBAL HEATING IN MAGNETIC NANOPARTICLE HYPERTHERMIA

Cristina Munoz Menendez[1,2], Sergiu Ruta[1], Roy Chantrell[1]

[1]University of York, York, UK, [2]University of Santiago de Compostela, Santiago de Compostela, Spain

Magnetic nanoparticle hyperthermia (MNH) is a promising cancer therapy based on the heating effects of nanoparticles subjected to an alternating magnetic field. Although MNH is in use as a therapy its effectiveness is by no means optimised. Holding back the use of MNH is a lack of detailed understanding of the basic magnetisation processes and heating mechanisms, which are strongly dependent, in addition to intrinsic material properties, on the magnetostatic interaction between the particles: the latter factor bringing in a dependence on the degree of dispersion of the nanoparticles, ranging from well dispersed to highly aggregated states which can occur in tumour cells. Optimisation of treatment and dosage, in addition to the development of nanoparticles with superior properties must be based on sophisticated computational and theoretical models. Opinions also differ on the nature of the heating itself. One school of thought assumes that the heat generated by the nanoparticles leads to a uniform temperature increase characterised by a specific absorption rate. An alternative model is based on experiments by Dias et.al. [1], which show large local changes in temperature within a few nm of the nanoparticle surface. We will first outline the current status of experimental investigations. We then proceed to describe a computational model of the magnetic properties of magnetic nanoparticle systems taking into account the effects of magnetostatic interactions. This model was shown [2] to encompass both superparamagnetic and hysteretic heating processes. In order to investigate the possibility of local heating of the nanoparticles we investigate a simple system of two nanoparticles coupled via the magnetostatic interaction. Within this model we investigate the major channels for energy transfer and dissipation, specifically storage of energy in the magnetostatic interactions and dissipation during switching of the magnetisation. It is found that the individual switching events can be related to the total hysteresis area, but each is associated with localised energy release into the immediate surroundings of the nanoparticle and hence localised heating. We will also describe dynamic calculations of heating and finally consider the implications for optimisation of MNH.

[1] Jorge T. Dias et. al., Angew. Chem. Int. Ed., 52, 11526 –11529 (2013)

[2] S. Ruta, O. Hovorka and R. Chantrell, Sci. Rep. 5, 9090 (2015).

MON 30

NANOPARTICLE HEATING TO IMPROVE THERAPEUTICS, DIAGNOSTICS AND REGENERATIVE MEDICINE

John Bischof

University of Minnesota, Departments of Mechanical and Biomedical Engineering, Minneapolis, MN, USA

Gold and iron oxide nanoparticles have unique and tunable properties that allow transduction of optical (light), or radiofrequency (RF) electromagnetic fields to affect heating of biomaterials at multiple scales. This talk will explore the underlying physics and relative advantages of each form of nanoparticle heating for therapeutic treatment of cancer or other disease by hyperthermia. Second, laser heating of gold nanoparticles will be shown to achieve an order of magnitude or more improvement in sensitivity for common point-of-care (POC) diagnostic assays (i.e. a lateral flow immunoassay or LFA) through "thermal" vs. visual contrast. This increase in sensitivity addresses the main weakness of the LFA, increasing opportunities for use in POC settings and avoiding the cost, time and labor of laboratory tests. Finally, both gold and iron oxide nanoparticle heating can be used in regenerative medicine by "nanowarming" vitrified biomaterials at sufficiently rapid and uniform rates to avoid crystallization and cracking. This addresses an important technology bottleneck for both large systems (i.e. tissues and organs) as well as smaller systems (i.e. embryos and oocytes). In summary, this talk demonstrates the growing opportunities for nanoparticle heating in biomedical applications

MON 31

MAGNETIC NANOPARTICLES IN VISCOUS MEDIA - HEATING AND REORIENTATION UNDER AC FIELDS

David Serantes[1,2]

[1]The University of York, York, UK, [2]Universidade de Santiago de Compostela, Santiago de Compostela, Spain

The field of nanomagnetism recommends itself as especially suitable for biomedicine, since magnetic fields are in principle innocuous to the human body and some magnetic materials are very biocompatible. Thus, external magnetic fields can be used to remotely guide magnetic nanomagnets within the body and, when desired, promote specific responses *in situ*. These aspects promoted huge attention to applications as imaging, hyperthermia, or drug delivery/release.

Despite the promising perspectives the obtained results have not, however, fulfilled the expectations for magnetic nanomaterials to become major players in the routine medical practice. The hampering limitations include limited control, toxicity, poor efficiency, and biodegradability. Therefore, towards a higher success for their clinical use it is necessary interdisciplinary work ranging from chemistry (synthesis), physics and engineering (behaviour), to biology (toxicity), and medicine. From the physics point of view, the main problem is that there are no accurate physical models correctly describing what happens with the nanomagnets in the viscous biological tissues. Particularly, a main challenge is to understand the *in situ* behaviour of the particles under external AC fields, which may be used to promote the heat dissipation for hyperthermia or heat-triggered drug release. In this work we will discuss the double functionality of particle shape for synergistic heating and spatial reorientation, what opens the way to combined hyperthermic/mechanical nanoactuators for nanomedicine [1].

References:

[1] K. Simeonidis et al., "*In-situ* particles reorientation during magnetic hyperthermia application: Shape matters twice", Sci. Rep. 6, 38382 (2016).

MON 32

PHYSICAL ASPECTS OF MAGNETIC NANOPARTICLE HYPERTHERMIA

Nikolai Usov[1,2], Vadim Tarasov[1]

[1]National University of Science and Technology «MISiS», Moscow, Russia, [2]Pushkov Institute of Terrestrial Magnetism, Ionosphere and Radio Wave Propagation RAS, Troitsk, Moscow, Russia

In magnetic nanoparticle hyperthermia it is desirable to get useful therapeutic effect with as low as possible concentration of magnetic nanoparticles in biological media. In this report we discuss a possibility of using magnetic vortices as efficient nano heaters in biomedical applications. Magnetization curling state arises in soft magnetic nanoparticles with diameters larger than the single-domain one. Using micromagnetic numerical simulation we show that in an optimal range of particle diameters the magnetization reversal of the vortex is possible for moderate amplitudes of external alternating magnetic field, $H_0 < 100$ Oe. It is shown that in contrast to the case of superparamagnetic nanoparticles [1], the corresponding hysteresis loop area increases with increase of alternating field frequency, so that enormous values of the specific absorption rate, on the order of kW/g, can be obtained at sufficiently high frequencies, $f \sim 0.5 - 1.0$ MHz. Because the diameter D of a non single-domain particle is several times larger than the diameter d of a superparamagnetic particle, the volume of heat generation turns out to be $(D/d)^3$ times larger. We consider also the distribution of the heat generated by assemblies of magnetic nanoparticles in heterogeneous biological media taking into account the effect of mutual magneto- dipole interactions.

[1] N.A. Usov, J. Appl. Phys. 107 (2010) 123909.

MON 33

OPTIMIZING HEATING EFFICIENCY OF MAGNETIC FLUIDS FOR MAGNETIC RESONANCE NANO-THERANOSTIC HYPERTHERMIA

Chencai Wang

University of California, Los Angeles, Los Angeles, CA, USA

The Magnetic Resonance Nano-Theranotic Hyperthermia system has been proposed and constructed recently to diagnose and treat cancer diseases at the same time. The success of this promising clinical application depends on the development of magnetic nanoparticles having precisely controlled physical and magnetic properties to optimize the heating efficiency. For this purpose, we have established a novel model to evaluate the heating efficiency based on three major findings:

(i) Magnetic nanoparticles are interacting in the colloidal suspension. In magnetic fluids, magnetic nanoparticles were found to exhibit several interactions such as magnetic dipole-dipole interaction, steric repulsion and van der Waals attraction. Those interactions can altogether contribute to the formation of aggregates, which experimentally affects the heating mechanisms and the magnitude of heat generated.

(ii) Magnetic susceptibility and magnetic field amplitude are nonlinearly related. As the particle size and magnetic field amplitude increase, the heat generation mechanism becomes more complicated since the linear regime only holds for the case of high temperature and/or weak magnetic field. And larger magnetic field can induce loss process and heating effects, driving the nonlinear response of the magnetic susceptibility.

(iii) Relaxation times due to the Brownian or Néel relaxation mechanisms depend on the amplitude of the applied magnetic field. The well-known zero-field relaxation times underestimate the actual relaxation times and, in particular, can underestimate the Néel relaxation time by many orders of magnitude as it is more sensitive to the magnetic field amplitude. In addition, for Magnetic Resonance Nano-Theranotic Hyperthermia system, the heating effect will be reduced due to the magnetic saturation effects on the nanoparticle suspension associated with the large DC magnetic field.

In order to assess the accuracy of our proposed theoretical model with the consideration of aggregation, nonlinear response of the magnetic susceptibility and magnetic field effects on relaxations times, calculations used this model was compared to previously published experimental data and previous proposed models. From the excellent agreement between the theory and experiments, it is concluded that our proposed new model is able to accurately predict the heating efficiency and the specific loss power as a function of mean magnetic nanoparticle size, even under strong magnetic fields. With the advances in the Magnetic Resonance Nano-Theranotic Hyperthermia system, this new model will become increasingly important to understand the heating mechanisms and to optimize and control the heat efficiency of magnetic nanoparticle.

MON 34

TRANSURETHRAL HIGH INTENSITY ULTRASOUND FOR TREATMENT OF STRESS URINARY INCONTINENCE (SUI): SIMULATION STUDIES WITH PATIENT SPECIFIC MODELS

Dong Liu[1], Matthew Adams[1], Clif Burdette[2], Chris Diederich[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Acoustic MedSystems Inc, Savoy, IL, USA

Introduction: SUI is prevalent in adult women, and often attributed to weakening of the endopelvic fascia and supporting tissues. We aim to investigate transurethral high intensity ultrasound for precise thermal therapy of tissues lateral of the mid-urethra, as a possible means to stiffen supporting tissues and provide a minimally-invasive alternative to surgery. This study's objective is to perform thermal simulations in 3D patient-specific models for two transurethral applicator configurations: dual-sectored tubular transducer with fixed positioning, and curvilinear-focused transducer with sequential rotation.

Methods: 3D patient-specific finite-element models, based on MRI images of pelvic anatomy, were constructed using Mimics. Acoustic pressure distributions were simulated using the rectangular radiator method, and FEM-based thermal simulations were performed using COMSOL Multiphysics, incorporating heterogeneous tissue acoustic and thermal properties. The transducer assembly was positioned in the mid-urethra within a 7mm OD inflatable cooling balloon. Parametric simulations of each configuration were performed: dual-sector tubular transducer (3.5 mm OD, 10 mm length, 6.5 MHz) with two opposing 90° active sectors, and b) curvilinear transducer (3.5 mm x10mm, 4.5-6.5 MHz, radius-of-curvature (ROC) 12mm-28mm). Acoustic powers of 2-3 W for 2-5 min were applied for the tubular device. The curvilinear transducer was sequentially rotated in 20-30° increments, with acoustic power 1.4-1.75W for 90-110 s per shot, to sweep through ~60° target tissue. Parametric studies over ranges of frequency, ROC, power, and duration were applied to determine optimal designs for protection of urethral mucosa and vagina, as well as extent of coverage. Performance measures such as maximum temperature isotherms, lethal thermal dose (>240 EM43°C), thermal effective dose (10-50 EM43°C), safety (<5 EM43°C) profiles, and therapeutic volumes were calculated.

Results: Tubular applicators created maximum temperature 50.6-57.6 °C, 0.9-1.7mm sparing for urethral protection and 11.5-14.9mm penetration depth (45-47°C, >10 EM43°C) from the balloon, varying with applied power levels. Curvilinear applicators generated similar maximum temperature ranging (50-57°C), with greater sparing of urethra (1.3-2.4mm) and deeper penetration (15.0-18.1mm) from the balloon, varying with power levels. Curvilinear applicators with lower frequency (4.5MHz) and large ROC (28mm) can provide better urethral sparing (>2.0mm) and deeper penetration (18 mm).

Conclusion: Transurethral ultrasound applicators are able to treat targeted pelvic tissues lateral and adjacent to the mid- urethra while protecting the urethral mucosa and avoiding the vagina. The tubular applicator can create two large therapy zones without applicator movement. The curvilinear applicator with sequential rotation affords precision placement with greater penetration, more flexibility, and better sparing of the urethra.

MON 35

CHARACTERIZING UTERINE FIBROID TISSUE PROPERTIES FOR THERMAL THERAPIES

Christopher Dillon, Margit Janát-Amsbury, Allison Payne

University of Utah, Salt Lake City, Utah, USA

Background: Magnetic resonance-guided focused ultrasound (MRgFUS) has repeatedly been demonstrated as a safe, non-invasive therapy for uterine fibroids. However, challenges remain including long procedure times and poor treatment response of fibroids with high T2-weighted signal intensity (T2wSI). Accurate pretreatment modeling has the potential to reduce procedure times and improve efficacy through targeted ablations, optimized heating patterns, locations and durations, and model-predictive control. However, models will only be as useful as the accuracy of the tissue properties that inform them. Property values in the literature specific to the myometrium and different types of fibroids are scarce. This abstract presents an innovative excised, perfused human uterine fibroid model that has been designed to accurately characterize the MR, thermal, and acoustic properties of uterine fibroids.

Methods: In this study, women undergoing hysterectomy due to symptomatic fibroids receive a preoperative MRI (Siemens 3T Trio/Prisma) to quantify fibroid MR properties (T1, T2). Immediately following surgical removal, both uterine arteries are cannulated, and the specimen is perfused and immersed in a modified Krebs Henseleit Buffer maintained at a temperature of 37 °C. This setup keeps tissue viable up to 8 hours post surgery. Thermal diffusivity and conductivity are determined with a commercially available thermal property analyzer. Density is measured by the water displacement method. Acoustic attenuation and speed of sound are evaluated by insertion loss with the radiation force balance and through transmission techniques, respectively.

Results: MR properties of 15 fibroids [T1(ms)- Range:675-1451, Ave±SD:1104±187 and T2(ms)- Range:30-91, Ave±SD:51±16] were generally lower than those of 7 myometrium samples [T1(ms)- Range:1077-1660, Ave±SD:1348±195 and T2(ms)- Range:42-71, Ave±SD:58±10]. Thermal diffusivity (*D:* mm ^ 2/s) and thermal conductivity (*k:* W/m/K) for fibroids (N=49, *D* Ave±SD:0.215±0.060 and *k* Ave±SD:0.537±0.047) and myometrium (N=20, *D* Ave±SD:0.196±0.037 and *k* Ave±SD:0.550±0.044) were comparable. Also comparable were acoustic properties of density (Fibroid range(N=6):1042-1085 kg/m ^ 3, Myometrium(N=1):1069 kg/m ^ 3) and speed of sound (m/s) (N=3, Fibroid range:1555-1597, Myometrium range:1575-1620). Initial results suggest that fibroid attenuation (N=2, Range:0.097-0.108 Np/cm@1MHz) is greater than myometrial attenuation (N=1, 0.053 Np/cm@1MHz). Participant recruitment and data collection are ongoing.

Conclusion: This unique setup to characterize fibroid properties has great potential for improving pretreatment modeling as well as the safety, efficacy, and procedure times of uterine fibroid MRgFUS therapies. As more data are collected, property differences based on T2wSI may be identified that will help explain the variable treatment response of fibroids and translate into modified therapeutic regimens.

MON 36

THERMOREGULATION BY AGE: A CARDIOVASCULAR MRI STUDY

A. Colleen Crouch, Joan Greve

University of Michigan, Ann Arbor, MI, USA

Introduction

Thermoregulation is affected by changes in: convective heat transfer from skin to environment, autonomic nervous system and metabolic processes, and cardiovascular (CV) system. The CV system plays a vital role in thermoregulation because of the influence of convection and regulation of regional blood flow. Age is an important factor to consider since elderly subjects are the most likely to experiences deaths due to hypothermia or hyperthermia. Not only does metabolic rate decrease with age, but changes in composition of the skin may also contribute to this decrease in thermoregulation ability. Little is known about the impact of age on the CV system response to core temperature changes. The purpose of this study is to determine age differences in the cardiovascular system's response to core temperature changes, eventually quantifying tissue thermal properties. A better understanding of the physiological contributors to thermoregulation will aid in thermal medicine.

Methods

Male and female, adult and aged, mice were anesthetized and imaged at 7T. Anatomical and functional data included the head (Circle of Willis, CoW), torso (heart and infrarenal aorta), and periphery (femoral, saphenous, popliteal arteries). Data was acquired at 35, 36, 37, and 38°C. Cross-sectional area of the cerebral and peripheral arteries was calculated using thresholding methods. Endocardial area and infrarenal area across the cardiac cycle were quantified, with the former used to calculate stroke volume and cardiac output.

Results

The CoW area remained the same for all animal groups. In the heart, we see statistical differences in ejection fraction for adult and aged males, and differences in cardiac output in adult and aged females. Ejection fraction decreased in males, and remained relatively the same in females with age. In the torso, the infrarenal aorta cross-sectional area and cyclic strain showed similar trends in adult and aged animals. Age had the largest impact on the peripheral vessels response to temperature. Aged males, in particular, had a diminished response to temperature in addition to having smaller cross-sectional areas compared to the adult males. The femoral artery in adult males was 74.3% greater than aged males, and in adult females was only 22% greater than aged females. The femoral artery, in adult males, on average, increased by 21.1%/1°C, adult females by 22.6%/1°C, aged males by 0.578%/1°C, and aged females by 19.8%/1°C.

Conclusion

This work is a novel approach to studying thermoregulation by using imaging techniques to quantify functional changes due to altered core temperature.

MON 37

PHASE I TRIAL OF MR-HIFU MILD HYPERTHERMIA WITH RADIATION AND CHEMOTHERAPY FOR RECURRENT RECTAL CANCER: SECOND PATIENT

William Chu[1,3], Samuel Pichardo[5,6], Yuexi Huang[1,2], Robert Staruch[4], Ari Partanen[5], Merrylee McGuffin[1], Gregory Czarnota[1,2], Kullervo Hynynen[2,3]

[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Sunnybrook Research Institute, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Philips Research, Cambridge, MA, USA, [5]Philips Healthcare, Andover, MA, USA, [6]Thunder Bay Regional Research Institute, Thunder Bay, ON, Canada, [7]Lakehead University, Thunder Bay, ON, Canada

INTRODUCTION: Inoperable rectal cancer recurrence is associated with marginal outcomes when treated with radiation (RT) and chemotherapy (CT). Mild hyperthermia (HT) may sensitize tumors to RT and CT, improving control and quality of life. We report on the second patient treated in a Phase I trial of MR-HIFU HT as an adjuvant to RT and CT for locally recurrent rectal cancer.

METHODS: This study is approved by the local Research Ethics Board. Enrolled patients receive 30.6 Gy over 17 fractions with daily oral capecitabine, plus MR-HIFU HT immediately before RT on days 1, 8, and 15. HT was delivered with the Philips Sonalleve MR-HIFU system on an Achieva 3T MRI, under Investigational Testing Authorization from Health Canada. Feedback control parameters were prescribed to achieve an average temperature of 42.5°C in a 18 mm diameter target region for 30 minutes, without exceeding 45°C.

RESULTS: Of eight screened patients, two have been enrolled, and six excluded due to patient and tumor factors. The second treated patient had an unresectable T3 tumor with a large exophytic component (5 x 8 x 4 cm) extruding from the anus. Patient positioning required careful stacking of two ultrasound gel pads, and application of liquid ultrasound gel directly onto the tumor. Sonication at 1.2 MHz and 60W achieved average target region temperatures of 41.6 to 42.6°C, with T90 and T10 temperatures of 40.5 to 41.7°C and 42.6 to 44.0°C. In each of three sessions, temperatures above 41°C were maintained for at least 30 minutes, with the volume heated above 41°C for at least 10 minutes having average width and length of 35 and 90 mm. Average thermal doses were 8.3, 14.2, and 18.9 CEM43. MR thermometry precision measured as the temporal average of the spatial SD outside the heated region was 1.2±0.4°C. Post-treatment T2-weighted images did not indicate any unintended tissue damage. The patient did not report any sensations of heating, nerve stimulation, or pain during MR-HIFU, and has not reported any adverse events two months post-treatment. Sonications took 34, 32, and 34 min, cooling time between sonications that were restarted because of patient motion took 30, 10, and 13 min, and total MRI suite times were 185, 120, and 120 min.

CONCLUSION: In the second patient treated with MR-HIFU HT, prescribed temperatures and durations were successfully achieved in each of three sessions, with no treatment-related toxicity, and with decreasing overall procedure time.

MON 38

WOUND CARE MANAGEMENT FOLLOWING RE-IRRADIATION AND CONCURRENT HYPERTHERMIA

Nasarachi Onyeuku, Tejan Diwanji, James Snider, Pradip Amin, Zeljko Vujaskovic

University of Maryland, Baltimore, MD, USA

Background: External Thermal Therapy and concurrent radiotherapy (ETT-RT) is a common approach in the setting of recurrent disease, and can improve local control. Poor wound healing and lymphedema are potential complications of any re-treatment strategy. Here, we present three cases to highlight various successful strategies for wound management following ETT-RT.

Methods/Results: Patient #1 is a 67 yo male with testicular mesothelioma s/p right hemiscrotectomy adjuvant carboplatin/pemetrexed and adjuvant RT with progressive disease. He underwent re-ETT-RT to the primary site and regional lymphatics. Treatment complications included persistent open wounds; lymphatic leakage of the lower extremities and scrotum; and surrounding skin erythema, irritation, and pain.

Wound care management included wound clinic every 2-3 weeks and lymphedema clinic weekly. Calendula and calmoseptine were successfully employed to address symptoms of persistent moisture and irritation of the skin in his genital area. Silvadene and clotrimazole were also recommended.

Comprehensive lymphedema management strategies included manual lymphatic drainage practices such as ace wrap bandage placement alternating with compression socks from ankles to his knees and a trial of gradient, sequential, pneumatic pump therapy (Flexitouch Trunk program). Finally, therapeutic exercises encompassing ROM, strength, and aerobic conditioning were also recommended.

Patient #2 is a 50 yo female with recurrent melanoma of the LLE s/p ETT-RT. Treatment was complicated by three areas of non-healing wounds, associated hyperpigmentation, and edema in the treatment field.

A course of antibiotics with clindamycin was prescribed. Santyl BID was also recommended as part of her management.

Patient #3 is a 68 yo M with recurrent epithelioid angiosarcoma of the left inguinal region who completed ETT-RT with EBRT to 45Gy, and interstitial brachytherapy. Following therapy, a malodorous wound developed in the left inguinal region.

Aggressive debridement was performed as regular wound care. Using moist saline gauze, adherent fibrinous slough from the wound surface was mechanically removed. Tenacious fibrinous slough was removed using a #1 curette. A nickel layer of Santyl was placed, followed by which 4 x 4 gauze, ABD, and bolstered by a cover bandage.

Conclusions: Overall, the use of ETT-RT in the setting of re-RT can improve disease control rates. Unfortunately, consequent risks of wound complications and lymphedema exist for all aggressive re-treatment strategies. Poor wound healing can also result from several factors including the recurrent disease itself. Regular follow-up is recommended; and aggressive wound care, utilizing the wide array of options available, is paramount.

MON 39

IMMUNOTHERAPY IN COMBINATION WITH THERMORADIOTHERAPY FOR THE TREATMENT OF REFRACTORY MELANOMA

Dan Kunaprayoon, Zeljko Vujaskovic

University of Maryland, Baltimore, MD, USA

Hyperthermia can have significant clinical effects mediated by the immune system, notably through heat shock protein release, dendritic cell activation, and changes in immune trafficking and surveillance. Radiotherapy also has effects mediated by the immune system and has been shown to promote immune response through cytokine release and neoantigen formation. The addition of hyperthermia to radiation has shown substantial benefits for overall survival and local control in multiple disease sites.

The emergence of immunotherapies, especially checkpoint inhibitors targeting CTLA4 and PD1 pathways and their rapid uptake into clinical practice have increased interest in combining immunotherapy with radiotherapy and hyperthermia, and together present a compelling biological argument for potentiating and augmenting immune response. However, little is known about the clinical effects of combining these therapies in real practice. We report our experience with a patient treated with the combination of immunotherapy, radiotherapy, and thermal therapy to explore the potential benefit and risk of combining immunotherapy with thermoradiotherapy in eliciting treatment response.

TUES 1

CANCER CELL BIOLOGY IN 3D

Denis Wirtz

Johns Hopkins University, Baltimore, MD, USA

Two-dimensional (2D) *in vitro* culture systems have for a number of years provided a controlled and versatile environment for mechanistic studies of cell adhesion, polarization, and migration, three interrelated cell functions critical to cancer metastasis. However, the organization and functions of focal adhesion proteins, protrusion machinery, and microtubule-based polarization in cells embedded in physiologically more relevant 3D extracellular matrices is qualitatively different from their organization and functions on conventional 2D planar substrates. This talk will describe the implications of the dependence of focal adhesion protein-based cell migration on micro-environmental dimensionality (1D vs. 2D vs. 3D), how cell micromechanics plays a critical role in promoting local cell invasion, and associated validation in mouse models. We will also discuss the molecular and biophysical mechanisms used by cancer cells to negotiate different matrix microstructures. Finally, we will discuss the implications of this work in metastatic cancer.

TUES 2

HOST IMMUNE STATUS DETERMINES THE UPTAKE AND RETENTION OF TARGETED ANTIBODY CONJUGATED NANOPARTICLES.

Preethi Korangath, James Barnett, Anirudh Sharma, Jacqueline Stewart, Elizabeth Henderson, Shu-han Yu, Sri Kamal Kandala, Rajeev Hatwar, Mohammed Hedayati, Brian Simons, Saraswati Sukumar, Robert Ivkov

Johns Hopkins University, Baltimore, MD, USA

Background: With current understanding of tumor biology and interaction between a given nanoparticle construct with the tumour microenvironment, there are immense opportunities to fine tune nanoparticles as therapeutic agents or drug delivery vehicles. In the current study, our objective was to study the impact of variations of host immune system on the distribution of ferrite nanoparticles using an allograft model of human HER2 overexpressing breast tumour that develop in a range of mouse model from most immunocompromised to fully immune-competent models.

Methods: Bionized nanoferrite nanoparticles, either conjugated with a monoclonal antibody to human HER2 protein (BNF-HER) or unconjugated nanoparticle (BNF-Plain) were compared to that of PBS-treated allografts. Allograft tumour line was established by transplanting tumour harvested from spontaneous tumours developing in donor FVB/N mice in MMTV-driven mouse model of human HER2 overexpression, by serial transplantation to FVB/N mouse. For this study, allograft tumors were implanted into the 4^{th} mammary gland of individuals representing immunocompetent FVB/N, mature T cell-deficient athymic nude, or highly immunocompromised NOD-SCID gamma (NSG) female mice. When tumor volume reached 150-200 mm^3, animals were randomized into 3 groups, and depending upon cohort, received PBS, BNF-plain, or BNF-HER intravenously. Mice were sacrificed 24 hours post injection to collect tumours. We compared the nanoparticle content and distribution among the tumours and among the three models using histology, immunohistochemistry and inductively-coupled mass spectrometry (ICPMS).

Results: ICP-MS and analysis of Prussian blue stained tissue sections showed significantly higher uptake of iron across all groups in animals injected with BNF-HER than with BNF-Plain. Across the immune-strata of mice, tumour iron concentration of BNF-HER injected subjects were lowest in immunocompromised NSG, increasing in the least immunocompromised athymic nude to highest measured concentrations in tumours grown in fully immunocompetent FVB/N animals. Moreover, there is an increase in the amount of iron content in BNF-Plain treated animals compared to PBS alone in fully immunocompetent FVB/N mouse model. Immunohistochemical analysis revealed that a substantial amount of particles are associated with IBA-1 positive monocytes/ macrophages.

Conclusion: This systematic study using same nanoparticle constructs and tumor model developed in animals of varying immune status showed a profound difference in the uptake and retention of nanoparticles at a given time point. Antibody-conjugated nanoparticles were taken up by tumour-associated immune cells, and animals with efficient immune system had higher uptake due to the interaction between human antibody and mouse immune cells. This shows that the host immune status plays a significant role in nanoparticle uptake.

TUES 3

EFFECT OF HYPERTHERMIA DURATION ON MR-HIFU MEDIATED DOXORUBICIN DELIVERY FROM THERMOSENSITIVE LIPOSOMES: IN VIVO BIODISTRIBUTION AND COMPARISON WITH NUMERICAL MODELS

Robert Staruch[1,2], Sumbul Shaikh[1], Chenchen Bing[1], Joris Nofiele[1], Debra Szczepanski[1], Yu Hong[1], Michelle Wodzak[1], Dieter Haemmerich[3], Noelle Williams[1], Theodore Laetsch[1,4], Rajiv Chopra[1]

[1]UT Southwestern Medical Center, Dallas, TX, USA, [2]Philips Research, Cambridge, MA, USA, [3]Medical University of South Carolina, Charleston, SC, USA, [4]Children's Health, Dallas, TX, USA

BACKGROUND: Doxorubicin (DOX) is effective against many cancers, but its cumulative dose is limited by cardiotoxicity. Localized DOX delivery from thermosensitive liposomes (TSLs) using MR-HIFU hyperthermia (HT) might improve local control in solid tumors without increasing toxicity. Here we investigate the effect of mild HT duration on the relative deposition of DOX in heated rabbit Vx2 tumors compared to unheated tumors, heart, lung, liver, kidney, and spleen. We compare in vivo results to a published multi-compartment pharmacokinetic model of HT-mediated DOX delivery [1].

METHODS: Rabbits bearing bilateral Vx2 tumors were treated with mild HT (42°C) to one tumor for either 10 or 40 minutes (n=10, n=9). HT was delivered using prototype software on a clinical MR-HIFU system (Sonalleve V2 and Ingenia 3T, Philips). TSL-DOX (Celsion) was infused during HT at 2.5 mg/kg over 5-6 min. Tissue samples were harvested 3 hours after drug infusion for DOX quantification using silver nitrate extraction and liquid chromatography-mass spectrometry detection. Numerical simulation of DOX pharmacokinetics was performed using Matlab to solve ordinary differential equations that describe free and liposomal DOX concentrations in systemic plasma, tumor plasma, tumor interstitium, heart, and lump body tissue [1]. We used model parameters previously validated for mouse tumors, so only trends are compared.

RESULTS: MR-HIFU achieved stable, uniform HT of 10 mm diameter regions in rabbit tumors with mean, T90, and T10 of 42.0°C, 41.2°C, and 42.7°C. Target regions for the 10 and 40 min heating groups exceeded 40°C for 11.3±1.5 and 40.4±2.2 min. Measured DOX concentrations in unheated organs did not change significantly between 10 and 40 min: unheated tumor (4.6 vs 5.4 μg/g), heart (6.8 vs 6.8 μg/g), lung (10.0 vs 9.2 μg/g), liver (6.8 vs 4.9 μg/g), kidney (35 vs 28 μg/g), and spleen (29 vs 28 μg/g), using t-tests with Bonferroni correction. DOX in heated tumors increased significantly with longer heating, from 13.4 to 31.2 μg/g (p=0.0005). Therapeutic ratio (TR) between tumor and heart DOX concentrations increased from 2.0 to 4.8 (p=0.0025). Simulations demonstrated a similar increase in TR when heating for 40 vs 10 min. Simulations suggested that further increase in heating duration increases TR, but less rapidly; decreasing injected dose and heated tumor volume increases TR.

CONCLUSION: Our results confirm that prolonged heating increases the therapeutic ratio of HT-mediated doxorubicin delivery from TSLs.

[1] Gasselhuber et al, Comparison of conventional chemotherapy, stealth liposomes and temperature-sensitive liposomes in a mathematical model. PLOS ONE, 2012.

TUES 4

LYSO-THERMOSENSITIVE LIPOSOMAL DOXORUBICIN FOR TREATMENT OF BLADDER CANCER

Andrew Mikhail[1], Ayele Negussie[1], William Pritchard[1], Dieter Haemmerich[2], David Woods[1], Ivane Bakhutashvili[1], Juan Esparza-Trujillo[1], John Karanian[1], Sam Brancato[1], Piyush Agarwal[1], Bradford Wood[1]

[1]National Institutes of Health, Bethesda, MD, USA, [2]Medical University of South Carolina, Charleston, SC, USA

Introduction: Cancer of the urinary bladder has a high rate of recurrence and progression despite locoregional therapy and may be superficial or muscle invasive and is often multifocal, all of which may be amenable to new drug device combinations. The incomplete response of bladder tumours to intravesical drugs has been attributed in part to inadequate drug delivery resulting in insufficient drug concentrations in the bladder wall. Our laboratory has previously demonstrated high levels of doxorubicin (DOX) in tumours when lyso-thermosensitive liposomal doxorubicin (LTLD, ThermoDox®, Celsion Corp.) is administered intravenously with tumor-localized mild hyperthermia (40–42 °C). In addition, we have recently demonstrated the feasibility of drug delivery to the bladder wall following IV administration of LTLD and bladder-localized mild hyperthermia by warm water irrigation. The primary objective of this study was to quantify the accumulation and microdistribution of drug in the bladder wall in order to assess the potential of this method of targeted drug delivery for treatment of bladder cancer.

Methods: Porcine in vivo studies were performed with the following groups: 1) Intravenous (IV) LTLD with hyperthermia; 2) IV doxorubicin (DOX) with hyperthermia; and 3) IV LTLD without hyperthermia. Drug formulations were delivered via 30 min IV infusion coinciding with one-hour bladder irrigation (45 °C water for HT groups, 37°C for non-HT group), followed by immediate bladder resection. DOX penetration was examined in cross sections of the bladder wall by fluorescence imaging. DOX concentrations were measured in consecutive sections parallel to the bladder lumen by liquid chromatography following drug extraction. Computer models were developed to simulate tissue heating and drug release from LTLD.

Results: DOX concentrations in the urothelium/lamina and muscularis, respectively, were 9.7 ± 0.67 and 4.09 ± 0.81 μg/g for IV LTLD with hyperthermia (posterior bladder wall), 1.2 ± 0.39 and 0.86 ± 0.24 μg/g for IV DOX with hyperthermia, and 1.15 ± 0.38 and 0.62 ± 0.15 μg/g for IV LTLD without hyperthermia. Computational model results were consistent with measured DOX levels with some variation attributed to differences in vascularity within the bladder wall. The models suggest adequate temperatures within the bladder wall, and demonstrate importance of adequate hyperthermia duration.

Conclusion: Greater doxorubicin accumulation and distribution within the bladder wall was achieved by mild bladder hyperthermia combined with systemic delivery of LTLD compared to free IV doxorubicin and LTLD without heat. Potentially therapeutic concentrations of DOX were achieved in superficial and muscle layers of the bladder wall using this targeted method of drug delivery justifying further study as a potential treatment for bladder cancer.

TUES 5

BNF-IGG NANOPARTICLE BASE MAGNETIC HYPERTHERMIA FOR TARGETED BREAST CANCER THERAPY

Chun Ting Yang[1,2], Preethi Korangath[2], Jackie Stewart[2], Anirudh Sharma[2], Sri Kandala[2], James Barnett[2], Feng Huei Lin[1], Robert Ivkov[2]

[1]National Taiwan University, Taipei, Taiwan, [2]Johns Hopkins University School of Medicine, Baltimore/Maryland, USA

Purpose: Magnetic hyperthermia (MHT) has been demonstrated to provide potential benefit to treat cancer in preclinical and clinical studies. Magnetic iron oxide nanoparticles (MIONs) can generate heat when exposed to alternating magnetic fields (AMFs). To date, much of the demonstration of therapeutic benefits with MHT have been developed with percutaneous deliver of MIONs directly to site of solid tumors. More challenging has been development of MHT following systemic delivery of the MIONs. In part, localization of MIONs to tumor instead of liver and spleen presents the significant barrier to development of 'targeted' MHT. In study, we aim to characterize the therapeutic effects of MHT following systemic delivery of antibody-labeled MIONs.

Material and Methods: BNF nanoparticles are MIONs that have been used in previous preclinical studies of MHT, and have demonstrated good biocompatibility, heating potential, and contrast for MR imaging. BNF nanoparticles were conjugated with (human) immunoglobulin G (IgG) based upon our previous observations that immune cells within the tumor microenvironment predominantly interact with antibody-labeled MIONs. Approximately fifty female nude mice bearing orthotopic xenograft mammary tumors (HCC1954 human breast cancer cell line) were divided into control and therapy cohorts. When tumors reached a volume of 150 mm3, measured with calipers, mice received a bolus injection into the tail venin of either IgG labeled BNF particles, unlabeled (plain) BNF particles, or saline. 24 hours after injection, mice were anesthetized and treated for 20 min in AMF device as previously described. Rectal temperatures were monitored during treatment, and tumor growth delay was measured as the primary therapy endpoint. Additional endpoints included iron content analysis in tumor, liver, and spleen; blood liver enzyme panels, and histopathology of tumor.

Results: Tumors of control (PBS) and plain BNF injected mice grew at similar rates. Tumors of IgG-BNF treated mice, however, demonstrated significant growth arrest and even regressed in some individuals. Analysis of liver and splenic iron contents revealed significantly lower iron accumulation in mice injected with IgG-BNF MIONs than those injected with BNF-plain; however, both groups had higher organ Fe content than PBS controls. Analysis of liver enzyme levels collected from blood of treated mice showed significantly higher concentrations of enzymes in mice treated with BNF-plain than with either IgG-BNF or PBS controls, suggesting more significant liver damage in that cohort. **Conclusions:** Antibody-labeled MIONs offer significant potential to enhance targeted MHT for cancer. In our ongoing studies, we continue to explore the role of immune cells residing the tumor microenvironment to regulate uptake of these particles and effects of MHT.

TUES 6

CHARACTERIZATION OF A DUAL DRUG-LOADED STEALTH NANOSCALE LIPOSOMAL CARRIER FOR DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

Fred Lam[1], Stephen Morton[1], Jeffrey Wyckoff[1], Amanda Maffa[1], Elena Balkanska-Sinclair[3], Paula Hammond[1], Scott Floyd[3], Michael Yaffe[1,2]

[1]Koch Institute for Integrative Cancer Resarch at MIT, Cambridge, USA, [2]Harvard Medical School, Boston, USA, [3]Duke University School of Medicine, North Carolina, USA

Introduction - The dependence on EPR effects for intravascular delivery of nanoparticles (NPs) to tumors limits the efficacy of nanomedicines for cancer therapy. The ability to package multiple cargo within a single NP can also help ameliorate emergence of treatment resistance to single agent therapies. To address these issues, we developed a functionalized stealth liposomal NP that can achieve time-staggered release of dual combination therapies.

Methods – Dually loaded liposomal carriers (56:39:5 DSPC:Cholesterol:POPG) were fabricated using a traditional thin film-hydration method. Cy3-labeled liposomes were functionalized with DSPE-PEG_{2K}-transferrin (Tf-NP) to assess their ability to cross the intact BBB in non-tumor bearing mice using *in vivo* multiphoton microscopy through a cranial window technique. Biodistribution studies were also performed to assess percent uptake of liposomes in the brain. The tumor-targeting ability of the liposomes were then assessed *in vivo* in U87MG and GL261 intracranial orthotopic mouse models of glioblastoma. Mice were treated with either liposomes loaded with the bromodomain inhibitor JQ1, the DNA damaging agent Temozolomide (TMZ), dual-loaded (JQ1+TMZ) combination therapy, or equivalent dosing of free drug, and assessed for changes in tumor signal and survival benefits. At the end of the treatment course, mice were euthanized, their brains perfused and fixed, and IHC performed to look for signs of DNA damage and apoptosis. Blood samples were collected throughout the treatment course to assess signs of systemic toxicity between liposome-loaded *vs* free drug arms.

Results – Biodistribution studies demonstrated 1.7% total uptake of the injected dose of Tf-NP in the brains of non-tumor bearing mice 24 hours post IV injection. Confocal and multiphoton microscopy demonstrated transport of Tf-NPs across the intact BBB with accumulation in the surrounding subarachnoid space of the brain as well as accumulation on the surface of intracranial U87MG and GL261 tumors. Mice treated with JQ1, TMZ, or JQ1+TMZ loaded in Tf-NPs demonstrated significantly decreased tumor signal and prolonged survival compared to mice treated with free drugs. Finally, mice treated with liposomes demonstrated protection from the systemic effects of TMZ and JQ1 compared to mice in the free drug treatment arms. IHC analyses of post-mortem brain sections demonstrated increased markers of DNA damage and apoptosis and decreased proliferative index in the liposome vs free-drug treatment arms, suggesting superior therapeutic efficacy in liposome-treated mice.

Conclusion – Use of a simple, functionalized, dual-loaded liposome with stealth properties may have translation potential for delivering novel combination therapies to improve treatment resistance in patients with glioblastomas.

TUES 7

EXPLOITING SYNTHETIC LETHALITY WITH NANOTECHNOLOGY: A NEW PARADIGM TO TARGET P53 MUTANT TUMORS.

Yi Wen Kong[1], Erik Dreaden[1], Sandra Morandell[1], Mohiuddin Quadir[3], Paula Hammond[1], Michael Yaffe[1,2]

[1]Massachusetts Institute of Technology, Cambridge, Massachusetts, USA, [2]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, [3]North Dakota State University, Fargo, North Dakota, USA

Lung cancer is the leading cause of cancer death in the United States. The frontline chemotherapeutic regimen used for treatment is only moderately effective: only 30% of patients with advance non-small cell lung cancer (NSCLC) respond to therapy, and even those who respond to treatment eventually develop resistance. Standard-of-care treatment for NSCLC includes platinum chemotherapy, which has, at its core, agents that exert cytotoxic effects by causing DNA damage. However, the striking success of these cytotoxic agents in curing hematopoietic malignancies has, for the most part, not been transferrable to solid tumors due to an incomplete understanding of what governs sensitivity or resistance to DNA damage.

Recently, we identified a novel downstream signal effector in the p38 MAPK stress response pathway – the protein kinase MK2 (MAPKAP-K2) – that modulates the response of cells to DNA damage. We showed that MK2 depletion is synthetically lethal with mutation of the tumor suppressor p53 in NSCLC (~50%) following treatment with platinum chemotherapy *in vitro*. Importantly, this dramatic chemo-sensitization effect is not seen in the non-tumor cells that have functional p53. Thus MK2 depletion enhances tumor cell killing *in vitro*. We therefore hypothesize that tumor-specific silencing of MK2 *in vivo* will dramatically enhance tumor killing by DNA-damaging chemotherapy in NSCLC tumors that lack functional p53. To exploit this new tumor vulnerability, we have developed a novel strategy to achieve synthetically lethal drugging of NSCLC tumors *in vivo* by nanoparticle-based RNAi delivery in combination with platinum-based drugs. To silence MK2, we have engineered a series of lipid-like peptide co-polymers that self-assemble into nanoscale drug carriers that efficiently package and deliver small interfering RNA (siRNA) to NSCLC tumors. Small interfering RNA delivered to cells with functional p53 is non-toxic, while potent cell killing is observed in NSCLC tumor treated with platinum therapy.

Our newly developed understanding of cellular signaling changes that drive the progression and survival of the cancer, coupled with recent advances in self-assembled polymer nanotechnologies, provide unique opportunities to enhance response of NSCLC to current standard-of-care chemotherapeutics.

TUES 8

A COMPREHENSIVE HISTOLOGICAL ANALYSIS OF NANOPARTICLE TARGETING IN HER2+ BREAST CANCER

Elizabeth Henderson, Preethi Korangath, Brian Simons, Robert Ivkov

Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background:

The current paradigm in nanomedicine focuses on the physical properties of nanoparticles and ICP-MS, but we believe that the fate of systemically delivered nanoparticles is determined by host biology, and that the host immune system interacts with both the nanoparticles and the tumor to determine the targeting of the nanoparticles. To date, no extensive histology studies on nanoparticle distribution have been conducted using targeted or non-targeted nanoparticles. In this study, we aim to use histology to thoroughly examine HER2 targeted and non-targeted iron oxide nanoparticle distribution and its co-localization with other cell types in HER2 positive and negative tumor microenvironments grown in animals with varying immune status.

Methods:

Orthotopic xenografts of mammary gland tumors were grown in both Nude and NOD/SCID-gamma (NSG) mice. Cell lines used to generate tumors comprised MB-AMB-231, HCC1954, BT474, and the isogenic pair MCF7/neo and MCF7/HER (which has 1 scrambled gene or 1 HER2 gene insert, respectively). In all, 50 mice were injected on two sides with tumor cells. When tumors reached 150mm^3, mice received an intravenous tail vein injection of bionized nanoferrite (BNF) particles, BNF-HER, particles, or PBS. Tumors were harvested 24 hours later; half were analyzed for total iron content (using ICP-MS), while the other half were formalin fixed, paraffin embedded, and processed for histopathological analysis. Parafilm blocks were sectioned and tissues were prepared for staining and immunohistochemistry with hematoxylin and eosin, Prussian Blue for iron distribution, IBA1 to characterize macrophages, CD31 for vascularity, and HER2 for its expression levels. Tissue slides were digitally scanned for archiving and scored by a pathologist as well as being analyzed digitally using Aperio ImageScope software. In ongoing studies, we are determining the spatial distribution of nanoparticles relative to the tumor edge, middle, and center, and trying to ascertain how nanoparticle distribution is affected by differences in tumor type and structure. Various strategies to quantify nanoparticle spatial distribution are being explored.

Results:

Nanoparticles appear to co-localize with IBA1+ immune cells rather than HER2 expressing tumor cells. Additionally, there is little evidence of BNF-Plain uptake, but BNF-HER is internalized about 3x higher in all tumors, regardless of their HER2 status.

Conclusions:

Initial results from ICP-MS and histology scoring indicate little to no correlation between nanoparticle uptake and tumor HER2 status. Histology analysis reveals marked differences in nanoparticle uptake and distribution across different tumor types and mouse models. Results of spatial distribution patterns and other analyses will be presented.

TUES 9

COMPACT ULTRASOUND APPLICATOR FOR HYPERTHERMIA TREATMENT OF THE TRANSGENIC ADENOCARCINOMA MOUSE PROSTATE MODEL (TRAMP) WITH MR THERMOMETRY IN A 14T MRI SCANNER

Jessie Lee, Matthew Adams, Peter Jones, Eugene Ozhinsky, Viola Rieke, John Kurhanewicz, Chris Diederich

University of California - San Francisco, San Francisco, CA, USA

Introduction: Hyperthermia combined with radiation or chemotherapy remains a promising potential treatment option for prostate cancer. Understanding tumor physiology changes in response to hyperthermia is crucial in determining the timing and dose of adjuvant radiation or chemotherapy. Hyperpolarized C^{13} MRI can monitor metabolism and perfusion in tumor tissue before/after hyperthermia exposure. This study will be performed in a 40mm-bore 14T MRI scanner using the TRAMP mouse model, but requires a compact applicator for conformal, well-controlled heating and integrated temperature monitoring to correlate C^{13} biomarkers with tissue temperature and thermal dose exposure. The objective of this study is to design and evaluate a compact ultrasound hyperthermia device and temperature-monitoring platform compatible with the 14T MRI system.

Methods: The ultrasound applicator consists of an air-backed planar transducer (4mmx8mm) mounted on a low-profile 3D-printed housing (18mmx12mmx5mm), coupling to the tissue with circulating degassed water within a distensible silicone membrane. The applicator was secured onto a TRAMP mouse with a solid prostate tumor ($5cm^3$), aiming from ventral to dorsal with a coupling water absorber on the dorsal side to prevent acoustic reflections. Two different treatments (25min, 10MHz, 1.34-2.28W/cm^2) were performed in a small-bore 14T MRI scanner. Multi-slice PRF-based thermometry was performed in ten 1.25mm-thick axial slices acquired using a gradient-echo sequence (TE/TR=2.5/65ms, 0.3125x0.3125mm). The temperature maps were updated every 10s during power on/off and 30s during pseudo-state-state.

Results: The acoustic efficiency of the applicator was 43% at 10MHz with acoustic beam dimensions 3mmx5mm. The temperature in 5.4-5.9mm width x 6.25mm length x 5.5-6.8mm depth of the tumor was increased to at least 40°C within 30s. After heating for 12 minutes, 1.4-1.9cm^3 of the tumor reached temperatures from 40°C-45°C and was maintained throughout the 30-minute treatment. 0.3-0.5cm^3 of the tumor volume was above 45°C (max width 5.5mm x depth 8.3mm). The applied power level could be lowered to decrease the maximum temperature as required.

Conclusions: A practical, low-profile, MR-compatible ultrasound device was fabricated and is capable of heating small animal tumor volumes with concurrent MRTI in a 14T 40mm-bore MRI scanner. Temperature maps can be overlaid with high-resolution anatomical images across the entire tumor at an adequate update time for hyperthermia treatment monitoring and control. For future studies, temperature maps will be correlated to tumor's metabolism, perfusion, and necrosis acquired with hyperpolarized C^{13}-labeled biomarkers pyruvate, urea, and fumarate. Automated feedback control over power can also be integrated to minimize temperature fluctuations and better maintain steady-state.

TUES 10

MR-GUIDED HIFU-INDUCED HYPERTHERMIA FOR LOCAL DRUG DELIVERY IN BREAST CANCER: MR THERMOMETRY EVALUATION AND PRECLINICAL VALIDATION

Roel Deckers[1], Charles Mougenot[1], Josanne S. De Maar[1], Manon N.G. Braat[1], Britt B.M. Suelmann[2], Sabine C. Linn[3], Elsken Van der Wall[2], Clemens Bos[1], Lambertus W. Bartels[1], Chrit T.W. Moonen[1]

[1]Imaging Division, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands, [3]Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

Introduction: Targeted drug delivery using temperature sensitive liposomes in combination with hyperthermia allows for more effective treatment by depositing high drug concentrations in the tumour[1]. In animal models, ThermoDox (i.e. temperature sensitive liposomal doxorubicin) has been shown to deliver up to 25 times more doxorubicin into tumours than intravenous infusion alone, and 5 times more doxorubicin than standard liposomal formulations of the drug[2-4]. ThermoDox is currently evaluated in clinical studies in combination with RFA in primary liver cancer[5] and in combination with mild hyperthermia in recurrent chest wall breast cancer[6]. We are preparing a phase I study to investigate the safety and tolerability of ThermoDox in combination with MR guided High Intensity Focused Ultrasound (MR-HIFU) in breast cancer. Here, we present the results of a preclinical study to evaluate the performance of MR-HIFU for inducing hyperthermia with an extended duration (i.e. > 15 min). The main points of interest were (i) the drift of the main magnetic field, (ii) respiration-induced susceptibility artefacts, and (iii) robustness of temperature control.

Methods: All experiments were performed on a dedicated breast MR-HIFU system (Philips Healthcare, Vantaa, Finland) integrated with a clinical 1.5-T MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands)[7]. Respiratory-gated segmented echo planar imaging (EPI) was used for PRFS-based thermometry. A motorized stage allowed for mimicking respiration induced magnetic field distortions in agar gel phantoms. Volunteers breathed in a regular pattern of 2 seconds inhalation, 2 seconds exhalation and 4 seconds breath hold. A similar breathing pattern is expected in anesthetized patients.

Results: Subtraction of the average magnetic field change from all voxels in two ROIs positioned outside the phantom/breast from all voxels in the temperature map allowed for correction of the baseline drift. Respiration-induced magnetic field fluctuations during MR temperature mapping were avoided by performing respiratory-gated MR thermometry. In the phantom the mean standard deviation (SD) of the temperature decreased from 2.3±0.9°C to 0.3±0.07 °C. In volunteers the mean SD of the temperature decreased from 6.4±4.6°C to 1.4±0.5°C. The T10 and T90 within the target region were 41.9±0.9 °C and 40.4±0.8 °C.

Conclusion: Drift-corrected, respiratory-gated MR thermometry allowed for accurate temperature mapping in breast tissue and allowed for well controlled heating in agar gel for at least 15 minutes.

References: [1]Landon, 2011, Nanomed J; [2]Kong, 2000, Cancer Res; [3]Ranjan, 2012, JCR; [4]Staruch, 2012, IJH; [5]Wood, 2012, Intervent Radial; [6]Zagar, 2014, IJH; [7]Merckel, 2013, Cardiovasc Intervent Radiol

Acknowledgements: Dutch Cancer Society; VoltaValo (CTMM)

TUES 11

REAL-TIME SPATIOTEMPORAL CONTROL OF TRANSCRANIAL FOCUSED ULTRASOUND IN VIVO

Dalong Liu[1,2], Kyle Schaible[1], Walter Low[1], Emad Ebbini[1]

[1]University of Minnesota Twin Cities, Minneapolis, MN, USA, [2]Siemens Health Solutions, Seattle, WA, USA

Background

Image-guided tFUS has been shown to produce localized thermal therapy for the treatment of brain tumors, essential tremor, Parkinson's disease, etc. Subtherapeutic applications of tFUS energy provide treatment options in neuromodulation and blood brain barrier opening for drug delivery. We have developed a dual-mode ultrasound array (DMUA) system for image-guided tFUS application in small-animal models in vivo. The goal of this study is to demonstrate the real-time closed-loop spatiotemporal control of tFUS patterns in vivo using DMUAs.

Methods

A 64-element, 3.5 MHz DMUA was used to target specific structures within the brain of Sprague Dawley rats (275 – 330 gm) under IACUC-approved protocol. The animals were prone positioned with their heads fixed to a stereotaxic stage. The DMUA provided imaging guidance utilizing synthetic-aperture (SA) imaging at 30 fps. Single-transmit focus (STF) imaging was used intermittently with (sub)therapeutic focus ultrasound (FUS) bursts (2 ms duration) at 400 fps. DMUA echo data was used for evaluating temperature change at the target location using our previously published ultrasound thermography (UST) algorithm. The UST imaging data (at 400 fps) was used as feedback for a closed-loop control of tFUS-induced temperature at the target location. This was performed for a variety of temperature set points (2 – 6 degree rise) and heating durations (4 – 16 seconds). For each animal, the bregma and lambda suture lines were located on the skull with the help of 3D ultrasound imaging. Transcranial FUS was then applied at specific locations within the brain with reference to the bregma. Animals were survived for a minimum of 2 days and histological evaluation was performed for the majority of the animals.

Results

Temperature level at the target was maintained =/- 0.2 degC of the set point, even in the presence of pulsation and gasping movements. This was due to the relatively high frame rate used for capturing temperature change. Spatiotemporal maps have shown localized heating with some shifting towards the transducer due to the lens effect of the skull. All animals treated the procedure well and survived till their scheduled sacrifice time. No damage to brain tissues was observed on H&E in any of the treated animals. Evidence of BBB opening was demonstrated by using Evans blue.

Conclusion

The results have demonstrated the feasibility of image-based closed-loop spatiotemporal control of thermal tFUS patterns in rat brain in vivo. Application of this technology in the treatment of stroke and epilepsy is being investigated.

TUES 12

INTEGRATING CATHETER-BASED THERAPEUTIC ULTRASOUND WITH DEPLOYABLE REFLECTORS AND FLUID LENSES TO ENHANCE FOCAL GAIN AND PENETRATION DEPTH.

Matthew Adams[1], Vasant Salgaonkar[1], Graham Sommer[2], Chris Diederich[1]

[1]UC San Francisco, San Francisco, CA, USA, [2]Stanford University Medical Center, Palo Alto, CA, USA

Introduction: Catheter-based endoluminal ultrasound applicators can generate spatially-precise thermal ablation of tissues adjacent to body lumens. Due to size constraints required for endoluminal applicators to navigate anatomical passages, integrated transducers have a small aperture, which limits acoustic and thermal penetration typically to within a few centimetres deep in tissue. This study explores general concepts and specific designs for integrating endoluminal ultrasound applicators with balloon-based deployable acoustic reflectors and fluid lenses, which can be expanded at target luminal sites to enhance the acoustic aperture for deeper and more selective heating generation. Acoustic and biothermal theoretical studies, along with benchtop measurements of proof-of-concept assemblies, were used to characterize the proposed applicator assemblies.

Methods: Applicator assemblies with either side-firing or end-firing capabilities were conceptualized and investigated. They consist of fixed arrays of tubular or planar transducers surrounded by an expandable reflective balloon that directs energy through a perfluorocarbon-based plano-convex fluid lens. Acoustic modelling of the assemblies was performed using the rectangular radiator method and secondary sources to account for wave refraction/reflection at material interfaces. Biothermal models simulated applicator placement in the stomach for endoluminal ablation of liver or pancreatic tissues at target depths between 1-10 cm. Proof-of-concept assemblies were fabricated and characterized using hydrophone measurements of beam distributions across a range of lens focal lengths.

Results: Simulations of the applicator assemblies indicate that as the expanded reflector-lens balloon diameter increases, smaller foci with greater focal gain and deeper potential penetration depth can be achieved. Simulated 1.5 MHz assemblies with a collapsed diameter of ~10-12 mm and expanded balloon diameters of ~40-50 mm could produce focal intensity gain >100 at depths between 24-84 mm and 12-65 mm in water for the end-firing and side-firing configurations, respectively. A proof-of-concept end-fire assembly (1.7 MHz, 4.75 mm tubular transducer radius, 31 mm brass reflector) illustrated focusing capabilities at variable depths between 10-70 mm by adjusting distension of the fluid lens, with a maximum focal intensity gain of ~60. Biothermal ablation simulations (75°C max, 30 s sonication duration) for assemblies with 40-50 mm expanded diameters demonstrated generation of selective thermal lesions that increased in size (end-fire: 9-42 mm length x 3.8-4.5 mm width; side-fire: 15-60 mm length x 3.9-7.2 mm width) as treatment depth increased from 20-100 mm in liver tissue.

Conclusions: Preliminary investigations illustrate that the incorporation of deployable reflectors and fluid lenses can significantly enhance focal gain and penetrative capabilities of inherently compact catheter-based ultrasound applicators.

TUES 13

IMPROVEMENT OF SPATIAL RESOLUTION FOR TEMPERATURE IMAGING WITH 1°C ACCURACY FROM 50 TO 2MM^2 USING A STOCHASTIC-SIGNAL FRAMEWORK ON MEASURED ULTRASONIC IMAGES

Martin Arthur, Jason Trobaugh

Washington University in St. Louis, St. Louis, MO, USA

Background: Thermal therapies from cryosurgery to ablation would benefit from a non-invasive, safe, inexpensive and convenient 3D thermometer to monitor heating patterns. Ultrasound is a modality that meets these requirements. Agreement among predicted, simulated and measured change in the backscattered energy (CBE) from both our *in vitro* and *in vivo* experiments has shown that CBE can be used for temperature imaging (TI) in both 2D and 3D during non-uniform heating. Previously we formalized a stochastic-signal framework for the CBE approach to TI and improved temperature accuracy in simulations. Here we applied this stochastic-signal framework to experimental data.

Methods: Our phased-array imaging system is a Terason 3000, which produces images with signal-to-noise-ratio (SNR) values from typical experiments that range from 18 to 28 dB. Using our stochastic-signal framework in simulation, assuming uniformly distributed tissue scatterers, the backscattered-energy (BE) probability density function (pdf) was found analytically. The pdf was used to estimate CBE resulting in an effective SNR >40 dB, which reduced the uncertainty in CBE to about 0.2 dB. After optimized, non-rigid motion compensation in 3D non-uniform heating studies of turkey breast, CBE was used to infer temperature with 1°C accuracy over 7x7 mm regions. Here we modified our stochastic-signal framework for use with measured images to determine the monotonicity, linearity and uncertainty in CBE with temperature as a function of region size in 3D calibration studies of turkey breast uniformly heated from 37-45°C.

Results: CBE was linear with or without our framework for 7x7 mm image regions. The residual norm for linear fits of CBE were 0.54±0.40 dB without and 0.22±0.18dB with our framework, respectively. For 2x2 mm image regions the residual norm for the linear fits of CBE were 1.24±0.67 dB without and 0.24±0.21dB with, respectively. At 2x2 mm, as the residual norms indicate, CBE was not linear without our framework, but it was with it. Therefore, using our framework for estimating CBE, TI region size can be reduced by a factor of 25, while maintaining 1°C accuracy.

Conclusions: Using our stochastic-signal framework improved spatial resolution of CBE TI by a factor of 25. The resulting improvement in spatial resolution without loss of accuracy makes CBE TI comparable to the accuracy and resolution of TI with MRI.

1) JW Trobaugh, RM Arthur, WL Straube and EG Moros, *UMB,* 34:289–298, 2008.

2) RM Arthur, D Basu, Y Guo, JW Trobaugh, and EG Moros, *IEEE Trans. UFFC,* 57:1724-1733, 2010.

3) Y Guo, *PhD Dissertation*, Washington University in St. Louis, 2009.

Support: R21-CA90531, R01-CA107558 and the Wilkinson Trust at Washington University, St. Louis.

TUES 14

TRANSURETHRAL ULTRASOUND TO INDUCE COLLAGEN REGENERATION FOR TREATMENT OF STRESS URINARY INCONTINENCE (SUI)

Goutam Ghoshal[1], Emery Williams[1], Paul Neubauer[1], Patrick Roady[3], Corrine Bromfield[3], Clifford Shipley[3], Laurie Rund[3], Chris Diederich[2], E. Clif Burdette[1]

[1]Acoustic MedSystems, Inc., Savoy, IL, USA, [2]University of California at San Francisco, San Francisco, CA, USA, [3]University of Illinois, Urbana-Champaign, Urbana, IL, USA

Background

SUI is the most common type of urinary incontinence symptomatic in 15 million adult women in the U.S. Current treatment strategies either have limitations, are ineffective, or lack applicability to a wide range of patients. Transurethral ultrasound thermal therapy is proposed to induce collagen regeneration to tighten surrounding supportive tissue structures near the urethra for treatment of SUI. Objective of this study is to develop the transurethral ultrasound applicator and evaluate in the GU tract of a large animal model.

Methods

Transurethral ultrasound applicators with bilaterally sectored 3.5mm OD x 10-15 mm long tubular transducers, operating at 6.5 MHz and within an expandable 7 mm urethral cooling balloon, were designed for urethral insertion and placement to precisely deliver thermal energy to discrete regions of endopelvic fascia, pubourethral ligaments, and supportive structures lateral to the urethra. A series of acute (n=4) and survival at 3-4 days (n=6) and 30 days (n=2) experiments were performed in ewes to assess the thermal dosimetry, localization of thermal energy and assess thermal damage and tissue effect. Ultrasound imaging was used to verify catheter placement at both 2 cm and 5 cm from the bladder neck in order for two trials to be performed per animal. Various applied power levels and duration of therapy delivery were evaluated. Post procedure, either acute or after survival, the urethra and surrounding tissues were harvested, gross observations of thermal damage performed, TTC staining, and fixed for histological evaluation with H&E staining.

Results

Both acute and survival in vivo experiments demonstrated that for a duration of 2 minutes at 3-4 Watts acoustic energy delivered at two longitudinal positions, laterally bi-directional in the tissues surrounding the urethra, can penetrate up to 10-15 mm. The histopathology analysis demonstrated thermally treated regions in the connective tissues beyond the urethra, with limited to no thermal damage to the urethral mucosa or the vaginal wall. Analysis of the tissue sections and histology of the survival animals indicates tissue healing, neocollagenisis, and regeneration in the treated region.

Conclusion

These preliminary results suggest catheter-based therapeutic ultrasound may be delivered transurethrally, and used for collagen regeneration and tissue tightening in the female endopelvic fascia, while preserving the urethral mucosa. These dual-sectored transurethral applicators may provide a novel and fast minimally-invasive treatment alternative to the traditional surgical treatment for stress urinary incontinence.

TUES 15

ELECTROTHERMAL MODEL OF PULSED RADIOFREQUENCY ABLATION FOR PAIN RELIEF: COMPUTER STUDY AND IN VITRO VALIDATION

Elzbieta Ewertowska[1], Borja Mercadal[2], Victor Muñoz[3], Antoni Ivorra[2,5], Macarena Trujillo[4], Enrique Berjano[1]

[1]Department of Electronic Engineering, Universitat Politécnica de Valéncia, Valencia, Spain, [2]Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain, [3]Neurotherm Spain, Barcelona, Spain, [4]Instituto Universitario de Matemática Pura y Aplicada, Universitat Politécnica de Valéncia, Valencia, Spain, [5]Serra Húnter Fellow Programme, Generalitat de Catalunya, Spain

Introduction: Bursts of radiofrequency current with a duration of 20 ms are used at present for pain treatment. This technique is known as pulsed radiofrequency (PRF) and it is believed that its mechanism of action is based on a direct effect of the electric field on the nerves rather than on thermal effects. Actually, the technique is applied minimizing thermal damage. A strategy employed in order to avoid thermal damage is to apply a temperature controller during the treatment. The present study analyses the influence of a set of pulse parameters on the electrical performance taking into account the accompanying thermal effects.

Methods: The study considered radiofrequency pulses of varying duration (20 - 5 ms), repetition frequency (2 – 5 Hz) and voltage (45 vs. 55 V). The impact of reducing pulse duration was analyzed in terms of tissue thermal damage by means of the Arrhenius damage function and the total magnitude of electrical field produced. A temperature control algorithm was included simultaneously to assess thermal evolution during each PRF treatment. An in vitro experimental validation of the modeling methodology was performed using PRF on an agar phantom model and was used to corroborate the results from computer modeling.

Results: The outcome of the study showed that the same energy provided by a PRF treatment with reduced pulse duration resulted in the magnitude of the provided electric field of up to 20% higher. Furthermore, thermal damage of tissue was prevented only in cases considering temperature control algorithm that reduced the total number of pulses up to 50%. The use of temperature controller showed no effect on the magnitude of electric field.

Conclusion: It is feasible to improve the electrical performance of PRF by adjusting the characteristics of the radiofrequency pulsation and hence the outcome of clinical treatment. Nevertheless, there is always a need to employ temperature controller to avoid thermal damage even if the reduction of pulse duration implies lower temperatures in tissue.

TUES 16

WINDOWS TO THE BRAIN (WTTB): A NEW PLATFORM FOR DIAGNOSIS AND THERAPY OF BRAIN PATHOLOGIES AND AN EXAMPLE OF BINATIONAL COLLABORATION BETWEEN USA-MEXICO

Guillermo Aguilar[1,2], Santiago Camacho-Lopez[2,1], Juan Hernandez-Cordero[3], Ruben Ramos-Garcia[4]

[1]University of California Riverside, Riverside, CA, USA, [2]CICESE, Ensenada, BC, Mexico, [3]UNAM, Mexico City, Mexico, [4]INAOE, Puebla, Pue, Mexico

At the laboratory of Transport Phenomena for Biomedical Applications (LTPBA) at UCR, we have carried out studies aimed at understanding how lasers can better assist in a variety of biomedical applications. Currently, one of the research thrusts in my research group aims at developing a novel transparent polycrystalline Yttria-Stablized-Zirconia (YSZ) cranial implant ("window") that enables life-long, non-invasive delivery and/or collection of laser light into and from shallow and deep brain tissue on demand. Such an implant would allow for real-time and highly precise visualization and treatment of diverse brain pathologies, such as those resulting from traumatic brain injury (TBI) or brain tumors, without the need of highly-invasive craniotomies or trepanation procedures. The window could be permanently covered with native scalp that can be rendered temporarily transparent on demand in a minimally-invasive manner using percutaneous drug delivery of optical clearing agents (OCAs) with microneedles. A summary of these results as well as ongoing and future studies pertaining to this research thrust will be presented.

TUES 17

BIOPHOTONICS: A GROWING NETWORK IN MÉXICO WHICH AIMS TO ADDRESS HEALTH ISSUES

Santiago Camacho-Lopez[1], Ruben Ramos-Garcia[2]

[1]CICESE, Ensenada, Baja California, Mexico, [2]INAOE, Puebla, Puebla, Mexico

The optics and biology communities in Mexico are both strong and state of the art. Recently a Biophotonics network, which is supported by CONACyT (Consejo Nacional de Ciencia y Tecnología), was created. This network with nearly 100 researchers (+100 students) brings in the expertise of many in the fields of optics, photonics, biology, medicine, chemistry and physics. Top institutions among universities, hospitals, and research institutes contribute with laboratory infrastructure and human resources to investigate current health issues. The Biophotonics network in Mexico is currently composed by the following areas: optical micromanipulation; light propagation in highly scattering media and speckle laser imaging; thermography and biosensors; photodynamic therapy; advanced optical microscopy and spectroscopy; materials for biophotonics; cavitation; optical processing of medical images; human vision optics and light sources. We are seeking for collaborations with the medical community for us to understand current health challenges. We aim to offer appropriate biophotonics tools developed within a joint effort between the optics/photonics researchers and physicians to the medical community. In this work we will present an overview of the biophotonics network and a few examples of current research that illustrate our long-term goals.

TUES 18

BIOMEDICAL PHOTONIC DEVICES USING PHOTOTHERMAL POLYMER MEDIA

Reinher Pimentel-Domínguez, Juan Hernández-Cordero

Instituto de Investigaciones en Materiales, UNAM, Cd. Universitaria, CD Mx, Mexico

Small-scale heat sources, capable to generate microbubbles in liquids, have shown to be useful for microfluidics, medical imaging and biomedical analysis. Localized heat delivery has also shown promising results for cancer treatment as well as for high-resolution patterning and processing of biocompatible polymers. While some of these applications require a rapid increase in temperature to produce phase transitions in fluids, others rely on generating a steady and controlled temperature gradient. Photothermal heaters, incorporating photothermal materials irradiated with laser light, have shown to be capable of producing rapid and highly localized heat. They have also shown promising results for biomedical applications owing to their simplicity, particularly when compared to other techniques such as radiofrequency generators, microwave antennas and ultrasound probes. The temperature increase obtained with photothermal heaters depends mostly on the optical power impinging on the photothermal material; nonetheless, the thermal properties of the photothermal material are evidently of paramount importance to obtain a targeted temperature for a specific application.

Interaction of laser radiation with metallic and carbon nanoparticles has shown to provide optically triggered responses in otherwise transparent media. As an example, incorporation of these materials in polymers has lead to generation of plasmonic and photothermal effects through the enhanced optical absorption of these nanoparticles. Although the potential toxicity of some materials at the nano-scale is still under debate, it is clear that they offer attractive features for developing phothermal devices. In this work, we will present advances on the application nanomaterials for developing photothermal photonic devices intended for biomedical applications. The devices are based on optical fibers incorporating either gold nanolayers or a biocompatible polymer (polydimethylsiloxane, PDMS) with embedded carbon nanoparticles (CNPs). Both materials are capable generate heat through laser absorption and can be easily incorporated in fiber waveguides to fabricate optical fiber probes. Laser light from a laser diode is launched in one end of the fiber and emerges at the coated end to interact with the nanomaterials. These serve as efficient optical absorbers releasing heat in the vicinity of the fiber tip owing to the photothermal effect. We will show the heating capabilities of these devices and present some results on the characterization of the temperature gradients achieved with these optical fiber micro-heaters. Finally, we show that these devices are capable to induce thermal lesions on biological tissue, thereby demonstrating their potential use for thermal treatments in biomedical applications.

TUES 19

THERMOGRAPHY OF THE PLANTAR SKIN OF OVERWEIGHT AND OBESE INDIVIDUALS.

Francisco-J Renero-C

INAOE, Puebla, Mexico

The thermoregulation in humans, is controlled by the hypothalamus, is part of the autonomic nervous system. It is a complex system of afferent sensors and effectors that work together to maintain the proper temperatures of the human body. In this work, the thermograms of two groups of volunteers are presented. The first composed of individuals with BMI < 25 Kg/m2, and the second composed of individual with BMI ≥ 25 Kg/m2. The thermograms of the first group show three main characteristics 1) symmetry, the temperature distribution on the right foot is a mirror image of the left foot, 2) thermograms of women can be distinguished from those of men's; and 3) the temperature distribution decrease distally from the medial longitudinal arc. From the thermograms of the second subgroup, it is impossible to distinguish between the gender, since the average temperature of the medial longitudinal arc on the women thermograms increased in an amount of three degrees, so that they look like the thermograms of men. Second, no symmetry can be observed within the left and right feet thermograms. Third, the average temperature of the plantar skin, on both feet, increased for women and men. The temperature distribution is still decreasing from the middle to the periphery of the foot. However, the standard deviation, for each angiosome averaged temperature, shows greater uncertainty. Thus, this overheating of the plantar skin evidences that the central nervous system may be misunderstanding the thermal signals from the organs or the periphery. Furthermore, these thermograms may help to understand the themograms of the diabetic patients.

TUES 20

SOCIETY OF THERMAL MEDICINE 2017 PRESIDENT'S SYMPOSIUM: COMPUTATIONAL MODELING AND SIMULATION IN THERMAL MEDICINE

R. Jason Stafford[1], Dieter Haemmerich[2], Punit Prakash[3], David Fuentes[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Medical University of South Carolina, Charleston, SC, USA, [3]Kansas State University, Manhattan, KS, USA

Thermal therapies embrace a diverse spectrum of disciplines including the biological, physical and clinical sciences. For over 30 years, the Society for Thermal Medicine has served as a proverbial 'melting pot' bringing scientists together to advance thermal therapies for patient benefit.

Computational modeling and simulation has played an ever increasingly important role within thermal medicine as the chief integrator of our biophysical and clinical theories and observations for translation into quantitative predictions. Biophysical models of heat generation and transfer for a diverse range of modalities – including hyperthermia and thermal ablation therapies - can be used to predict the distribution of temperature and integrated with appropriate feedback measurements. These models can be further expanded to investigate the impact of temperature on physiological or biological processes. Models based on observations of physiological or biological response to heat can be coupled with these biophysical models of heat transfer to predict effects of heating from new modalities as well as plan or guide treatment delivery. Computational modeling has brought thermal medicine from petri dish to patient as well as brought device from bench to bedside. Such models have been applied in various ways, including: (1) As a research tool to investigate biophysical effects, (2) integrated into the development of novel devices, and (3) for patient specific treatment planning of thermal therapies.

So, what has changed? As computational capacity and algorithms have advanced, and more user-friendly software tools have become available, so has the role of computational science within our discipline. Dynamic, data driven algorithms incorporating a variety of parametric and non-parametric methods and stochastic approaches to data assimilation produce increasingly more accurate predictions based on an accumulation of knowledge over time. Such predictions from these multiscale models can play a role in the investigation of physical or biological phenomena; development and validation of devices or procedures; treatment planning and simulation for patient selection; treatment guidance and control; as well as prediction of outcomes.

In this symposium, three outstanding society members working in the area of computational modeling and simulation of thermal therapy provide an overview of the role of computational science in thermal medicine. Essential and emerging techniques and the possibilities they facilitate, punctuated by examples from research will be presented as well as visions for the future.

TUES 21

EVALUATION OF DOXORUBICIN-LOADED GOLD NANOSPHERES COMBINED WITH PHOTOTHERMAL ABLATION FOR LIVER CANCER

Rahul Sheth[1], Xiaoxia Wen[2], Junjie Li[2], Marites Melancon[1], Chun Li[2], Sanjay Gupta[1]

[1]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [2]Cancer Systems Imaging, Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

Introduction

Thermal ablation is a cornerstone in the management of patients with liver cancer. However, conventional ablation modalities are limited by the lack of specificity for ablating tumor versus normal tissue. Doxorubicin-loaded hollow gold nanospheres (HAuNS) are a promising technique for tumor-targeted chemotherapy delivery and thermal ablation. In this study, we evaluate the efficacy intra-arterial delivery of doxorubicin-loaded HAuNS followed by photothermal ablation in a rabbit model of liver cancer.

Methods

HAuNS were synthesized by the cobalt nanoparticle-mediated reduction of chloroauric acid. Adult New Zealand white rabbits (N=19) were inoculated with VX2 tumors into the left lobe of the liver. The animals were then randomized into 4 groups: sham surgery (N=4), doxorubicin-loaded HAuNS only (N=6), HAuNS + PTA (N=4), and doxorubicin-loaded HAuNS + PTA (N=5). Two weeks after inoculation, selective catheterization of the proper hepatic artery was performed using a 2.8Fr microcatheter from the right common femoral artery. Nanoparticles were delivered as an emulsion with Lipiodol (Guerbet, France). Following nanoparticle delivery, a small midline incision was made, the left hepatic lobe was elaborated to the skin surface. PTA was performed using an 808nm fibered laser at 1.5W for 3 minutes. Response to therapy was measured by calculating the percent change in tumor volumes as measured by CT scans on post-operative days (POD) 7 and 14 compared to pre-procedure CT scans.

Results

The proper hepatic artery was successfully selectively catheterized in all animals. Of the rabbits who received intra-arterial HAuNS, tumoral delivery of the nanoparticles, defined as lipiodol staining seen on POD 7 imaging, was successful in 13/15 rabbits. Two animals in the doxorubicin-loaded HAuNS only group and one animal in the doxorubicin-loaded HAuNS + PTA were euthanized prior to POD 7 due to complications from the procedure. At POD 14, the percent changes (median, [range]) in tumor size for each group were as follows: sham surgery 1090.5% [749.1-2088.8%], doxorubicin-loaded HAuNS only -33.3% [-89.7-136.8%], HAuNS + PTA 244.4% [-83.5-177.2%], and doxorubicin-loaded HAuNS + PTA 18.4% [6.4-197.8%]. The tumors in the doxorubicin-loaded HAuNS only, HAuNS + PTA, and doxorubicin-loaded HAuNS + PTA were significantly smaller than those in the sham surgery group (P=0.001, 0.02, 0.03, respectively, by Dunn's test).

Conclusion

Doxorubicin-loaded HAuNS is a promising therapeutic agent for liver cancer.

TUES 22

DEVELOPMENT OF A HEAT-TRIGGERED RELEASE FORMULATION OF CYCLOPHOSPHAMIDE FOR USE IN A PEDIATRIC PATIENT POPULATION

Michael Dunne, Christine Allen

University of Toronto, Toronto, Ontario, Canada

Introduction: Rhabdomyosarcoma is a highly aggressive and locally invasive cancer that is the most common soft tissue sarcoma in children and adolescents. While first-line therapy is effective in achieving complete remission in 70-90% of cases, one third of children relapse with local disease at the primary site and experience a corresponding five-year survival rate of only 17-28%. The gold standard chemotherapy regimen for treatment of rhabdomyosarcoma includes vincristine, dactinomycin, and cyclophosphamide. Of these agents, cyclophosphamide is most associated with severe long-term effects, including development of secondary malignancies and infertility. Therefore, there is a clear need to develop less toxic formulations of cyclophosphamide. Efficacy of cyclophosphamide has been shown to improve with the addition of hyperthermia, allowing equivalent efficacy at lower doses. Additionally, hyperthermia-mediated drug release technologies such as Thermodox® have proven capable of further improving the therapeutic index of anticancer agents. For these reasons, this work aims to develop a heat-triggered release formulation of cyclophosphamide suitable for treating pediatric patients in combination with hyperthermia.

Methods: Empty thermosensitive liposomes were prepared by high-pressure extrusion, following which cyclophosphamide was passively loaded into the preformed liposomes at 50°C. Unencapsulated drug was removed by dialysis at 4°C. Liposomes were characterized in terms of size and size distribution, zeta potential, and cyclophosphamide loading. Temperature-dependant drug release was measured by heating liposomes to 37, 41, 42, 43, or 45°C for 1 or 5 min using a thermal cycler. The liposomes and free drug were separated via size exclusion chromatography and cyclophosphamide concentration in each fraction was determined by reverse phase HPLC using a C18 column and UV detection at 190 nm.

Results: Dynamic light scattering revealed the size distribution of the thermosensitive liposomes to be monomodal before and after drug loading with an intensity-based distribution average diameter of 195 nm and a polydispersity index of 0.08. The zeta potential of the cyclophosphamide-containing liposomes was -26 mV. Passive encapsulation yielded a cyclophosphamide loading efficiency of 18%. Heating to the physiologically relevant temperature of 37°C for 30 min resulted in less than 15% release. However, heating for short durations at higher temperatures lead to markedly increased release with 42% and 68% of drug released at 1 and 5 min heating at 42°C.

Conclusion: A stable thermosensitive liposome formulation of cyclophosphamide has been developed and drug release at appropriate physiologically relevant temperatures has been demonstrated. This formulation is suitable for further evaluation in relevant animal models of rhabdomyosarcoma.

TUES 23

FOLIC ACID TARGETED NANOPARTICLES FOR DETECTION, TARGETING, AND THERMAL TREATMENT OF PERITONEALLY DISSEMINATED COLORECTAL CANCER

Eleanor McCabe-Lankford, April Brown, Bryce McCarthy, Margarita Peterson, Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, NC, USA

Colorectal cancer is the third most common cancer and second most prominent cause of cancer-related deaths in the United States. This is primarily due to the challenge in accurate detection and treatment of micro-metastases once the disease has disseminated. A primary course of treatment at our institution for metastatic colorectal cancer is Hyperthermic Intraperitoneal Chemoperfusion (HIPEC). HIPEC is a dual combination therapy involving cytoreduction surgery and perfusion of (40-42°C) warmed chemotherapy circulated throughout the patient's abdomen. The HIPEC regimen has greatly improved the survival of metastatic colorectal cancer patients from a five-year survival rate of 12.5% to above 50%, but is still limited by the detection and treatment of remnant micro-metastases. Photothermal ablation therapy using specific formulations of fluorescent nanoparticles that can absorb light in the near-infrared (NIR) and emit the energy as heat allows for precise detection and destruction of metastasis. The utilization of nanoparticles can be further improved by functionalizing their surfaces with targets that bind to receptors overexpressed on cancer cell surfaces, such as folic acid. Our group has developed multi-purpose fluorescent-heating nanoparticles, called PolyDOTS (Polymer Dynamic Theranostic Spheres), synthesized using 95% (w%) of the fluorescent polymer Poly[(9,9-dihexylfluorene)-co-2,1,3-benzothiadiazole-co-4,7-di(thiophen-2-yl)-2,1,3-benzothiadiazole] (PFBTDBT10) to 5% (w%) of the heat producing polymer Poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b'] dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) that are functionalized with folic acid. Here, Balb/C mice were induced with luminescent colorectal cancer disseminated throughout the peritoneum and an abdominal perfusion of saline and/or nanoparticles was performed to model the use of nanoparticles as an adjuvant therapy to the HIPEC procedure. PolyDOTS were functionalized with folic acid, (335 +/- 61 ng / μg of nanoparticles), and 80 μg/mL of nanoparticles were perfused throughout the abdomens of the mice for 30 minutes. The abdomens of the mice were rinsed with 0.9% saline to remove unbound nanoparticles. Localization of the nanoparticles to tumor regions was determined using an In Vivo Imaging System (IVIS) with 465 nm excitation and an 810-875 nm filter. These data will help to determine whether functionalized PolyDOTS can target disseminated abdominal cancers precisely for inducing photothermal stimulation and initiation of hyperthermia.

TUES 24

HOW TO IMPROVE CHEMOTHERAPY WITH THERMOSENSITIVE NANOCARRIERS.

Timo ten Hagen

Erasmus MC, Rotterdam, The Netherlands

Drug delivery to tumors with liposomes is further away from optimal than anticipated. Typically doxorubicin is used both for neutral liposomes as well as liposomes responsive to external triggers. The preference of doxorubicin comes from its broad application in cancer and proven activity in patients. With respect to formulation in lipid-based nanocarriers doxorubicin is preferred because of loading capacity to high degree in liposomes, which can be established in a relatively easy way. When used in thermosensitive liposomes (TSL) release kinetics of doxorubicin are excellent and tumor accumulation is quite good. It is striking however that not yet a TSL with doxorubicin has been registered for clinical use. Costs and reproducibility of production may play a role. More important, performance of TSL has not been convincing enough to warrant large investments and clinical registration. We and others observed that TSL function well if they are heated well, which is easy in the test tube, quite easy in animals, but problematic in humans. The complexity of TSL-mediated drug delivery and hyperthermic tumor therapy hampers development towards the clinic. Next to these hurdles however it may also very well be that doxorubicin is not the ideal drug. Therefore we tried a different compound: idarubicin. Idarubicin is an anthracycline and closely related to doxorubicin but is more hydrophobic. The amphiphilic nature of doxorubicin provides certainly qualities which benefits release form lipid-based nanocarriers, solubility and diffusion as well as uptake by cells. We show that idarubicin has characteristics which affect liposomal encapsulation, triggered release, diffusion, cell uptake and cytotoxicity all in a positive way. Here we show results obtained with doxorubicin and idarubicin TSL and we project these results in a larger context indicating the fast number of individual factors which need to be considered to make heat-controlled drug delivery from thermosensitive liposomes a success.

TUES 25

HYPERTHERMIA MODULATED DELIVERY OF NAB-PACLITAXEL FOR THE TREATMENT OF MELANOMA

Mai Xu[1], Xing Liu[2], Albert C Lockhart[1], Robert J. Myerson[3], Imran Zoberi[3], Hong Chen[3], Lifei Zhu[3], Andrea Wang-Gillam[1]

[1]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA, [2]Department of Colorectal Surgery, Fujian Medical University Union Hospital, Fuzhou, China, [3]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri, USA

Introduction: One of the physiological functions of human serum albumin (HSA) is to deliver nutrients to cells by a possible mechanism of receptor (albondin) mediated endocytosis. Interestingly, the cellular metabolic rate increases as temperature rises in the temperature range of 38°C to 41°C. The increased cellular metabolism implies that the cells will uptake more HSA to obtain adequate nutrients to meet their high metabolic needs. Therefore, we hypothesized that mild/moderate hyperthermia (HT) could facilitate delivery of paclitaxel albumin-bound nanoparticles (nab-paclitaxel, Abraxane) into tumor cells and enhance therapeutic efficacy in the treatment of melanoma. The purpose of the proposed study is to test the hypothesis and develop a novel therapeutic approach for the treatment of melanoma patient.

Materials and Methods: Melanoma A375 and G361 cells were maintained in DMEM (A375) and McCoy's 5A medium (G361) supplemented with 10% human serum and 1% PenStrep. Human fibroblast GM05399 cells were obtained from Coriell Institute (Camden, NJ). Athymic NCr-nu/nu mice were bought from the Charles River Laboratories. Immunofluorescence staining and flow cytometry methods were used to measure HSA in tumor cells in vitro. To observe the biodistribution of nab-paclitaxel in vivo, we labeled nab-paclitaxel with NIR dye using an IRDye 800CW Protein Labeling Kit (Li-Cor Inc). The integrity of the nab-paclitaxel and its NIR dye conjugates were measured with Dynamic Light Scattering method after freezing, melting, labeling and heating. Biodistribution and kinetic changes of the nab-paclitaxel-NIR dye conjugates were examined and monitored after HT with the Pearl Imager in vivo. Furthermore, synergistic therapeutic efficacy of HT plus nab-paclitaxel was assessed in melanoma xenograft carrying animals.

Results: (1). HSA accumulated in melanoma cells after heating at 41°C for as little as 0.5 hour; there was no increase in the amount of HSA in human normal fibroblasts after the same heat treatment. (2). Integrity of the nab-paclitaxel was not interrupted after a single freezing and thawing cycle, and by the labeling procedures with fluorescent dye. (3). nab-paclitaxel and its NIR dye conjugates are stable after heating at 41°C for 1 hr. (4). Mild/moderate HT accumulated and retained the nab-paclitaxel-NIR dye conjugates for a longer period of time in heated tumors than unheated controls. (5). Combined treatment of HT and nab-paclitaxel is more efficient than HT and nab-paclitaxel used separately in the treatment of melanoma.

Conclusion: Mild/moderate HT facilitates delivery of nab-paclitaxel to tumors. The novel therapeutic approach, HT plus nab-paclitaxel, may improve local-regional tumor control.

TUES 26

A DRUG RELEASE ANALYSIS SYSTEM (DRAS) FOR ALTERNATING MAGNETIC FIELD MEDIATED DRUG RELEASE FROM NANOPARTICLES

Mahendran Subramanian, Carlton Neville Jones

nanoTherics Limited, Staffordshire, UK

Heat dissipation during magnetization reversal processes in magnetic nanoparticles (MNP), upon exposure to alternating magnetic fields (AMF), has been extensively studied in relation to thermal medicine. AMF-mediated drug delivery is non-invasive and remotely triggered. Controlled drug delivery systems have been a broad research interest for a number of years. The stimuli used here is the heat dissipated from surface functionalised magnetic nanoparticles exposed to AMF. This study demonstrates the design, fabrication, and evaluation of an efficient instrument, operating on this principle, for use as a drug release analysis system (DRAS). There are a few crude setups for performing such experiments using commercially available AMF systems, and the research community has discussed the prospects for the development of nanoparticle-based drug delivery testing apparatus. However, this requires certain modifications to be made to the United States Pharmacopeia (USP) type drug testing setups generally used in the pharmaceutical industry. Such modifications would have to take the following into account: nanoscale level fillers/binders, release patterns, the stimuli involved, the AMF generator, stirring mediated convection loss, precise sample positioning, the requirement for a water jacket, and the sampling method. The instrument development considered here looks at USP and flow-cell type apparatus in relation to the designing and fabrication of AMF-mediated drug delivery testing setups which facilitate precise physical and chemical measurements.

The unique features of the proposed drug release testing setup including: (A) a disposable dialysis tube holding a shaft capable of accommodating a 250 μL – 3 mL volume of sample; (B) a high resolution fibre optic temperature sensor for real time temperature measurements; (C) the sample-holding shaft driven by a stepper motor to allow continuous stirring of the solution – for enabling even distribution of the drug released into the dissolute; (D) the sampling port/shaft for manual spectrophotometer analysis and to accommodate a custom engineered non-metal fibre optic probe for real time UV-VIS spectrophotometer analysis, while performing the AMF mediated drug release experiment; and (E) a water jacket enclosing the dissolute holding chamber to maintain ambient temperature in the dissolute as well as in the MNP + Drug sample. These features are appropriate for the design of a working prototype and for recording SAR measurements at high precision. The AMF applicator was a solenoid coil (50 mm ID and 50 mm length). The proposed drug release analysis setup will allow researchers to perform and replicate their AMF mediated drug release experiments with accuracy and repeatability.

TUES 27

EMPLOYING HIGH-FREQUENCY ALTERNATING MAGNETIC FIELDS FOR THE NON-INVASIVE TREATMENT OF PROSTHETIC JOINT INFECTIONS

Rajiv Chopra, Sumbul Shaikh, Yonatan Chatzinoff, Imalka Munaweera, Bingbing Cheng, Seth Daly, Yin Xi, James Howard, Cecil Futch, Chenchen Bing, David Greenberg

UT Southwestern Medical Center, Dallas, Texas, USA

Introduction

Surface-dwelling biofilms which accompany prosthetic joint infections (PJI) exhibit increased resistance to antibiotics, rendering conventional antibiotic therapy ineffective. Treatment of (PJI) usually requires surgical replacement of the infected joint and weeks of antibiotic therapy, due to the formation of biofilm. We introduce a novel non-invasive method for thermal destruction of biofilm on metallic implants using high-frequency (> 100 kHz) alternating magnetic fields (AMF). Surface electrical currents generated on the implant lead to superficial heating which can eradicate biofilm. Further, remote acoustic sensing can be used to detect for any tissue boiling that might occur as a safety mechanism during AMF exposures.

Methods

The feasibility of this novel treatment concept has been evaluated through a combination of microbiological studies, scanning electron and confocal fluorescent microscopy, numerical modelling, measurements in tissue-mimicking phantoms, and in-vivo in mouse model. The microbiological and microscopy studies evaluate the bactericidal effect of AMF exposures in S aureus and P aeruginosa. Synergy studies were performed in vitro to evaluate the impact of AMF exposures on the effectiveness of antibiotics. The numerical simulations and experiments evaluate the scale up of this concept to a human prosthetic device. Finally, the animal studies evaluate the extent of surrounding tissue damaged produced by an AMF exposure, and the feasibility of monitoring acoustic emissions when excessive heating is achieved.

Results & Conclusion

In vitro investigations demonstrate a >5-log reduction in bacterial count after 5 minutes of AMF exposure. Confocal and scanning electron microscopy confirm removal of biofilm matrix within 1 minute of AMF exposure, and combination studies of antibiotics and AMF demonstrate a 5-log increase in the sensitivity of Pseudomonas aeruginosa to ciprofloxacin. Finite element analysis (FEA) simulations demonstrate that intermittent AMF exposures can achieve uniform surface heating of a prosthetic knee joint. In vivo studies confirm thermal damage is confined to a localized region (< 2 mm) around the implant, and safety can be achieved using acoustic monitoring for the presence of surface boiling. These initial studies support the hypothesis that AMF exposures can eradicate biofilm on metal implants non-invasively, and may enhance the effectiveness of conventional antibiotics.

TUES 28

NANOTECHNOLOGY: A TINY SOLUTION TO THE BIG PROBLEM OF BIOFILM-ASSOCIATED BACTERIAL INFECTIONS?

Mark Smeltzer[2], Daniel Meeker[2], Jingyi Chen[1]

[1]Univerisity of Arkansas, Fayetteville, AR, USA, [2]University of Arkansas for Medical Sciences, Little Rock, AR, USA

Introduction. Many bacterial infections are characterized by formation of a biofilm consisting of aggregates of bacterial cells contained within an extracellular matrix. Additionally, bacterial cells within the biofilm adopt unique metabolic characteristics. These factors provide a therapeutically-relevant degree of resistance to host defenses and conventional antibiotics. Carefully designed nanotherapeutic approaches may offer a novel solution to this growing clinical problem.

Methods. Gold nanocages (AuNCs) were coated with polydopamine and loaded with daptomycin, a membrane active antibiotic effective against methicillin-resistant *Staphylococcus aureus* (MRSA). Targeted delivery to bacterial cells was achieved by conjugating these antibiotic-loaded AuNCs to an antibody specific for *S. aureus* protein A (Spa), a surface-associated protein present on the surface of biofilm-associated *S. aureus* cells. Continuous wave laser irradiation was then used in an effort to achieve a photothermal (PT) effect and release of daptomycin directly at the bacterial cell surface.

Results. We demonstrate that laser irradiation at levels within the current safety standard for use in humans can be used to achieve both a lethal photothermal effect and controlled release of daptomycin from our antibody-conjugated, antibiotic-loaded AuNCs and that this results in a degree of therapeutic synergy that is capable of eradicating viable *S. aureus* cells. The system was validated using planktonic bacterial cultures of both methicillin-sensitive and methicillin-resistant *S. aureus* strains. It was subsequently shown to be capable of eradicating viable bacterial cells from an established biofilm, an effect that could not be achieved using conventional antibiotic therapy alone even when the antibiotic was delivered directly to the site of infection. Targeting specificity was confirmed by demonstrating a lack of binding to mammalian cells, reduced photothermal and antibiotic killing of the Spa-negative species *Staphylococcus epidermidis*, and reduced killing of *S. aureus* in the presence of unconjugated anti-Spa antibodies. Subsequent studies, while preliminary, also demonstrate the feasibility of this approach *in vivo* with respect to both the ability to achieve similar therapeutic effects via transdermal laser irradiation of a catheter-associated biofilm and the ability to systemically deliver our antibody-conjugated AuNCs to an active site of infection. Thus, our results indicate that this novel approach could be used to facilitate the effective treatment of intrinsically resistant biofilm-associated infections.

Conclusions. The results we present are highly promising with respect to developing more effective methods for the treatment of biofilm-associated *S. aureus* infections. Additionally, with appropriate modification, this approach could be applied to combat infections caused by any bacterial pathogen.

TUES 29

DEVELOPMENT OF A REMOTE ACOUSTIC SENSING SAFETY MECHANISM FOR BIOFILM ERADICATION USING ALTERNATING MAGNETIC FIELDS

Bingbing Cheng[1], Yonatan Chatzinoff[1], Omar Wyman[1], Debby Szczepanski[1], Sumbul Shaikh[1], Chenchen Bing[1], John Shelton[2], Cameron Perry[2], Jim Richardson[2], David Greenberg[4], Rajiv Chopra[1,3]

[1]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [3]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA, [4]Department of internal medicine and microbiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Introduction

The current standard of care for treating prosthetic joint infections involves surgical removal of the infected implant. Although effective, this method of treatment significantly impacts patient's quality of life and is very expensive. We are developing an alternative approach to treat biofilm on metal implants non-invasively using alternating magnetic fields (AMF). When exposed to an AMF, electrical currents generated on the surface of metal implants generate rapid heating which can destroy biofilm. To avoid overheating and unwanted thermal damage to surrounding normal tissue, a remote acoustic sensing method is proposed based on the detection of boiling at the implant-tissue interface.

Methods

A system comprised of a solenoid coil, matching circuit, sample holder and hydrophone was built. Acoustic emissions generated during *in vitro* and *in vivo* AMF exposures of a metal ball bearing were recorded with a hydrophone and analysed. For *in vitro* studies, a fiber-optic temperature sensor was attached to the ball to record the temperature data. The relationship between the implant surface temperature and acoustic emissions was investigated, as well as the time required to detect acoustic emissions at different AMF powers. The impact of the physical properties of the medium surrounding the ball on the strength and frequency of acoustic emissions was also evaluated. Finally, the damage to surrounding tissue for short and long durations AMF exposures was evaluated in mice.

Results and Conclusion

Acoustic emissions associated with boiling were reliably identified during AMF treatment both *in vitro* and *in vivo*. When the metal implant was exposed to an 800W and 200W AMF exposure, the boiling time was 5.9 $\pm$ 0.4s and 188 $\pm$ 57.6s, respectively. The histology after AMF exposures in mice revealed a reduced radius of thermal damage for high power, short duration AMF exposures. Overall, the use of acoustic emissions produced by tissue boiling at the interface of the metal implant may serve as a robust and wireless form of safety monitoring during AMF exposures for biofilm eradication.

TUES 30

TEMPERATURE-SENSITIVE LIPOSOMAL CIPROFLOXACIN FOR THE TREATMENT OF BIOFILM ON PROSTHETIC JOINT IMPLANTS USING ALTERNATING MAGNETIC FIELDS

Imalka Munaweera[1], Sumbul Shaikh[1], Yonatan Chatzinoff[1], Danny Maples[2], Nandhini Sethuraman[2], Adane Nigatu[2], Ashish Ranjan[2], David Greenberg[3], Rajiv Chopra[1]

[1]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA, [2]Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA, [3]Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

Prosthetic joint replacement has been used to successfully treat a variety of degenerative diseases in millions of individuals globally. Prosthetic joint infection (PJI) is a major problem in this area due to the formation of biofilm, a thick aggregate of bacteria and extracellular polymeric substances (EPS). Bacteria within biofilm are protected from antibiotics and the immune system, and can cause recurrent infection even after a course of antibiotics. In this study we investigated the combination of ciprofloxacin-loaded temperature-sensitive liposomes with alternating magnetic fields (AMFs) to treat biofilms on metallic implants. Since the proposed use of AMF exposures generates heating in the immediate vicinity of an infected metal implant, this nanoparticle strategy might enable local delivery of high concentrations of ciprofloxacin in the body at directly to the site of infection. The objectives of this study were to develop low- and high- temperature-sensitive liposomes (LTSLs and HTSLs) containing the antimicrobial agent ciprofloxacin for temperature-mediated antibiotic release, to characterize in vitro ciprofloxacin release and stability, and to study the efficacy of combining liposomal ciprofloxacin with AMF against *Pseudomonas aeruginosa* biofilms on metal implants. LTSL and HTSL were loaded actively with ciprofloxacin and release of ciprofloxacin from liposomes was assessed in a physiological buffer by fluorescence spectroscopy. Results indicated that < 5% ciprofloxacin was released from the LTSL at 37-40 °C in PBS and 37-39 °C in FBS. In both media, complete ciprofloxacin release (> 95%) from the LTSL is achieved by 41-42 °C. HTSLs show more gradual release of ciprofloxacin in FBS as compared to the release in PBS. Overall results demonstrated a lower transition temperature for both LTSL and HTSL formulations when incubated in serum as compared with PBS, with a more pronounced impact on the HTSL formulation. Bacterial eradication across different treatment groups for *Pseudomonas aeruginosa* biofilm was studied in vitro. When the LTSL or HTSL nanoparticles were added to the biofilm samples and exposed to an AMF, a 2-3 log reduction in CFU was observed as compared to free ciprofloxacin ($p > 0.05$). This indicates that the contents of the liposomes were fully released by the exposure, exposing the biofilm to an equivalent level of antibiotic. Preliminary in vitro data demonstrate that AMF exposures combined with temperature-sensitive liposomal ciprofloxacin are capable of killing bacteria in the biofilm, which raises the possibility to enhance biofilm eradication on prosthetic joint infection.

TUES 31

PHOTOTHERMAL NANO-COMPOSITE FOR AUGMENTING ANTIBIOTIC EFFICACY

Nicole Levi-Polyachenko, Anila Pullagura

Wake Forest Unviersity Health Sciences, Winston-Salem, NC, USA

Staphylococcus aureus is a common pathogenic bacterium prevalent in a wide variety of diseases, including progressive blood and tissue infections such as chronic ulcers, sepsis and osteomyelitis. Additionally, there exist many S. aureus subtypes which have developed resistance to broad-spectrum antibiotics. Part of the acquired antibiotic resistance may be attributed to the capacity for S. aureus to thrive in colonies within a protective matrix of polymers, polysaccharides, extracellular DNA and water (biofilm). Biofilm residing bacteria are known to be many times more resistant to select antibiotics than their planktonic counterparts.

One mechanism proposed for mediating biofilm-associated infections is to disrupt the polymer structure of the biofilm, leading to the release of planktonic bacteria which are more susceptible to antibiotic therapy. Chemical agents have been evaluated for accomplishing this; however, physical means, such as heat or ultrasound can serve two purposes by first disrupting the biofilm structure while also altering individual bacterial cell walls. Physical disruption may be especially advantageous for eradicating biofilms associated with implanted medical devices, alleviating the need for their removal and maintaining device function.

Silicone is a biocompatible elastomer that can either compose an entire medical device (catheters) or be used as a pliable surface coating on metal or ceramic implants. For the generation of heat, we have included photothermal donor–acceptor conjugated polymer nanoparticles based on poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b']dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe). The composite materials (with 1, 5, or 10 mg of nanoparticles) were evaluated for the killing of planktonic and biofilm-residing S. aureus, in either the presence or absence of the antibiotic gentamicin. In the absence of near-infrared laser stimulation of the composite, addition of the nanoparticles exhibited an unexpected bactericidal effect. Stimulation of silicone alone with 612 J/cm2 of 800nm light had no effect on planktonic or biofilm S. aureus, whereas ablative temperatures in the nanoparticle doped composites resulted in a 95-100% reduction in viable bacteria. Sub-ablative temperatures resulted in a 75% reduction in planktonic bacteria treated with gentamicin and a 90% reduction in biofilm-residing S. aureus, compared to controls treated with gentamicin alone and no infrared stimulation. Our results demonstrate the potential for heat-generating biocompatible nano-composites to augment antibiotics used to treat S. aureus biofilms.

TUES 32

GENERATION OF PHOTOTHERMAL EFFECTS FROM GOLD NANOCAGES FOR THE TARGETED TREATMENT OF *STAPHYLOCOCCUS AUREUS* BIOFILMS

Daniel Meeker[1], Karen Beenken[1], Jingyi Chen[2], Mark Smeltzer[1]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

Background: Acquired antibiotic resistance is a serious public health concern with the incidence of resistance rising faster than new antibiotics are developed and approved. This emphasizes the urgent need for alternative therapeutic strategies to combat bacterial infections. In addition to acquired resistance, formation of a biofilm results in a degree of intrinsic resistance such that biofilms rarely respond to systemic antibiotic therapy, regardless of the acquired resistance status of the pathogen or the antibiotic used. Biofilm formation often necessitates the surgical removal of infected tissue/hardware to completely eradicate infection, but the rate of recurrent infection remains high.

Methods: We used *Staphylococcus aureus* as a proof-of-principle "ESKAPE pathogen" to demonstrate that daptomycin can be incorporated into polydopamine-coated gold nanocages, which can then be conjugated to antibodies targeting a species-specific surface protein (protein A) to achieve selective delivery of nanocages directly to the bacterial cell surface. Gold nanocages can be tuned to absorb light at a wavelength in the near infrared (NIR) range and release this energy as heat. Experiments were performed with bacterial cells in planktonic culture and with an *in vitro* catheter model of biofilm formation. Subsequently, a murine model of catheter-associated biofilm infection has been used to test the *in vivo* efficacy of our nanocage design. Multispectral optoacoustic tomography (MSOT) was used to determine biodistribution of injected nanocages and their ability to reach a site of infection.

Results: We demonstrate that the resultant photothermal effect from laser-activated nanocages leads to direct bactericidal effects as well as controlled antibiotic release and that these synergistic effects are sufficient to eliminate viable bacteria. This was demonstrated in the context of planktonic cultures and in the context of an established biofilm *in vitro*. Further, owing to conjugation to a species-specific antibody, we demonstrate that this system can be used to specifically eliminate *S. aureus* cells with minimal off-target effects. Results from an *in vivo* model of biofilm infection demonstrate that our nanocage formulation is capable of reducing the number viable bacteria within a biofilm to a more significant degree than local administration of high concentrations of antibiotic alone. Moreover, MSOT data demonstrated that systemically injected nanocages accumulate in the spleen, liver, and kidney, but more importantly accumulate at localized sites of infection.

Conclusions: Our results suggest that gold-based nanoparticles can be used to design novel therapeutic strategies to overcome acquired and intrinsic resistance to conventional antibiotic therapy.

TUES 33

LASER INDUCED PRECISION HEATING FOR IMPROVED BACTERIAL DESTRUCTION WITH GENTAMICIN

Kenneth Vogel, Anila Pullagura, Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA

One of the most common infections of patients in a hospital setting is caused by Staphylococcus Aureus, which is responsible for approximately 1.2 million infections and 119,000 deaths in the US. The lethality of S. Aureus is partly due to strains which are resistant to current antibiotics. Therefore, treatments for increasing the efficacy of antibiotics are desirable. Previous research has shown that planktonic bacterial cultures treated with antibiotics then bulk heated to 45°C undergo a decrease in viable bacteria.

To better determine the effect of increased temperatures on bacterial cell death and find a rapid heating method, planktonic cultures of S. Aureus in the presence of the antibiotic gentamicin at its IC_{50} were incubated at 37°C, 40°C, 42°C, 44°C for 2 hours then incubated overnight on agar at 37°C to form colonies. Counts revealed that antibiotic treatment produced no appreciable difference in colony forming units at all temperatures. Heat production using an 800 nm continuous wave laser, which has precision heating ability, was attempted. A heat curve of TSB and IC_{50} gentamicin was generated, showing that stimulating the solution for 30, 60, and 90 seconds (6.39 W/cm^2) would increase temperature by 3°C, 5°C, and 7°C, respectively. Gentamicin and S. Aureus solution preheated to 37°C was treated with the laser for 0, 30, 60, or 90 seconds before being incubated overnight on agar. Groups with longer laser treatment times yielded significantly fewer colony forming units than those that were stimulated by the laser for a shorter period.

To ascertain that observations weren't due to either heating or laser treatment affecting the gentamicin, antibiotic and TSB solution was heated at 37°C, 40°C, 42°C, 44°C for 2 hours or stimulated by the laser for 30, 60, and 90 seconds before being treated against S. Aureus for another 2 hours. Absorbance measurements of the solution were taken before and after heating or laser treatment. Both the absorbance measurements as well as colony counts revealed no significant difference between heat treated and laser treated gentamicin.

These findings suggest that near infrared laser radiation induces hyperthermia, which is beneficial for improving bacterial susceptibility to antibiotics, and also lays the groundwork for future experiments laser treating bacteria at different wavelengths and powers.

TUES 34

THERMORADIOTHERAPY PLANNING: MEASUREMENT, ANALYSIS AND IMPLEMENTATION OF THE IMPACT OF TIME-INTERVAL, TEMPERATURE AND RADIATION DOSE USING BIOLOGICAL MODELING

Caspar van Leeuwen[1], Arlene Oei[1,2], R. ten Cate[1,2], Nicolaas Franken[1,2], Arjan Bel[1], Lukas Stalpers[1], Johannes Crezee[1], H. Petra Kok[1]

[1]Academic Medical Center, Department of radiation Oncology, Amsterdam, The Netherlands, [2]Academic Medical Center, Laboratory for Experimental Oncology and Radiobiology (LEXOR)/Center for Experimental Molecular Medicine, Amsterdam, The Netherlands

Purpose: Biological modeling of thermoradiotherapy may further improve patient selection and treatment plan optimization. This requires a model describing the biological effect as a function of variables that affect treatment outcome (e.g. temperature, radiation dose). This study aims to establish such a model and its parameters based on in vitro data, and presents a clinical example of a cervical cancer patient to illustrate the application.

Methods: The in vitro data involved cell survival assays performed at various combinations of radiation dose (0-8Gy), temperature (37-42°C), time interval/sequence (between -4h and +4h) for two cervical cancer cell lines (SiHa and HeLa).

Analysis was performed by fitting an extended linear-quadratic model to the data using maximum likelihood estimation. Contributions of both direct cytotoxic and radiosensitizing effects of hyperthermia were taken into account. Radiosensitization was assumed to depend on temperature and the time interval between radiotherapy and hyperthermia.

As an example application, a thermoradiotherapy plan (23×2Gy + weekly hyperthermia) was compared to a radiotherapy-only plan (23×2Gy) for a cervical cancer patient. The equivalent radiation dose in the tumor, including confidence intervals (CI), was estimated using the SiHa parameters. Finally, the resulting difference in tumor control probability (TCP) was estimated.

Results: The model was found to describe the dependency of cell survival on dose, temperature and time interval well for both SiHa and HeLa data (R^2=0.90 and R^2=0.91 respectively), making it suitable for biological modeling.

In the patient example, the thermoradiotherapy plan showed an increase in equivalent uniform dose that was robust against the uncertainty in radiobiological parameters: 9.8 (95%CI: 7.7-14.3) Gy. This dose escalation corresponds to a 20% (95% CI: 15-29%) increase in TCP.

Conclusions: This study presented a model suitable for describing the cell survival as a function of radiation dose, temperature and time interval, which is essential for biological modeling of thermoradiotherapy treatments.

TUES 35

ANALYSIS OF THE SPECIFIC ABSORPTION RATE (SAR) COVERAGE DURING SUPERFICIAL HYPERTHERMIA TREATMENT WITH AN ARRAY OF TWO CFMA ANTENNAS

Akke Bakker, Jasmijn Vink, Nathalie Zandbergen, Remko Zweije, Petra Kok, Hans Crezee

Academic Medical Center, Amsterdam, The Netherlands

Introduction. Hyperthermia for superficial tumors is often applied with microwave applicators and the specific absorption rate (SAR) coverage by the applicators has a strong influence on local tumor control. Simultaneous use of two or more applicators is necessary to cover very large tumor areas. Suboptimal SAR coverage at the junction of two applicators should be avoided. Aim of this study was to investigate the SAR coverage at the junction of different applicator configurations.

Methods. Two ALBA 4000-ON systems were used, each fitted with a contact flexible microstrip applicator (CFMA) operating at 434 MHz; applicators alfa, beta (ALBA, Italy), 1H and 2H (ISTOK, Russia) were used. An in-house built muscle equivalent phantom that was slightly curved and contained a grid of catheters for thermocouple probe placement at 10, 20, 30, 40 and 50 mm depth was used for the procedure. In-house built software determined the effective field size (EFS) at 10 mm depth and the penetration depth (PD) based on the 50% SAR isodose. Where 100% SAR is determined at the measurement point at 10 mm depth underneath the center of the applicator. Combinations of two different sizes of CFMA applicators were tested, these included the alfa/1H applicator (EFS 4x16 cm) and the beta/2H applicator (EFS 8x12 cm). Field directions of the two antennas were both placed in line and perpendicular. We analyzed the SAR distribution in the junction between the two applicators. A SAR lower than 50% was defined as a gap, when the SAR was higher than 50% the width of the junction was determined.

Results. The combination of two small applicators (alfa, 1H) resulted in a gap. While the combination of larger applicators with their field direction in line (beta, 2H) resulted in a single continuous 50% SAR region with a width at the junction of 8.6 cm (72%) for two 2H applicators. Increasing the distance between the 2H applicators with 5 cm resulted in two separate 50% SAR regions. Positioning of the applicators with the fields directions in line yielded smaller gap sizes and wider junctions than perpendicular field directions. No hotspots occurred between the two applicators.

Conclusion. The integrity of the 50% SAR region during superficial hyperthermia is influenced by the applicator configuration. When using multiple applicators these should be positioned with their field directions in line and as close together as possible. Combinations of larger applicators yield better SAR uniformity than combinations of smaller applicators.

TUES 36

INTEGRATED SYSTEM FOR SMALL-ANIMAL HYPERTHERMIA INVESTIGATIONS UNDER ULTRA-HIGH FIELD MRI GUIDANCE: AUTOMATIC CONTROL OF TISSUE TEMPERATURE

Pegah Faridi, Sergio Curto, Tej Shrestha, Marla Pyle, Leila Maurmann, Deryl Troyer, Stefan Bossmann, Punit Prakash

Kansas State University, Manhattan, KS, USA

Introduction: Real time monitoring of tissue temperature is a necessity for precise hyperthermia systems in order to ensure the delivered thermal dose is achieved and the temperature profile is within the desired range (~40-45 °C for 20-90 mins). We have recently reported a hyperthermia system for small-animal investigations integrating a custom 2.45 GHz microwave hyperthermia applicator within a 14.1 T ultra-high field magnetic resonance scanner. Here, we report on recent *in vivo* studies in mice with this system, as well as the development and evaluation of a feedback controller for maintaining the target temperature within the desired range during the treatment session.

Methodology: To establish technical feasibility of the system, hyperthermia was delivered to subcutaneously implanted 4T1 tumors in mice ($n = 2$) with a 2.45 GHz directional microwave applicator integrated within a 14.1 T (Bruker) small animal scanner. These experiments were performed with constant power during the course of heating (5 – 15 mins). The homogeneity of heating within the target tumor was assessed with MRI thermometry using the proton resonance frequency shift (PRFS) technique. A 3D electromagnetic-bioheat transfer model was implemented using the finite element method (FEM) to develop and evaluate feedback control algorithms for maintaining target temperatures during hyperthermia exposures. Simulations were employed to identify controller gains for a proportional integral controller, with the objective of maintaining temperature elevation within the range of 3 – 7 °C for the treatment volumes. For each setpoint temperature, the volume of tissue maintained within the hyperthermic range was assessed. The ability to adjust the extent of surface tissue sparing by modulating coolant temperature and flow profiles was investigated.

Result: By carefully positioning the applicator relative to the targeted region, we were able to obtain *in vivo* temperature maps with negligible motion artefact during hyperthermia exposures. These preliminary *in vivo* hyperthermia experiments yielded highly variable temperature profiles (Tmax = 4.2 – 8 °C) for the same applied power levels. To obtain thermal profiles that meet a defined thermal target, a PI controller with proportional gain = 12 and integral gain = 0.05 was implemented. Characterization of the target sizes that can be exposed to hyperthermic temperatures with our system is in progress and will be presented at the meeting.

Conclusion: We report on the range of target sizes and locations that can be heated to hyperthermic temperatures with our small animal microwave hyperthermia system that is integrated within the bore of the MR scanner.

TUES 37

ON-LINE ADAPTIVE HYPERTHERMIA TREATMENT PLANNING DURING LOCOREGIONAL HEATING TO IMPROVE TUMOR TEMPERATURES AND REDUCE HOT SPOTS

H.P. Kok, L. Korshuize - Van Straten, A. Bakker, R. De Kroon - Oldenhof, E.D. Geijsen, L.J.A. Stalpers, J. Crezee

Academic Medical Center, Department of radiation oncology, Amsterdam, The Netherlands

Background: Adequate tumor temperatures during hyperthermia are essential for good clinical response, but excessive heating of normal tissue should be avoided. This makes locoregional heating using phased array systems technically challenging. On-line application of hyperthermia treatment planning could help to improve the heating quality. The aim of this study was to evaluate the clinical benefit of on-line treatment planning during treatment of pelvic tumors heated with the AMC-8 locoregional hyperthermia system.

Methods: For on-line adaptive hyperthermia treatment planning a graphical user interface was developed. Electric fields were calculated in a pre-processing step using our in-house developed finite-difference based treatment planning system. This allows instant calculation of the temperature distribution for user-selected phase-amplitude settings during treatment and projection onto the patient's CT scan for on-line visualization. On-line treatment planning was used for 15 treatment sessions in 8 patients to reduce hot spot complaints or improve tumor temperatures.

Results: Measured and simulated changes in tumor temperature rise showed a good correlation ($R^2=0.58$; $p<0.001$). Treatment planning proved to be a very helpful tool to improve treatment quality. In total 17 hot spot complaints occurred and the alternative settings reduced complaints while maintaining 95% of the achieved tumor temperature rise. In one session steady state tumor temperatures were disappointing and using treatment planning the tumor temperature rise was increased more than 15% without inducing hot spot complaints.

Conclusion: On-line application of hyperthermia treatment planning is reliable and very useful to improve tumor temperatures or reduce hot spots.

TUES 38

NON-INVASIVE HEATING OF JOINT IMPLANT BIOFILMS IN ALTERNATING MAGNETIC FIELDS: FACTORS AFFECTING UNIFORMITY

Yonatan Chatzinoff[1], David Greenberg[1], Ji Chen[2], Rajiv Chopra[1]

[1]UT Southwestern Medical Center, Dallas, Tx, USA, [2]University of Houston, Houston, Tx, USA

Introduction

Surface-dwelling biofilms which accompany prosthetic joint infections exhibit increased resistance to antibiotics, rendering conventional antibiotic therapy ineffective. Current standard of care involves surgical replacement of the infected joint. A non-invasive alternative is to expose the prosthesis to a high-frequency alternating magnetic field (AMF). Surface electrical currents are generated on the implant, and resistive losses lead to heating. While this heating can be used to eradicate biofilm, it can also cause undesirable thermal damage in surrounding tissue. Mitigating this undesirable thermal damage is dependent on the dual goal of maximizing uniformity of heating on the implant surface, which eliminates "hot spots"; and concentrating the heating to the surface of the implant to avoid heating of the unaffected interior.

Methods

Finite Element numerical simulations were performed in COMSOL to investigate the importance of system design parameters such as AMF coil geometry, AMF frequency, implant geometry and magnetic field direction. Three quantities were calculated to compare different conditions: surface-to-volume heating ratio, normalized standard deviation of the power deposited on the implant surface, and the efficiency of heating.

Results

The surface-to-volume heating ratio increased with AMF frequency due to the skin effect, with no accompanying dramatic decrease in uniformity. Frequencies between 100 and 400 kHz were selected based on the operating characteristics of AMF generators on hand. The efficiency improved when the AMF coil was located close to the implant. For the case of a solenoid AMF coil, pitch and turn had some impact on uniformity, but less so than the actual shape of the implant did. Finally, maximum uniformity was achieved by exposing the implant to AMF along three orthogonal directions.

Discussion and Conclusion

An ideal AMF coil for surface heating of infected metal implants would operate at high frequencies and be placed as close as possible to the implant. With regards to coil geometry, combining multiple emitters with orthogonal AMF directions produces a relatively uniform power deposition across the implant. Future work will focus on the predicting the thermal impact on the implant and surrounding soft tissue of AMF coils selected from these initial simulations.

TUES 39

MRI-BASED REAL-TIME CHARACTERIZATION OF THERMOEMBOLIZATION

Samuel Fahrenholtz[1], Chunxiao Guo[2], Joshua Yung[1], Ken Hwang[1], R. Jason Stafford[1], Erik Cressman[2]

[1]Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Introduction: Thermoembolization is a new minimally invasive technique combining targeted delivery of hyperthermia from an exothermic reaction with ischemia and a local pH change. In this procedure, the hydrolysis of the electrophile dichloroacetyl chloride (DCACl) yields twice the energy of acid/base neutralization. Delivered via catheter, DCACl reacts with water or other nucleophiles in situ. In addition to hyperthermia and ischemia, this novel method also rapidly generates a substantial amount of acid locally, increasing the endovascular ablative effect. Additionally, dichloroacetate (DCA) has known anti-tumor activity via reversal of Warburg metabolism. MRI-derived thermal dose measurements and localization of tissue damage relative to the reagent are key to understanding thermoembolization outcomes.

Methods: Heparinized, fresh kidneys were explanted and flushed with saline. The renal artery in each case was cannulated and two fluoroptic MR-compatible temperature probes were placed in one pole and the interpolar region. Temperatures were recorded at 1 Hz, beginning 5 minutes prior to and 15 minutes after injection. 4 mL of 4 M DCACl in mineral oil was infused over 30 seconds.

MRI images were obtained before and after delivery of DCACl. 3D T1- and T2-weighted images illustrated morphological changes. Crucially, a multi-echo fast gradient-recalled echo acquisition monitored changes over time in the chemical shift, amplitude, and T2* signals. That delineated the distribution of lipid and visualized the spatiotemporal distribution of heat transfer during cooling. The kidneys were stored overnight at 4°C while lesions developed, followed by histological sectioning.

Results: Temperatures increased 15-22°C above baseline abruptly within 5-10 seconds after beginning each injection. Kidneys appeared mottled immediately after infusion but coagulative lesions were confluent within several hours post procedure. On MRI, the injectate region was characterized by the presence of a lipid peak and a water peak shift versus background at the renal boundaries. MRI-derived temperature estimates in this area indicated large temperature changes in excess of 50°C above baseline. Proton resonance frequency shift thermometry and T1-weighted signal changes were used to observe changes in temperature over time. MRI showed excellent correlation with the injectate region and observed damage.

Conclusions: Early results suggest thermoemboliazation will prove a powerful new method with significant tumorcidal potential. Simultaneous exothermic, ischemic, and acidic insults in the local environment were shown to cause profound coagulative necrosis.

TUES 40

THERMAL-STRUCTURAL CHARACTERIZATION OF NON-INVASIVE SELECTIVE CRYOLIPOLYSIS, A COMPREHENSIVE NUMERICAL STUDY.

Reza Monazami[1,2], Dieter Manstein[1,2]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Harvard Medical School, Boston, MA, USA

Selective cryolipolysis is a non-invasive treatment method to induce localized and selective destruction of subcutaneous fatty tissue. The selective adipocyte damage is induced by crystallization of intracellular lipids due to cooling. We developed a comprehensive numerical model to investigate the temperature profile and crystallization of subcutaneous fat during selective cryolipolysis. The model includes the variation of thermo-physical properties for water and fat containing tissues with respect to temperature as well as the energy exchange due crystallization (phase change). The model also considers other dynamic, cooling-induced changes of thermal properties during the procedure as the variation of blood perfusion. Our results demonstrate that dynamic, cooling induced thermal-structural characteristics of the tissue affect significantly the progression of the crystallized lipid front and consequently the thermal damage to the target tissue. The results for the proposed dynamic numerical thermal model are in agreement with the experimental data and provide guidance to optimize the cooling exposure parameters.

AUTHOR INDEX

A

Abraham, Edward MON 11
Adams, Matthew TUES 12
Aguilar, Guillermo TUES 16
Arca, Hale SUN 36
Arthur, Martin TUES 13
Azevedo, Ricardo SAT 04

B

Bakker, Akke TUES 35
Barnett, James SUN 18
Bischof, John MON 30
Brousell, Steven MON 23
Bull, Joan MON 26
Bunz, Fred SUN 17
Burdette, E. Clif SUN 42, TUES 14

C

Camacho-Lopez, Santiago TUES 17
Cammin, Jochen MON 21
Cano-Mejia, Juliana SUN 24
Chantrell, Roy MON 29
Chatzinoff, Yonatan TUES 38
Cheng, Bingbing TUES 29
Chhabra, Arpit MON 20
Chopra, Rajiv TUES 27
Chu, William MON 37
Cintra, Emilio Ramos POS 17
Clarke, Robert MON 1
Cressman, Erik SUN 21, SUN 48
Crezee, Hans SUN 11
Crouch, A. Colleen MON 36

D

Datta, Niloy SUN 35
Deckers, Roel TUES 10
De la Rosa, Elder SAT 02
de Maar, Josanne MON 17
De Maio, Antonio SUN 16
De Morais, Paulo SUN 27
Dewhirst, Mark SUN 39
Dillon, Christopher MON 35
Dobsicek Trefna, Hana SUN 10, SUN 55
Dunne, Michael TUES 22

E

Ebbini, Emad TUES 11
Eguía Eguía, Sandra Irene POS 12
Ellsworth, Jason SUN 15
Eranki, Avinash POS 23
Ewertowska, Elzbieta TUES 15

F

Fahrenholtz, Samuel TUES 39
Fan, Timothy SUN 41
Feng, Yusheng POS 8
Fiering, Steven MON 2
Floriano, Pierre SUN 52
Fonseca, Monique T MON 27
Franken, Nicolaas SUN 46
Fuentes, David MON 14

G

Gough, Michael MON 3
Goya, Gerardo SUN 02
Goya, Gerardo F. SUN 30
Graner, Michael SUN 20
Griffin, Robert J. SUN 22

H

Helenius, Mikko MON 6
Henderson, Elizabeth TUES 8
Hernández-Cordero, Juan TUES 18
Hilger, Ingrid SAT 03
Hoopes, P. Jack MON 4, SUN 40
Hovorka, Ondrej MON 28
Hurwitz, Mark MON 15
Hylander, Bonnie MON 25

I

Ibelli, Taylor POS 24
Ibitoye, Ayo SUN 54
Issels, Rolf SUN 32

J

Jacinto, Carlos SUN 26
Jackson, Michael POS 15
Jenkins, Samir MON 8
Jones, Carlton Neville TUES 26
Joo, Jong-Cheon POS 27

K

Kim, Wonwoo POS 6
Koh, Eun-young SUN 08
Kok, H.P. TUES 37
Kong, Yi Wen TUES 7
Korangath, Preethi POS 10, TUES 2
Kothapalli, Satya V.V.N. SUN 14
Kunaprayoon, Dan MON 39

L

Laetsch, Theodore TUES 3
Lam, Fred TUES 6
Lee, Jessie TUES 9
Levi-Polyachenko, Nicole TUES 31
Liu, Christina MON 22
Liu, Dong MON 34
Li, Wentao MON 18
Longo, Thomas POS 1
Lucci, Carolina POS 11

M

Manuchehrabadi, Navid POS 19, SUN 50
Martinez, Raquel POS 28
McCabe-Lankford, Eleanor TUES 23
Meeker, Daniel TUES 32
Mikhail, Andrew TUES 4
Molitoris, Jason SUN 37
Monazami, Reza TUES 40
Motamarry, Anjan SUN 29
Mulder, Tim SUN 13
Munaweera, Imalka TUES 30
Munier, Sean MON 13

N

Negussie, Ayele H POS 18
Nwoye, Ephraim SUN 53

O

Oei, Arlene L. SUN 19
Onyeuku, Nasarachi MON 38
Ozayral, Sanem POS 20

P

Page, Rodney SUN 38
Pellegrino, Teresa SUN 04
Penate Medina, Oula SUN 06
Pereira Garcia, Monica POS 13
Piorkowska, Karolina SUN 47
Prakash, Punit TUES 36
Purschke, Martin SUN 45

R

Ramírez-Núñez, A.L. POS 9
Ranjan, Ashish SUN 44
Renero-C, Francisco-J TUES 19
Repasky, Elizabeth SUN 01
Rodrigues, Dario SUN 49

S

Salimi, Marzieh SUN 31
Santoyo-Salazar, Jaime SUN 05
Schooneveldt, Gerben SUN 51
Serantes, David MON 31
Shafirstein, Gal SUN 23
Shaikh, Sumbul POS 26
Shao, Qi MON 7
Sheth, Rahul MON 10, TUES 21
Siqueira, Elis Regina POS 7
Smeltzer, Mark TUES 28
Snider, III, James MON 16
Song, Tae-Jin POS 5
Stafford, R. Jason POS 16, SUN 28, TUES 20
Stauffer, Paul SUN 12
Stewart, Jacqueline POS 21
Sweeney, Elizabeth E. MON 5
Szasz, Oliver MON 19

T

Telling, Neil SUN 03
ten Hagen, Timo TUES 24
Tian, Li SUN 25
Trivedi, Hari POS 22
Trujillo, Macarena POS 2

U

Usov, Nikolai MON 32

V

van der Zee, J. SUN 33
van Leeuwen, Caspar TUES 34
van Rhoon, Gerard SUN 09
Vaupel, Peter MON 12
Vogel, Kenneth TUES 33

W

Wang, Chencai MON 33
Wang, Xiangyang SUN 43
Weigelin, Bettina MON 24
Wessalowski, Ruediger SUN 34
Wirtz, Denis TUES 1
Woodrum, David MON 9

X

Xu, Mai TUES 25

Y

Yamamoto, Itsuo POS 14
Yang, Chun Ting POS 25, TUES 5
Yavuz, Bihter POS 3

Z

Zeng, Like POS 4
Zhu, Liang SUN 07

NOTES

NOTES

NOTES

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

The JKTG Foundation is pleased to support the 34th Annual Meeting of the Society for Thermal Medicine. Enjoy the meeting!

The Jayne Koskinas Ted Giovanis Foundation for Health and Policy (JKTG) supports independent research, data analysis, events and other projects that improve health care and move health policy conversations beyond politics to achieve cost reduction, expand access and improve quality.

JKTGFoundation.org
@JKTGFoundation

JAYNE KOSKINAS TED GIOVANIS | Foundation for Health and Policy

Supported by the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, a Maryland private foundation dedicated to effecting change in health care for the public good. The opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and not necessarily those of the JAYNE KOSKINAS TED GIOVANIS FOUNDATION FOR HEALTH AND POLICY, its directors, officers, or staff.