SOCIETY FOR THERMAL MEDICINE

2015 PROGRAM & ABSTRACT BOOK

32nd Annual Meeting

Buena Vista Palace Hotel & Spa, Lake Buena Vista, Florida

April 14 – 17, 2015

2015 Meeting of the Society for Thermal Medicine

April 14-17, 2015 ◊◊◊ Buena Vista Palace, Orlando, Florida

	Tuesday, April 14th	Wednesday, April 15th	Thursday, April 16th	Friday, April 17th
7:00 a.m.		Breakfast *Events Center*	Breakfast *Events Center*	Breakfast *Events Center*
8:00 a.m.		Tumor Immunology **Alexzander Asea** *Great Hall E/W* 7:45-8:30 a.m. NPs and HT **Nichole Levi-Polychenko** *Events Center ABC*	Cryobiology **Jeunghwan Choi** *Great Hall E/W* 7:45-8:30 a.m. Nano Drug Delivery **Timo ten Hagen** *Events Center ABC*	Thermal Modeling **John Pearce** *Great Hall E/W* 7:45-8:30 a.m. HSPs and Exosomes **Michael Graner** *Events Center ABC*
9:00 a.m.		Mass Spectrometry with Metabolomics **Richard Yost** *Great Hall East/West* 8:45-9:45 a.m.	Metabolic Alterations in Cancer **Matthew Vander Heiden** *Great Hall East/West* 8:45-9:45 a.m.	Polymeric Micelles **Alexander Kabanov** *Great Hall East/West* 8:45-9:45 a.m.
10:00 a.m.		Coffee Break *9:45-10:15 a.m.*	Coffee Break *9:45-10:15 a.m.*	Coffee Break *9:45-10:15 a.m.*
11:00 a.m.	Finance Committee *Oxford Room (Lobby Level)*	**Plenary Session: Analytical Methods** *Great Hall East/West* 10:15-Noon	**Clinical Studies** *Great Hall E/W* 10:15-Noon **Biological Aspects** *Events Center ABC*	**Thermosensitive Drug Delivery** *Great Hall E/W* 10:15-Noon **Thermal Medicine Biological & Chemical** *Events Cntr ABC*
Noon	IJH Editorial Board *Oxford Room (Lobby Level)* Exhibit Hall & Poster Set-up *Events Center (Convention Level)* *Noon – 4:30 p.m.*	**Lunch on Own** Noon-1:30 p.m.	**Lunch on Own** Noon-1:00 p.m. **NIH Update**, Rosemary Wong	**STM Business Meeting & Luncheon** *Great Hall East/West* Noon-1:30 p.m.
1:00 p.m.				
2:00 p.m.	STM Council Meeting *Oxford Room (Lobby Level)*	**Thermal Modeling & Devices** *Great Hall E/W* 1:30-3:15 p.m. **Nanotherapeutics** *Events Center ABC*	**Updates in Prostate Cryoablation 2015** sponsored by the American College of Cryosurgery *Great Hall East/West* 1:30-4:45 p.m.	**George M. Hahn Award** **Plenary Session: Sensitization** *Great Hall East/West* 2:00-3:30 p.m.
3:00 p.m.		Coffee Break *3:15-3:30 p.m.*		Coffee Break *3:30-4:00 p.m.*
4:00 p.m.		**Presidential Symposium** *Great Hall East/West* 3:30-5:00 p.m.		**New Investigator Symposium** *Great Hall E/W* 4-5:30 p.m.
5:00 p.m.	**Welcome Reception** *20Seven (27th Floor)* *5:30 – 7:30 p.m.*	**Robinson Award Lecture** *Great Hall East/West,* 5:15-6:15 p.m.	**Poster Session & Reception** *Events Center,* 5:00-7:00 p.m.	
6:00 p.m.			ICHO Planning Committee Working Dinner *Veranda Room* 6:15-8:00 p.m.	
7:00 p.m.		**Robinson Dinner** 7:00 p.m. *Fulton's Crab House* *Downtown Disney*		**New Investigator Award Dinner** *Location TBD* 6:30-9:30 p.m.
8:00 p.m.				

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SOCIETY FOR THERMAL MEDICINE

Dear Colleagues,

On behalf of my fellow members of the Governing Council, it is my pleasure to welcome you to the 32nd Annual Meeting of the Society for Thermal Medicine and what has shaped up to be another excellent line-up of respected speakers addressing important topics in the field of thermal medicine. The Society for Thermal Medicine is pleased to present an impressive schedule of topics, exceptional guest speakers, and an abundance of excellent abstract presentations from colleagues. We are particularly excited to welcome the American College of Cryosurgery (ACC) to this year's event. The ACC will be sponsoring a plenary session on Thursday afternoon for an update on clinical applications of cryotherapy. Since the inception of the North American Hyperthermia Society in 1981, we have grown and expanded to include the entire range of thermal therapies and this will provide increased depth at the lower range of the temperature spectrum. We are hopeful it will prove fruitful for future interaction between the two societies.

This event continues to grow because of the free exchange of research data and ideas along with colleagues and corporate partners continuing to give us positive feedback on the line-up of quality speakers and timely topics. We thank you for attending this year's meeting and hope that you find some time to enjoy all of the sights and sounds around Disney ®, Universal Studios ®, and other local attractions.

With Regards,

Erik Cressman, PhD, MD, FSIR
STM 2015 Program Chair
MD Anderson Cancer Center

32nd Annual Meeting of the Society for Thermal Medicine

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32nd Annual Meeting of the Society for Thermal Medicine

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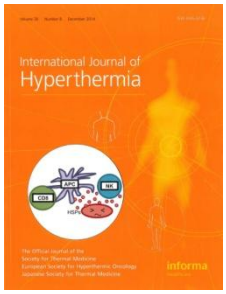

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RADIATION RESEARCH SOCIETY

STM 2015

Program Organizing Committee

Committee Members

Chair: Erik Cressman, PhD, MD, FSIR	University of Texas MD Anderson Cancer Center
Elizabeth Repasky, PhD	Roswell Park Cancer Institute
Bruno Odisio, MD	University of Texas MD Anderson Cancer Center
Dieter Haemmerich, PhD	Medical University of South Carolina
Chris Brace, MSEE, PhD	University of Wisconsin
Robert J. Griffin, PhD	University of Arkansas for Medical Sciences
Jason Stafford, PhD	University of Texas MD Anderson Cancer Center
John Pearce, PhD	University of Texas at Austin
Jennifer Yu, PhD	Cleveland Clinic
John Baust, PhD	American College of Cryosurgery
Nicole Levi-Polyachenko, PhD	Wake Forest University
Rivka Colen, MD	University of Texas MD Anderson Cancer Center
Muneeb Ahmed, MD, FSIR	Beth Israel Deaconess Medical Center

Special Thanks to:

Association Manager **Chris Lapine** of Allen Press, Inc. and Meeting Planner **Kathryn Harth** and **Nicole Schwartz** from Kansas State Conference services, for their assistance with the STM 2015 Annual Meeting and medical student **Lindsey Shea** (University of Illinois), graduate student **Eleanor McCabe** (Wake Forest University) and Associate Professor **Wilton Remigio** for helping with audiovisual and operational items during the meeting.

Meeting info/maps

Registration Desk Hours of Operation:

Tuesday, April 14: 1:00pm – 5:00pm – Great Hall Assembly

Tuesday, April 14: 5:30pm – 7:30pm – Outside of *20Seven* – 27th Floor

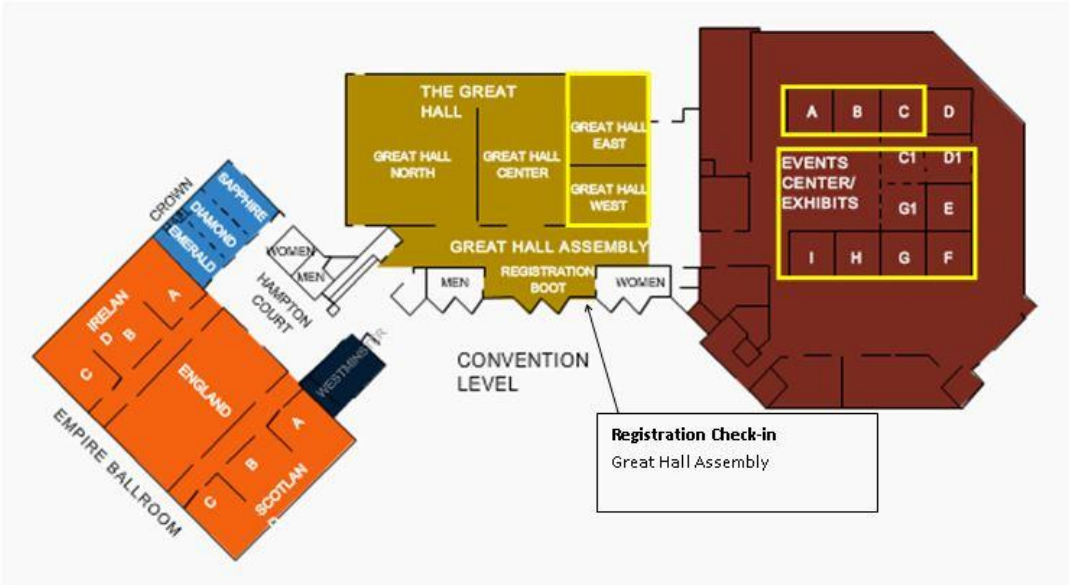
Wednesday, April 15: 7:00am – 5:30pm – Great Hall Assembly

Thursday, April 16: 7:00am – 7:00pm – Great Hall Assembly

Friday, April 17: 7:00am – 12:00pm – Great Hall Assembly

CONFERENCE WIFI PASSWORD: STM2015

Buena Vista Palace Floor Plan



Registration Area:
Great Hall Assembly

Exhibits & Poster Hall:
Events Center

General Session Room:
Great Hall East/West

Secondary Presentation Room:
Events Center ABC

Governing Council

Society for Thermal Medicine (2015 -16)

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.

President: Robert J. Griffin, PhD
University of Arkansas for Medical Sciences
Dept. of Radiation Oncology
Little Rock, AR

Past President: Dieter Haemmerich, PhD, DSc
Medical University of South Carolina
Department of Pediatrics
Charleston, SC

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University of Texas MD Anderson Cancer Center
Department of Interventional Radiology
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Baltimore, MD

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University of Texas MD Anderson Cancer Center
Department of Imaging Physics
Houston, TX

IJH Editor: Mark W. Dewhirst, PhD, DVM
The International Journal of Hyperthermia
Duke University Medical Center
Department of Radiation Oncology
Durham, NC

Councilors

Councilors: Biology /Chemical Sciences

2014-2015 Nicole Levi-Polyachenko, PhD - Wake Forest University

Councilors: Clinical/Medical Sciences

2014-2015 Jennifer Yu, MD, PhD - Cleveland Clinic

Councilors: Engineering/Physical Sciences

2014-2015 Robert McGough, PhD - Michigan State

Keynote Speakers

Richard A. Yost - Professor and Head, Analytical Chemistry

Wednesday, April 15th 8:45am – 9:45am

Great Hall East/West

"Integrating Imaging Mass Spectrometry with Metabolomics"

Co-Director, Southeast Center for Integrated Metabolomics

Affiliate Professor, UF Pathology, Immunology, and Laboratory Medicine

Affiliate Professor, UF School of Natural Resources and Environment

Adjunct Professor, University of Utah Pathology and ARUP

Past Member, Florida Board of Governors

Department of Chemistry, University of Florida

Prof. Yost received his Ph.D. in 1979 and assumed the position of Assistant Professor at the University of Florida. He has risen through the ranks at UF to Professor and Head of the Analytical Chemistry Division. His research has involved 100 graduate students funded by over $20 million in research grants, and has led to the publication of over 160 papers and 16 patents. Over $30 billion worth of instruments have been sold based on these patents. Also contributing to these research efforts have been a number of collaborators at UF and around the world, visiting scientists, plus undergraduate and high school researchers. Current research interests center on instrumental developments, fundamental studies, and analytical applications of tandem mass spectrometry and ion mobility, including imaging mass spectrometry and FAIMS. Prof. Yost recently completed a two-year term as member of the Florida Board of Governors (Regents) and Chair of the Advisory Council of Faculty Senates of Florida. He is past Chair of the UF Faculty Senate and has served on the UF Board of Trustees. He has served as the Treasurer and Secretary of the American Society for Mass Spectrometry, and has served on the editorial boards of The Journal of the American Society for Mass Spectrometry and The International Journal of Mass Spectrometry. Prof. Yost's research was recognized with the 1993 ASMS Award for Distinguished Contribution in Mass Spectrometry.

Keynote Speakers

Matthew Vander Heiden MD, PhD

Thursday, April 16th 8:45am – 9:45am

Great Hall East/West

"Metabolic Alterations in Cancer"

Eisen and Chang Career Development Professor

Associate Professor of Biology

Koch Institute for Integrative Cancer Research

Massachusetts Institute of Technology and Dana-Farber Cancer Institute

Dr. Vander Heiden is the Eisen and Chang Associate Professor in the Koch Institute for Integrative Cancer Research and the Department of Biology at the Massachusetts Institute of Technology. He is also an Instructor of Medicine at the Dana-Farber Cancer Institute and Harvard Medical School. Dr. Vander Heiden received his MD and PhD degree from the University of Chicago. He also completed clinical training in Internal Medicine and Medical Oncology at the Brigham and Women's Hospital / Dana-Farber Cancer Institute prior to completing a post-doctoral fellowship at Harvard Medical School.

Keynote Speakers

Alexander (Sasha) V. Kabanov, Ph.D., Dr.Sc.

Friday, April 17th 8:45am – 9:45am

Great Hall East/West

"Polymeric Micelles – A Transformative Technology at the Clinical Stage"

Director, Center for Nanotechnology in Drug Delivery

Mescal S. Ferguson Distinguished Professor at UNC Eshelman School of Pharmacy

Co-Director, Carolina Institute for Nanomedicine

University of North Carolina, Chapel Hill

Alexander "Sasha" Kabanov, PhD, DrSci, is the Mescal Swaim Ferguson Distinguished Professor and director of the Center for Nanotechnology in Drug Delivery at the UNC Eshelman School of Pharmacy and co director of the Carolina Institute for Nanomedicine at the University of North Carolina at Chapel Hill. Prior to joining UNC-Chapel Hill in July 2012, Kabanov served for nearly eighteen years at the University of Nebraska Medical Center where he was the Parke-Davis Professor of Pharmaceutical Sciences and director of the Center for Drug Delivery and Nanomedicine, which he founded in 2004. Kabanov received his PhD in chemical kinetics and catalysis in 1987 at Moscow State University, USSR.

Kabanov has conducted pioneering research on polymeric micelles, DNA/polycation complexes, block ionomer complexes and nanogels for delivery of small drugs, and nucleic acids and proteins that have influenced considerably current ideas and approaches in drug delivery and nanomedicine. His work led to the first-in-man polymeric micelle drug (SP1049C) to treat cancer, which successfully completed Phase II clinical trial and is under further evaluation. He cofounded Supratek Pharma, Inc. (Montreal, Canada), which develops therapeutics for cancer, and Neuro10-9, Inc. (Omaha, Nebraska, and Chapel Hill, North Carolina), which focuses on diseases of the central nervous system.

Kabanov has published more than 240 scientific papers and has more than 100 patents worldwide. His work has been cited over 16,700 times (Hirsch index 71). His cumulative research support in academia has been more than

$50 million. His inventions have attracted nearly $60 million in private, foundation, and company-sponsored R&D funding in industry. He founded the ongoing Nanomedicine and Drug Delivery Symposium series in 2003 and cochaired the Gordon Research Conference on Drug Carriers in Medicine and Biology in 2006.

Kabanov received the Lenin Komsomol Prize in 1988, an NSF Career Award in 1995, the University of Nebraska ORCA Award in 2007, and the University of Nebraska Medical Center Scientist Laureate in 2009, among other distinctions. He is also the recipient of a Russian Megagrant (2010). In 2013, he was elected as a member of Academia Europaea.

Kabanov was director of the Nebraska Center for Nanomedicine, an NIH Center of Biomedical Research Excellence, from 2008 to 2012 and is a director of the Moscow State University Laboratory of Chemical Design of Bionanomaterials, which he founded at in 2010 with Megagrant support.

The George M. Hahn Award & Lecture

Friday, April 17th 1:30pm – 2:00pm in Great Hall East/West

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.

Paul R. Stauffer, PhD

Paul Stauffer received a BA-Physics from the College of Wooster and MS-Electrical Engineering from the Univ. of Arizona. He is board certified in Clinical Engineering (1983) and Medical Physics (1991). Since 1978, his work has focused primarily on the development of new technology for heating and monitoring tissue temperature for applications in diagnosis and therapy of cancer. He has worked in the laboratory designing improved heating technology, and taken new RF, microwave and ultrasound devices through the approval process into clinical practice. To control increasingly complex heat applicators, he has developed novel thermal monitoring approaches that optimize use of thermocouple and fiberoptic arrays for superficial disease, and microwave radiometry and MR thermal imaging technologies for non-invasive deep tissue measurements. He held the same title (Director of Hyperthermia Physics) for 23 years at the Univ. of California San Francisco and 7 years at Duke University. In 2013, he was recruited to Thomas Jefferson University as Professor and Director of Thermal Oncology Physics. Over this time, he has mentored 19 postdoc and MD fellows, 26 graduate students, and 9 undergraduate students in Hyperthermia Physics – a group that has contributed over 200 publications and 9 patents. At the same time, he has been the Medical Physicist responsible for clinical hyperthermia treatment of over 1000 patients. Paul is a charter member of the Society of Thermal Medicine and has served on numerous committees and executive posts, including President in 2007. He also received the Eugene Robinson Award for career achievement in 2007. He has participated in RTOG, AAPM, STM and ESHO task forces on Quality Assurance of clinical hyperthermia, and is currently an Associate Editor for the International Journal of Hyperthermia.

Summary of Talk:

Which is Evolving Faster – Thermal Therapy Tools or the Clinical Needs

Paul Stauffer

George Hahn was a true pioneer. He helped blaze a new trail by introducing the biological rationale and potential clinical applications for a new therapy – Hyperthermia. His high impact radiobiology investigations into the effects of heat and drugs on tumor cells were carried out with the tools of the time, a simple hot waterbath. The accompanying clinical investigations of his large team at Stanford were accomplished with custom built radiofrequency electrodes, lightly focused ultrasound array, or microwave spiral applicators – none of which have ever been available commercially.

Regardless of wildly positive early research success, two RTOG clinical trials interjected reservations about the clinical applicability of hyperthermia. At the very least they demonstrated a need for more controllable heat applicators and more extensive thermal dosimetry for feedback control. This resulted in multiple scattered development efforts to generate more controllable energy delivery and non-invasive thermal monitoring. It also spawned development of a new generation of electromagnetic and thermal modeling programs to define the heating capabilities of existing applicators and assist the design of new applicator technology.

Fast forward 25 years. Numerous radiofrequency, microwave, and ultrasound devices now exist with 4, 8, 16, 32 and even 512 independently controllable sources. Non-invasive thermometry capable of monitoring volumetric temperature distributions is becoming more commonplace, and integration within commercial heating systems has begun. Each year, new clinical applications are promoted that take advantage of this growing arsenal of thermal therapy equipment. Nevertheless, with all these tools there are as yet only a handful of clearly defined clinical applications with distinct treatment goals, responses, and reimbursement.

At present, our Society of Thermal Medicine continues to expand in scope. There are evolving clinical applications finding new uses for existing technology, while there are traditional clinical applications still begging for technology advancements. This presentation will take a brief tour through the current maze of heating technology and look for correlations with the rapidly expanding range of clinical applications for thermal medicine.

26th J. Eugene Robinson Award & Lecture

Wednesday, April 15th 5:15pm – 6:15pm in Great Hall East/West

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.

Elizabeth A. Repasky, PhD

Dr. Elizabeth A. Repasky's research is devoted to identifying physiological systems in the tumor bearing host that can be manipulated to alter the tumor microenvironment and improve efficacy of cancer therapies, especially radiation- and immunotherapies. Dr. Repasky graduated from Seton Hill College with a BA in Biology, received her MS and PhD degrees from the State University of New York at Buffalo in the areas of Mammalian Physiology and Anatomy and completed a Postdoctoral Fellowship at the California Institute of Technology in Cell Biology. It was not until she came to Roswell Park Cancer Institute, initially working in Radiation Medicine Department under the leadership of the late Dr. Richard Johnson, that she became interested in hyperthermia, and in particular, mild, physiologically relevant, increases in body temperature and the impact it has on tumor biology and immunology. Her interest in tumor immunology grew when she became a member of the Immunology Department at RPCI, and was eventually promoted to full Professor. Currently, she is also Co- Leader of the Cell Stress and Biophysical Therapies Program in the Cancer Center. She has over 156 peer-reviewed publications in the areas of cancer biology/immunology, hyperthermia and thermoregulation, stress responses and heat shock protein biology, in addition to many invited review articles.

Dr. Repasky enjoys mentoring graduate students and young investigators and has trained 20 Ph.D students as major thesis advisor. She has actively served the Society for Thermal Medicine- as a board member and past-president, scientific program chair and Senior Editor for the I*nternational Journal of Hyperthermia* since 2006. She has also served as Editor for several *Special Issues* of the Journal.

Summary of Talk:

Temperature has a profound influence on cells and organisms and their metabolic processes. Throughout nature, it is clear that thermoregulation assumes a very high physiological priority. The goal of this lecture will be to share some insights we have gained from studying immunological and physiological effects of mild hyperthermia in normal cells, tissues and tumors and how these effects influence therapeutic sensitivity. Emphasis will be given to recent work demonstrating the impact of thermogenesis on metabolism and anti-tumor immunity in the tumor bearing host.

2015
STM New Investigator Awards
Sponsored by
NCI/NIH R13CA174356 and
Radiation Research Society

Twelve New Investigators have earned Travel Awards to the 32nd Annual Meeting of the Society for Thermal Medicine. $600 grants will be awarded based on applications and abstracts judged by a Committee of STM members chaired by Dr. Jason Stafford of the University of Texas MD Anderson Cancer Center. The awards are funded in part by the National Institutes of Health through grant R13CA174356 from the National Cancer Institute as well as the Radiation Research Society. These New Investigators will present their abstracts April 17th at 4:00pm in Lake Buena Vista. STM Officers and guests will also host the New Investigators at a private luncheon on Wednesday, April 15th.

Edmond Balidemaj – Academic Medical Center, University of Amsterdam
"In vivo conductivity values of cervical cancer patients reconstructed with a 3T MR system"

Lindsey Shea – University of Texas MD Anderson Cancer Center
"Increasing Energy Density with Polyprotic Acids and Polyamines for Use in Thermochemical Ablation"

Gerben Schooneveldt - Academic Medical Center, University of Amsterdam
"Thermophysical fluid modelling for loco-regional hyperthermia treatment of Non-Muscle Invasive Bladder Cancer"

Sri Kamal Kandala- Johns Hopkins University
"Simulation of magnetic nanoparticle hyperthermia in prostate tumor models"

Taylor Ibelli - Wake Forest Baptist Health Medical Center
"Photothermal Ablation of *Streptococcus pyogenes* using Fluorescent Bio-Polymeric Nanoparticles"

Tao Lu - Erasmus Medical Centre
"A novel stealth idarubicin thermosensitive liposome for ultrafast triggered release using mild hyperthermia"

2015
STM New Investigator Awards
Sponsored by
NCI/NIH R13CA174356 and
Radiation Research Society

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Sergio Curto - Kansas State University
"Design and optimization of a conformal microwave antenna for a wearable breast hyperthermia applicator"

Mark Bucsek - Roswell Park Cancer Institute
"Destressing laboratory mice reveals new relationships between heat production, anti-tumor immunity and β-adrenergic receptor signaling"

Enid Choi - University of Maryland
"External thermal therapy with concurrent radiation therapy results in rapid and durable regression of multiply-recurrent, debilitating verrucous vulgaris: a case report"

Harishankar Natesan - University of Minnesota
"Integrated micro-thermal sensor for planning and guidance of pulmonary vein ablation"

Alicia Petryk - Dartmouth College
"Fractionated nanoparticle hyperthermia and radiation improves tumor treatment efficacy"

Mustafa Sarimollaoglu - Arkansas Nanomedicine Center, University of Arkansas for Medical Sciences
"Photothermal cancer therapy guided by in vivo photoacoustic flow cytometry"

NIH/NCI UPDATES 2014/2015

Thursday, April 16, 1:00pm – 1:30pm
Great Hall/East West

Rosemary Wong, PhD
National Cancer Institute
Radiotherapy Development Branch
Rockville, MD

NIH and NCI Grant-Related Changes during Fiscal Years 2014/2015

The 2014 fiscal year continues to be challenging for all federal agencies despite the Congressional strategies proposed to address the U.S. budget deficit. The Bipartisan Budget Act of 2013 passed by the House and Senate in December 2013 approved a two-year spending bill cancelling the proposed sequester cuts (i.e., 4-5% NIH/NCI budget reductions) required in 2014 and 2015, but extending the sequestration period through 2023. What impact this passage will have on the final NIH/NCI appropriations for 2014 and subsequent number of NIH/NCI grants funded in 2014 remains to be seen.

The overall success rate and funding paylines for NIH/NCI applications in all areas of research besides the Hyperthermia and Thermal Therapy research field will be provided for the past few years. Information on new initiatives and funding opportunities including Dr. Varmus' Provocative Question initiative during the past two years will also be discussed.

The new NIH grant-related policy changes implemented in 2014 and those proposed for 2015 will be highlighted. These changes could impact the grant application and award process for STM applicants and their academic institutions. Information on various NIH resources available for grant applicants and their institutions will also be provided.

In September 2014, Congress passed a Continuing Resolution to keep the government operational until December 11, 2014 and finally passed the NIH FY2015 budget on December 16, 2014 with overall funding similar to FY2014. While inflation continues to erode into the NIH and NCI budget for the past 10 years since the doubling of the NIH budget ended in 2003, NIH and NCI is committed to fund the best research showing the highest impact within the field of research being proposed. Basic mechanistic research projects are important, but those having clinical translational applicability will continue to be valued as having high impact and more likelihood of being funded in these critical budget periods.

Refresher Courses

Refresher on Tumor Immunology

Alexzander Asea, PhD
Deanship for Scientific Research
University of Dammam
Dammam, Saudi Arabia

Wednesday, April 15, 7:45am-8:30am
Great Hall E/W

Refresher on NPs and HT

Nicole Levi-Polychenko, PhD
Wake Forest University Health Sciences
Winston-Salem, NC

Wednesday, April 15, 7:45am-8:30am
Events Center ABC

Refresher on Cryobiology

Jeunghwan Choi, PhD
East Carolina University
Greenville, NC

Thursday, April 16, 7:45am-8:30am
Great Hall E/W

Refresher Courses

Refresher on Nano Drug Delivery

Timo ten Hagen, PhD
Erasmus MC
Rotterdam, the Netherlands

Thursday, April 16, 7:45am-8:30am
Events Center ABC

Refresher on Thermal Modeling

John Pearce, PhD
The University of Texas at Austin
Austin, TX

Friday, April 17, 7:45am-8:30am
Great Hall E/W

Refresher on HSPs and Exosomes

Michael Graner, PhD
University of Colorado Denver
Anschutz Medical Campus
Aurora, CO

Friday, April 17, 7:45am-8:30am
Events Center ABC

Plenary Session – Sponsored by the American College of Cryosurgery

Updates in Prostate Cryoablation 2015

Thursday, April 16, 2015 1:30pm-4:45pm
Great Hall East/West

1:30pm- 1:40pm	Welcome and Introductions	Aaron E. Katz, MD President, ACC
1:40pm- 2:15pm	Is There an Advantage to Combinatorial Cryo/Thermal Therapy (*Contributors: John G. Baust, Kenneth Bowman, Kristi Snyder, Robert Van Buskirk John M. Baust)*	John G. Baust, PhD Immediate Past President, ACC
2:15pm- 2:45pm	Focal Cryoablative Technologies 2015	Aaron E. Katz, MD
2:45pm-3:15pm	Patient Selection and Oncologic Outcomes for Focal Cryoablation of the Prostate	Thomas Polascik, MD
3:15pm-3.45pm	Multiparametric Prostate Ultrasound, Targeted Biopsy & Individualized Ablation of the Prostate	Daniel Rukstalis, MD
3:45pm-4:45pm	Panel Discussion & Case Management	Aaron E. Katz, MD John G. Baust, PhD Thomas Polascik, MD Daniel Rukstalis, MD

Welcome to Lake Buena Vista, FL and STM 2015

Tuesday, April 14th

STM Finance Committee Meeting

10:30am - 11:30am Oxford Room - Lobby Level

Private Meeting of the STM Finance Committee. Chaired by Paul Stauffer and Rob Ivkov.

Exhibit & Poster Hall Set-up

12:00pm - 4:30pm Events Center - Convention Level

Time for Exhibitor Booth Set-up and hanging of Posters for presentations.

IJH Editorial Board Meeting

12:00pm - 1:30pm Oxford Room - Lobby Level

Private Luncheon Meeting of the IJH Editorial Board and Staff from Informa/Taylor & Francis.

Registration Desk Open

1:00pm - 5:00pm Great Hall Assembly - Convention Level

Registered attendees can check-in and pickup name badges and welcome packets. Walk-up registrations can be processed on-site and speakers can upload PowerPoint presentations to laptops to be used during oral presentations.

STM Governing Council Meeting

2:00pm - 4:00pm Oxford Room - Lobby Level

Private meeting of the Governing Council and Invited Guests. Chaired by STM President Robert Griffin.

Welcome Reception

5:30pm-7:30pm 20Seven - 27th Floor

The welcome reception is open to all registered meeting attendees. The registration desk will be near the entry for any registered guests who have not already picked up welcome packets. Heavy hors d'oeuvres will be served.

Wednesday, April 15th

Registration

7:00am - 5:30pm **Great Hall Assembly - Convention Level**

Registered attendees can check-in and pickup name badges and welcome packets. Walk-up registrations can be processed on-site and speakers can upload PowerPoint presentations to laptops to be used during oral presentations.

Breakfast

7:00am - 8:30am **Events Center - Convention Level**

Breakfast with Exhibits & Posters in Events Center. This room is open all day. Your name badge is your admission to breakfast.

Refresher on Tumor Immunology

7:45am - 8:30am **Great Hall E/W**

Alexzander Asea, PhD, of the Deanship for Scientific Research, University of Dammam, Dammam, Saudi Arabia

WED 1 Cancer Immunology - Tumor Microenvironment
Alexzander Asea
Deanship for Scientific Research, University of Dammam, Dammam, Saudi Arabia

Refresher on NPs and HT

7:45am - 8:30am **Events Center ABC**

Nicole Levi-Polychenko, PhD, of Wake Forest University, Winston-Salem, NC.

WED 2 Evolution of nanoparticle-induced photothermal therapy; gold standards and new frontiers
Nicole Levi-Polyachenko
Wake Forest University Health Sciences, Winston-Salem, NC, USA

Keynote Address: Integrating Imaging Mass Spectrometry with Metabolomics

8:45am - 9:45am **Great Hall East/West** **Chair: Erik Cressman**

Richard A. Yost, Professor and Head, Analytical Chemistry, Department of Chemistry at the University of Florida.

WED 3 Integrating Imaging Mass Spectrometry with Metabolomics
Richard Yost

University of Florida, Gainesville, FL, USA

Coffee Break with Exhibitors

9:45am - 10:15am Events Center - Convention Level

Plenary Session: Analytical Methods

10:15am - 12:00pm Great Hall East/West Chair: Erik Cressman & Jason Stafford

WED 4 The Power of Full Spectrum Molecular Imaging: More than Just A Pretty Picture
Darwin Asa
Waters Corporation, Milford, MA, USA

WED 5 MALDI Imaging MS: Visualizing Biology and Chemistry in Drug Development
Stepehn Castellino, Reid Groseclose
GSK, RTP, NC, USA

WED 6 Optical imaging and spectroscopy techniques and application to functional evaluation of therapeutic response
Greg Palmer
Duke University Medical Center, Durham, NC, USA

WED 7 Mass Spectrometry Imaging: An Industry Perspective
Katherine Kellersberger, PhD, Soeren-Oliver Deininger, PhD
Bruker Daltonics, Inc, Billerica, MA, USA

Open Lunch

12:00pm - 1:30pm

Symposium: Thermal Modeling and Devices

1:30pm - 3:15pm Great Hall East/West Chair: Punit Prakash & Christopher Brace

WED 8 Nanoheating with natural protein-nanoclusters (membrane rafts)
Gabor Andocs[1], Takashi Kondo[1], Mati Ur Rehman[1], Edina Papp[2], Tamas Vancsik[3], Oliver Szasz[4]
[1]Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Science, University of Toyama, Toyama, Japan, [2]Faculty of Information Technology and Bionics, Pazmany P. Catholic University, Budapest, Hungary, [3]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary, [4]Department of Biotechnics, St. Istvan University, Godollo, Hungary

WED 9 Temporal and spatial resolution of fiber-optic, copper-constantan and manganin-constantan thermocouple probes
Akke Bakker, Gerben Schooneveldt, Willemijn Kolff, Petra Kok, Jan Sijbrands,

Geertjan van Tienhoven, Coen Rasch, Erik Schwing, Gerard van Stam, Hans Crezee
AMC, Amsterdam, The Netherlands

WED 10 First impressions on the performance of the new BSD2000-3D GE450W hybrid deep hyperthermia system
Gerard van Rhoon, Ali Ameziane, Daniel de Jong, Maarten Paulides, Martine Franckena
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

WED 11 A Magnetic field guiding and focusing system for pancreatic cancer treatment via MNP hyperthermia
Fridon Shubitidze, Robert Stigliano, Katsiaryna Kekalo, Ian Baker
Thayer School of Engineering at Dartmouth, Hanover, USA

WED 12 Methods for accurate simulations of microwave ablation
Mark Hagmann[1], Kent Moore[1], Garron Deshazer[2]
[1]BSD Medical Corporation, Salt lake City, Utah, USA, [2]University of Rhode Island, Kingston, Rhode Island, USA

WED 13 Results of cross validation from a trained model for laser induced thermal therapy
Samuel Fahrenholtz[1,2], John Hazle[1,2], Anil Shetty[3], R. Jason Stafford[1,2], David Fuentes[1,2]
[1]UT MD Anderson Cancer Center, Houston, TX, USA, [2]UT Houston Graduate School of Biomedical Sciences, Houston, TX, USA, [3]Medtronic, Inc., Houston, TX, USA

WED 14 Irreversible Electroporation: thermal or non-thermal, that is the question
Hans Crezee, Jantien Vogel, Gerben Schooneveldt, Akke Bakker, Petra Kok, Marc Besselink
Academic Medical Center, Amsterdam, The Netherlands

WED 15 Magnetic Resonance Based Quantification of Nanoparticle Distribution and Heating in Nanoparticle Mediated Laser Interstitial Thermal Therapy (npLITT)
Christopher MacLellan[1,2], Marites Melancon[1,2], Ferandre Salatan[1], Yang Qiao[1], Ken-Pin Hwang[3], David Fuentes[1,2], Jason Stafford[1]
[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, [3]GE Healthcare, Waukesha, Wisconsin, USA

WED 16 INTEGRATION OF DEEP HYPERTHERMIA WITH MR IMAGING
Paul Turner
BSD Medical Corp., Salt Lake City, UT, USA

Symposium: Nanotherapeutics

1:30pm - 3:15pm Events Center ABC Chair: Bruno Odisio & Rob Ivkov

WED 17 Polymer Dynamic Organic Theranostic Spheres (PolyDOTS) for Detection and

Photothermal Ablation of Breast Cancer
Nicole Levi-Polyachenko[1,2], Elizabeth Graham[1,2], Christopher MacNeill[1], Sneha Kelkar[2], Narayanan Kuthirummal[3], Aaron Mohs[2]
[1]Wake Forest University Health Sciences, Winston-Salem, NC, USA, [2]Virginia Tech/ Wake Forest University School of Biomedical Engineering and Sciences, Winston-Salem, NC, USA, [3]College of Charleston, Charleston, SC, USA

WED 18 Conjugated Nanoparticles for Detection and Thermal Therapy in Colorectal Cancer
Eleanor McCabe, Nicole Levi-Polyachenko
Wake Forest University, Winston-Salem, NC, USA

WED 19 Experimental analysis of amplitude- and frequency-dependent specific loss power measurements of magnetic nanoparticles
Frederik Soetaert[1,2], Sri Kamal Kandala[1], Guillaume Crevecoeur[2], Luc Dupré[2], Robert Ivkov[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Ghent University, Ghent, Belgium

WED 20 Methods to control non-target heating for iron oxide nanoparticles hyperthermia.
Elliot Kastner[1], Aditi Misra[1], Will Bennet[1], Jim Petryk[1], Alicia Petryk[1], P. Jack Hoopes[2]
[1]Thayer School- Dartmouth, Hanover, NH, USA, [2]Geisel School of Medicine, Hanover, NH, USA

WED 21 Toxicity and Biodistribution of Iron Oxide Nanoparticles
Adwiteeya Misra[1], Alicia Petryk[2], Rendall Strawbridge[2], P. Jack Hoopes[1,2]
[1]Thayer School of Engineering, Hanover, NH, USA, [2]Geisel School of Medicine, Hanover, NH, USA

WED 22 Nanoparticle-enhanced microwave hyperthermia: effects of nanoparticle size and shape on heating
Brogan McWilliams, Sergio Curto, Hongwang Wang, Stefan Bossmann, Punit Prakash
Kansas State University, Manhattan, Kansas, USA

WED 23 Development of a novel cisplatin-loaded low temperature-sensitive liposome: effect on cisplatin loading/release and anti-tumor effects with hyperthermia
Chen-Ting Lee, Chelsea Landon, Jihong Tong, Kathleen Ashcraft, Christina Hofmann, Yulin Zhao, David Needham, Mark Dewhirst
Duke University, Durham, NC, USA

Coffee Break with Exhibitors

3:15pm - 3:30pm Events Center - Convention Level

Presidential Symposium: Combined modality approaches in thermal therapy

3:30pm - 5:00pm **Great Hall East/West** **Chair: Robert Griffin**

WED 24 Revisiting intracranial hyperthermia and radiation for brain tumors
Jennifer Yu, Alireza Mohammadi
Cleveland Clinic, Cleveland, OH, USA

WED 25 Combining thermal ablation with adjuvant therapies - current and future applications
Muneeb Ahmed
Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA

WED 26 Synergistic Effect of Thermal and Immune Response for Metastatic Cancer Therapy
Xuemin(Lisa) Xu
Shanghai Jiao Tong University, Shanghai, China

Break

5:00pm - 5:15pm

J. Eugene Robinson Award Lecture

5:15pm - 6:15pm **Great Hall East/West** **Chair: Mark Dewhirst**

STM Presents the 26th J. Eugene Robinson Award to Elizabeth A. Repasky, PhD, of the Roswell Park Cancer Institute, Department of Immunology, Buffalo, NY

Robinson Dinner

7:00pm - 9:00pm **Fulton's Crab House, Downtown Disney**

Advanced reservations are required for this private event. $85 per person. This year's dinner will be held at Fulton's Crab House in Downtown Disney. Ticket price includes a salad, entrée, dessert, wine, coffee/tea, and gratuity.

Thursday, April 16

Registration

7:00am - 7:00pm **Great Hall Assembly - Convention Level**

Registered attendees can check-in and pickup name badges and welcome packets. Walk-up registrations can be processed on-site and speakers can upload PowerPoint presentations to laptops to be used during oral presentations.

Breakfast

7:00am - 8:30am **Events Center - Convention Level**

Breakfast with Exhibits & Posters in Events Center. This room is open all day. Your name badge is your admission to breakfast.

Refresher on Cryobiology

7:45am - 8:30am **Great Hall East/West**

Jeunghwan Choi, PhD, of East Carolina University, Greenville, NC.

THUR 1 The Effect of Cold Temperatures on Cellular Freeze Injury
Jeunghwan Choi[1,2], Saravana Balasubramanian[2], Jing Jiang[2], John Bischof[2]
[1]East Carolina University, Greenville NC, USA, [2]University of Minnesota, Minneapolis MN, USA

Refresher on Nano Drug Delivery

7:45am - 8:30am **Events Center ABC**

Timo ten Hagen, PhD, of Erasmus MC, Rotterdam, The Netherlands.

THUR 2 Nanocarrier-based hyperthermia-guided drug delivery to solid tumors
Timo L.M. ten Hagen
Erasmus MC, Rotterdam, The Netherlands

Keynote Address: Metabolic Alterations in Cancer

8:45am - 9:45am **Great Hall East/West** **Chair: Muneeb Ahmed**

Matthew Vander Heiden, MD, PhD, of the Koch Institute for Cancer Research, Cambridge, MA.

THUR 3 Metabolic alterations in cancer
Matthew Vander Heiden
Koch Institute for Cancer Research, Cambridge, MA, USA

Coffee Break with Exhibitors

9:45am - 10:15am Events Center - Convention Level

Symposium: Clinical Studies

10:15am - 12:00pm Great Hall East/West Chair: Dieter Manstein

THUR 4 Preliminary Results of the Impact of the Extent of Laser Ablation on the Median Overall Survival in patients with Glioblastoma Multiform

Mahmoud Abbassy, Gene H. Barnett, Alireza M. Mohammadi
Cleveland Clinic, Cleveland, OH, USA

THUR 5 Interstitial thermal therapy combined with interstitial brachytherapy after chemoradiation for pelvic local recurrence in a patient with muscle invasive bladder cancer

Hunter Boggs, Kruti Patel, Jolinta Lin, Mariana Guerrero, Shifeng Chen, Pradip Amin, Fred Moeslein, Zeljko Vujaskovic
University of Maryland Medical System, Baltimore, MD, USA

THUR 6 Hyperthermia And Radiation For Recurrent Breast Cancer

Sharvari Dharmaiah, Vinay Rao, Andrew Godley, Jennifer Yu
Cleveland Clinic, Cleveland, OH, USA

THUR 7 Concurrent External Beam Radiotherapy and External Thermal Therapy for the Treatment of Extramedullary Plasmacytomas: A Case Report.

James Snider, III[1], Enid Choi[1], Adam Reese[2], Rishabh Chaudhari[3], Navesh Sharma[1], Zeljko Vujaskovic[1]
[1]University of Maryland Medical Center, Baltimore, MD, USA, [2]Einstein Medical Center, Philadelphia, PA, USA, [3]NorthShore University Health System, Chicago, IL, USA

THUR 8 Focal laser ablation of prostate cancer-- technique and outcomes in 85 patients

Eric Walser, Jackie Aoughsten, Ryan Mikus
UTMB, Galveston, Texas, USA

THUR 9 EMF hyperthermia in Childhood Cancer

Ruediger Wessalowski[1], Richard Canters[2], Anette Schweda[1], Oliver Mils[1], Reinhard Willers[3], Patric Kröpil[4], Sultan Abdel-Rahman[5], Rolf D. Issels[5], Gerald C. van Rhoon[2]
[1]Clinic of Pediatric Hematology and Oncology, Medical Faculty, Heinrich Heine University, Duesseldorf, NRW, Germany, [2]Department Radiation Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, [3]Clinic of Pediatric Hematology and Oncology, Medical Faculty, Heinrich Heine University, Duesseldorf, NRW, Germany, [4]Clinic of Pediatric Hematology and Oncology, Medical Faculty, Heinrich Heine University, Duesseldorf, NRW, Germany, [5]Institute of Statistics, Heinrich-Heine-University Düsseldorf,, Duesseldorf, NRW, Germany,

[6]Department of Diagnostic and Interventional Radiology, Medical Faculty, University of Düsseldorf, Duesseldorf, NRW, Germany, [7]Department Internal Medicine, Klinikum Grosshadern, Munich, Germany, [8]Department Internal Medicine, Klinikum Grosshadern, Munich, Germany, [9]Department Radiation Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

THUR 10 EARLY EXPERIENCE WITH INTERSTITIAL LASER THERMAL ABLATION THERAPY (NEUROBLATE SYSTEM) IN GRADE 2 AND 3 GLIOMAS.
Mithun Sattur, Danilo Silva, Gene Barnett, Alireza Mohammadi
Rose Ella Burkhardt Brain Tumor Center, Cleveland Clinic, Cleveland Clinic, Ohio, USA

Symposium: Biological Aspects

10:15am - 12:00pm Events Center ABC Chair: Ashish Ranjan

THUR 11 The Immune Checkpoint Inhibitors: A mounting excitement with an imperative to combine with Hyperthermia
Joan Bull
The University of Texas Medical School at Houston, Houston, Texas, USA

THUR 12 Hyperthermia treatment overcomes temozolomide resistance in glioma cells by downregulating MGMT expression and increasing temozolomide uptake
Chen-Ting Lee, Aaron Blackley, Chelsea Landon, Ivan Spasojevic, John Kirkpatrick, Mark Dewhirst
Duke University, Durham, NC, USA

THUR 13 Self-assembling viral-like nanoparticles for tumor immunotherapy by in situ vaccination
Patrick Lizotte[1], Amy Wen[2], Nicole Steinmetz[2], Steven Fiering[1]
[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [2]Case Western Reserve University School of Medicine, Cleveland, OH, USA

THUR 14 Myeloid-Derived Suppressor Cells Subvert the Immunostimulatory Activity of Thermal Therapy by Blocking T cell Trafficking in the Tumor Microenvironment
Amy Ku, Jason Muhitch, Scott Abrams, Sharon Evans
Roswell Park Cancer Institute, Buffalo, NY, USA

THUR 15 Defining immunological impact and therapeutic benefit of mild heating in a murine model of arthritis
Chen-Ting Lee, Kathleen Kokolus, Nicholas Leigh, Maegan Capitano, Bonnie Hylander, Elizabeth Repasky
Roswell Park Cancer Institute, Buffalo, NY, USA

THUR 16 Housing Temperature-induced Stress in Laboratory Mice drives Therapeutic Resistance Through β2-adrenergic Receptor Activation

Jason W-L Eng, Chelsey B Reed, Kathleen Kokolus, Rosemarie Pitoniak, Mark Bucsek, Adam T Utley, Wen Wee Ma, Elizabeth E Repasky, Bonnie L Hylander
Roswell Park Cancer Institute, Buffalo, NY, USA

THUR 17 Radiation enhancement by tumor stromal thermotolerance
Nathan Koonce, Azemat Jamshidi-Parsian, Peter Corry, Robert Griffin, Ruud Dings
University of Arkansas for Medical Sciences, Little Rock, AR, USA

THUR 18 A Novel High Throughput Model to Study Islet Amyloid Aggregation and β-Cell Death in Type 2 Diabetes Mellitus: Role of Hsp70 (HSPA1A)
Paola Rosas[1], Punit Kaur[2], Alexzander Asea[3,4]
[1]Department of Medical Physiology, Texas A&M Health Science Center, College of Medicine, Temple, TX, USA, [2]Department of Microbiology, Biochemistry & Immunology, Morehouse School of Medicine, Atlanta, GA, USA, [3]Deanship for Scientific Research, University of Dammam, Dammam, Saudi Arabia, [4]Section of Translational Medicine, Department of Cutting-Edge Medicine and Neuroscience, The Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

Open Lunch

12:00pm - 1:00pm

NIH Update

1:00pm - 1:30pm **Great Hall East/West**

Featuring Dr. Rosemary Wong, Program Director at NCI will present an overview of NIH and NCI efforts and objectives.

THUR 19 NIH and NCI Grant-Related Changes During Fiscal Years 2014/2015
Rosemary Wong
National Cancer Institute, Rockville, MD, USA

Plenary Session: Updates in Prostate Cryoablation 2015 - Sponsored by the American College of Cryosurgery

1:30pm - 4:45pm **Great Hall East/West** **Chair: Aaron E. Katz**

THUR 20 Is There an Advantage to Combinatorial Cryo/Thermal Therapy?
John G. Baust[1], Kenneth Bowman[1,2], Kristi Snyder[2], Kimberly Santucci[1,2], Robert van Buskirk[1,2], John M. Baust[2]
[1]State University of New York, Binghamton, NY 13902, USA, [2]CPSI Biotech, Inc., Owego, NY 13827, USA

THUR 21 Focal Cryoablative Technologies 2015

Aaron E. Katz
Winthrop University Hospital, Mineola, NY, USA

THUR 22 Patient Selection and Oncological Outcomes of Focal Cryoablation of the Prostate
Thomas Polascik
Duke Cancer Institute, Durham, NC, USA

THUR 23 Multiparametric Prostatic Ultrasound, targeted biopsy individualized ablation of the prostate
Daniel Rukstalis
Wake Forest School of Medicine, Winston-Salem, NC, USA

Poster Session & Reception

5:00pm - 7:00pm Events Center

POS 1 Thermal Profile of Acetic Acid Analogues for Potential Use in Thermochemical Ablation
Travis Miles, Erik Cressman
Department of Interventional Radiology, MD Anderson Cancer Center, Houston, Texas, USA

POS 2 Analysis of Exotherms of Ethanolamine Derivatives in Reactions with Acetic Acid
Travis Miles, Erik Cressman
Department of Interventional Radiology, MD Anderson Cancer Center, Houston, Texas, USA

POS 3 A robust power deposition scheme for large counter-current blood vessels in tumor during hyperthermia treatment
Huang-Wen Huang
Tamkang University, I-Lan county, Taiwan

POS 4 Fabulous neurological recovery in spinal cord compression from solitary fibrous tumor of pleura with concurrent thermoradiotherapy : A case report.
Poompis Pattaranutaporn
Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

POS 5 NF-κB is involved in regulating the microRNA generating enzyme dicer during fever range hyperthermia
Anand Devasthanam[1], Thomas Tomasi[1,2]
[1]State University of New York at Buffalo, Buffalo, NY, USA, [2]Roswell Park Cancer Institute, Buffalo, NY, USA

POS 6 Combining electromagnetic, thermal and human virtual models for MNP hyperthermia treatment planning and optimization
Fridon Shubitidze[1], Robert Stigliano[1], Levan Shoshiashvili[2], Alicia Petryk[1], P. Jack Hoopes[1]

[1]*Thayer School of Engineering at Dartmouth College, Hanover, NH, USA,* [2]*Tbilisi State University, Tbilisi, Georgia*

POS 7 Use of Waterbolus to Adjust Heating Patterns from Microwave Waveguide Applicators

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

POS 8 A motion phantom for ex vivo experiments of MRgFUS in moving organs

Caroline v. Dresky[1], Florian Hagen[3], Richard Rascher-Friesenhausen[3], Daniel Demedts[1], Joachim Georgii[1], Christian Schumann[1], Tobias Preusser[1,2]
[1]*Fraunhofer MEVIS, Bremen, Germany,* [2]*Jacobs University, Bremen, Germany,* [3]*Hochschule Bremerhaven, Bremerhaven, Germany*

POS 9 The impact of the water bolus temperature during locoregional hyperthermia

Petra Kok, Akke Bakker, Lukas Stalpers, Arjan Bel, Hans Crezee
Academic Medical Center, department of Radiation Oncology, Amsterdam, The Netherlands

POS 10 Effects of hyperglycemia on lonidamine-induced acidification and deenergization of human melanoma xenografts

Kavindra Nath[1], David Nelson[1], Rong Zhou[1], Ronald Coss[2], Jerry Glickson[1], Dennis Leeper[2]
[1]*University of Pennsylvania, Philadlphia, PA, USA,* [2]*Thomas Jefferson University, Philadelphia, PA, USA*

POS 11 Photoacoustic Ultrasound-Guided Real-Time Imaging of Thermochemical Ablation in Ex Vivo Porcine Liver

Lindsey Shea[1,3], Katherine Dextraze[4,2], Trevor Mitcham[4,2], Joshua Gray[4,2], Richard Bouchard[4,2], Erik Cressman[2]
[1]*University of Illinois College of Medicine at Chicago, Urbana, IL, USA,* [2]*University of Texas MD Anderson Cancer Center, Houston, TX, USA,* [3]*SIR Foundation Summer Medical Student Research Internship Program, Fairfax, VA, USA,* [4]*University of Texas at Houston Department of Imaging Physics, Houston, TX, USA*

POS 12 Use of E-field measurements in the Sigma-60 water bolus for antenna feed point correction

Gerard van Rhoon, Daniel de Jong, Maarten Paulides
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

POS 13 Accurate Modelling of Laser Induced Thermal Therapy in Presence of Heterogeneous Tissue

Reza Madankan[1], Samuel Fahrenholtz[1], John Hazle[1], Jason Stafford[1], Anil Shetty[2], David Fuentes[1]
[1]*University of Texas MD Anderson Cancer Center, Houston, USA,* [2]*Medtronic Inc., Houston, USA*

POS 14 THERMAL-STABLE IMMUNOGLOBULIN G ANTIBODY EPITOPES IN BIOFLUIDS OF PATIENTS WITH MULTIPLE SCLEROSIS

Michael Graner, Xiaoli Yu
University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA

POS 15 A new method for triggered release of hydrophobic drugs from heat-sensitive imageable liposome

Aaron Deese, Kaustuv Sahoo, Danny Maples, Ashish Ranjan
Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, Oklahoma, USA

POS 16 Evaluation of Deep Heating Characteristics of 13.56 MHz Radio-frequency Hyperthermia Device in Phantom Models

M. Tamim Hossain, Bibin Prasad, Ki Sun Park, Hee Joon Lee, Jung Kyung Kim
Kookmin University, Seoul, Republic of Korea

POS 17 Study on the heating characteristics of Oncothermia heating devices

Wonwoo Kim[1], Mi-Sook Kim[1,2], Jae-Hoon Jeong[1]
[1]Research Center for Radiotherapy, Korea Institute of Radiological and Medical Sciences, SEOUL, Republic of Korea, [2]Department of Radiation Oncology, Korea Cancer Center Hospital, SEOUL, Republic of Korea

POS 18 Triple-Negative Breast Cancer Stem Cells (TNBC-CSC) Exhibits an Aggressive Phenotype: Role of HSPA1A-Containing Exosomes

Punit Kaur[1], Alexzander Asea[2,3]
[1]Department of Microbiology, Biochemistry & Immunology, Morehouse School of Medicine, Atlanta, GA, USA, [2]Deanship for Scientific Research, University of Dammam, Dammam, Saudi Arabia, [3]Section of Translational Medicine, Department of Cutting-Edge Medicine and Neuroscience, The Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

POS 19 Approaches for improved spatial control of microwave ablation with interstitial applicators

Punit Prakash, Sergio Curto, Brogan McWilliams
Kansas State University, Manhattan, KS, USA

POS 20 Retrospective analysis of nerve sparing technique used in cyrotherapy ofthe prostate

Gary Kalser
Florida Hospital Cancer Institute, Orlando, FL, USA

Friday, April 17

Registration

7:00am - 12:00pm **Great Hall Assembly - Convention Level**

Registered attendees can check-in and pickup name badges and welcome packets. Walk-up registrations can be processed on-site and speakers can upload PowerPoint presentations to laptops to be used during oral presentations.

Breakfast

7:00am - 8:30am **Events Center - Convention Level**

Breakfast with Exhibits & Posters in Events Center. This room is open all day. Your name badge is your admission to breakfast.

Refresher on Thermal Modeling

7:45am - 8:30am **Great Hall East/West**

John Pearce, PhD, of the University of Texas at Austin.

FRI 1 Refresher Course: "Biological Heat Transfer Modeling Including Perfusion, Hyperthermia, and Ablation"
John Pearce
The University of Texas at Austin, Austin, TX, USA

Refresher on HSPs and Exosomes

7:45am - 8:30am **Events Center ABC**

Michael Graner, PhD, of the University of Colorado Denver Anschutz Medical Campus.

FRI 2 A HOT MESS: STRESS, HEAT SHOCK PROTEINS, AND EXTRACELLULAR VESICLES
Michael Graner
University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA

Keynote Address: Polymeric Micelles – A Transformative Technology at the Clinical Stage

8:45am - 9:45am **Great Hall East/West** **Chair: Nicole Levi-Polychenko**

Alexander Kabanov, PhD, Dr.Sc., of the University of North Carolina at Chapel Hill.

FRI 3 Polymeric Micelles – A Transformative Technology at the Clinical Stage
Alexander Kabanov

, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Coffee Break with Exhibitors

9:45am - 10:15am Events Center - Convention Level

Symposium: Thermosensitive Drug Delivery

10:15am - 12:00pm Great Hall East/West Chair: Pavel Yarmolenko

FRI 4 Echogenic thermosensitive liposomes for image-guided drug delivery and real-time nanothermometry

Danny Maples[1], Venkatesan Perumal[1], Kevin McLean[1], Ryan Newhardt[1], Ankur Kapoor[2], Bradford Wood[3], Ashish Ranjan[1]

[1]Oklahoma State University, Stillwater, OK, USA, [2]Siemens Corporation Corporate Technology, Princeton, NJ, USA, [3]National Institutes of Health, Bethesda, MD, USA

FRI 5 Preliminary clinical experience of magnetic resonance guided focused ultrasound surgery for bone metastasis in Taiwan.

Hsin-Lun Lee[1,3], Chia-Chun Kuo[2], Che-Yu Hsu[2], Fang-Chi Hsu[1], Jo-Ting Tsai[4], Jeng-Fong Chiou[1,2]

[1]The Ph.D. Program for Translational Medicine, College of Medical Science and Technology, Taipei Medical University and Academia Sinica, Taipei, Taiwan, [2]Department of Radiation Oncology, Taipei Medical University Hospital, Taipei, Taiwan, [3]Taipei Cancer Center, Taipei, Taiwan, [4]Department of Radiation Oncology, Shuang Ho Hospital, Taipei, Taiwan

FRI 6 TRANS-FUSIMO - Software support for clinical application of MRgFUS in the liver

Sabrina Haase[1], Mario Bezzi[2], Jürgen Jenne[9], Thomas Lango[3], Yoav Levy[4], Michael Müller[5], Giora Sat[6], Christine Tanner[7], Stephan Zangos[8], Matthias Günther[1], Andreas Melzer[10], Tobias Preusser[1]

[1]Fraunhofer MEVIS, Bremen, Germany, [2]Universita Degli Studi Di Roma La Sapienza, Rome, Italy, [3]Stiftelsen SINTEF, Trondheim, Norway, [4]InSightec Ltd, Tirat Carmel, Israel, [5]IBSmm Engineering spol s.r.o., Brno, Czech Republic, [6]GE Medical Systems Israel, Tirat Carmel, Israel, [7]Eidgenoessische Technische Hochschule (ETH), Zurich, Switzerland, [8]Johann Wolfgang Goethe University, Frankfurt, Germany, [9]Mediri GmbH, Heidelberg, Germany, [10]University of Dundee, Dundee, UK

FRI 7 In-vitro evaluation of thermal dose accuracy for high intensity focused ultrasound hyperthermia therapy: MRgFUS experience.

Fang-Chi Hsu[1,2], Hsin-Lun Lee[1,3], Tung-Ho Chen[2], Jing-Fu Wu[2], Yang-Bin Lin[2], Shiu-Chen Jeng[2], Jeng-Fong Chiou[2]

[1]The Ph.D. Program for Translational Medicine, College of Medical Science and Technology, Taipei Medical University and Academia Sinica, Taipei, Taiwan, [2]Department of Radiation Oncology, Taipei Medical University, Taipei, Taiwan,

[3]Taipei Cancer Center, Taipei, Taiwan

FRI 8 MR-HIFU hyperthermia for drug delivery: translation to a clinical platform for pediatric applications

Robert Staruch[2,1], Chenchen Bing[1], Michelle Ladouceur-Wodzak[1], Joris Nofiele[1], Cecil Futch[1], Theodore Laetsch[3], Rajiv Chopra[1]
[1]UT Southwestern Medical Center, Dallas, Texas, USA, [2]Philips Research, Briarcliff, New York, USA, [3]Children's Medical Center, Dallas, Texas, USA

FRI 9 MR-HIFU mild hyperthermia as an adjuvant to radiotherapy and chemotherapy for recurrent rectal cancer: preliminary validation studies and clinical trial design

William Chu[1], Samuel Pichardo[2,6], Robert Staruch[5], Max Köhler[4], Matti Tillander[4], Yuexi Huang[3], Mika Ylihautala[4], Gregory Czarnota[1,3], Kullervo Hynynen[3]
[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Thunder Bay Regional Research Institute, Thunder Bay, ON, Canada, [3]Sunnybrook Research Institute, Toronto, ON, Canada, [4]Philips Medical Systems, Vantaa, Finland, [5]Philips Research, Briaircliff Manor, NY, USA, [6]Lakehead University, Thunder Bay, ON, Canada

Symposium: Thermal Medicine Biological & Chemical

10:15am - 12:00pm Events Center ABC **Chair: Elizabeth Repasky & Bonnie Hylander**

FRI 10 Engineered Prussian blue nanoparticles for photothermal therapy of tumors

Rohan Fernandes[1,2]
[1]Children's National Health System, Washington, DC, USA, [2]George Washington University, Washington, DC, USA

FRI 11 Evaluation of Exotherms of the Polyamine Spermine Analog, Diethylenetriamine With Partial to Complete Neutralization by Acetic Acid

Travis Miles, Erik Cressman
Department of Interventional Radiology, MD Anderson Cancer Center, Houston, Texas, USA

FRI 12 Investigating Thresholds and Mechanisms of Injury in Multiple Cell Types after Cryo, Heat and Electroporation Focal Therapies.

Jeunghwan Choi[1,2], Chunlan Jiang[2], Paul Westhoff[2], Dushyant Mehra[2], John Bischof[2]
[1]East Carolina University, Greenville NC, USA, [2]University of Minnesota, Minneapolis MN, USA

FRI 13 The effect of heat treatment in Sarcoma 180 cells: Comparison between in vitro and in vivo studies

Elisângela Silveira-Lacerda, Wanessa Carvalho, Francyelli Mello, Sônia Santos, Harley Rodrigues, Gustavo Capistrano, Andris Bakuzis
Universidade Federal de Goias, Goiânia, Goiás/Centro-Oeste, Brazil

FRI 14 Bacterial Lipopolysaccharide (LPS) Augments Expression and Extracellular Release of HSP70 in cells exposed to Febrile Range Hyperthermia (FRH)
Mohan E Tulapurkar[1], Jeffrey D Hasday[1,2], Ishwar S Singh[1,2]
[1]University of Maryland, Baltimore, MD, USA, [2]VA Medical Center, Baltimore, MD, USA

FRI 15 Synergistic cytotoxic effects of combined thermal and osmotic stress are consistent across multiple cell lines.
Erik Cressman, Nina Muñoz
MD Anderson Cancer Center, Houston, TX, USA

FRI 16 Tumor specific drug uptake prediction for temperature sensitive liposomes
Dieter Haemmerich[1], Timo ten Hagen[2]
[1]Medical Univ. of SC, Charleston, SC, USA, [2]Erasmus Medical Ctr, Rotterdam, Netherlands, The Netherlands

FRI 17 Hyperthermia mediated change in biofilm matrix microenvironment in combination with antimicrobial loaded Thermally Sensitive liposomes improves bactericidal activity
Michele Harbeson, Rachel Wardlow, Danny Maples, Jerry Malayer, Ashish Ranjan
Oklahoma State University, Stillwater, Oklahoma, USA

FRI 18 Body Warming to Alter [thermo]Regulation and the Microenvironment [B-WARM] Therapy: A Pilot Study
Gal Shafirstein, Timothy Winslow, Laurie Rich, Mukund Seshadri, Arindam Sen, Elizabeth Repasky, Anurag Singh
Roswell Park Cancer Institute, Buffalo, NY, USA

STM Business Meeting Luncheon

12:00pm - 1:30pm Great Hall East/West

George M. Hahn Award

1:30pm - 2:00pm Great Hall East/West Chair: Zeljko Vujaskovic

STM Presents the George M. Hahn award to Paul Stauffer, PhD, of Thomas Jefferson University, Philadelphia, PA

Plenary Session: Sensitization

2:00pm - 3:30pm Great Hall East/West Chair: Jennifer Yu & Nicole Levi-Polychenko

FRI 19 Magic Bubbles: Sensitizing Nanoparticles for Targeted Enhancement of Tumor Thermal Ablation and Radiotherapy
Agata Exner

Case Western Reserve University, Cleveland, OH, USA

FRI 20 Biodegradable plasmonic nanoparticles for cancer imaging and therapy

Robert Stover[1], Pratixa Joshi[1], Soon Joon Yoon[1], Avinash Murthy[1], Stanislav Emelianov[1,2], Keith Johnston[1], Konstantin Sokolov[1,2]
[1]The University of Texas at Austin, Austin, TX, USA, [2]The UT M.D. Anderson Cancer Center, Houston, TX, USA

FRI 21 Localized hyperthermia in rodent models for targeted delivery of antibiotic agents

Rajiv Chopra[2], Chenchen Bing[2], Joris Nofiele[2], Michelle Ladouceur-Wodzak[2], Robert Staruch[3,2], Michele Harbeson[1], Cassandra Mclain[1], Danny Maples[1], Jerry Malayer[1], Ashish Ranjan[1]
[1]Oklahoma State University, Stillwater, Oklahoma, USA, [2]UT Southwestern Medical Center, Dallas, Texas, USA, [3]Philips Research, Briarcliff, New York, USA

FRI 22 Theranostic Polymer Nanoparticles for Photothermal Ablation and Fluorescent Imaging of the Breast Cancer *In Vitro* and *In Vivo*

Elizabeth Graham[1,2], Nicole Levi-Polyachenko[1]
[1]Wake Forest University, Winston-Salem, NC, USA, [2]VT-WFU School of Biomedical Engineering and Sciences, Winston-Salem, NC, USA

Coffee Break

3:30pm - 4:00pm **Great Hall Assembly**

New Investigator Symposium

4:00pm - 5:30pm **Great Hall East/West** **Chair: Jason Stafford**

12 New Investigator Travel Award Winners present their Abstracts.

FRI 23 Thermophysical fluid modelling for loco-regional hyperthermia treatment of Non-Muscle Invasive Bladder Cancer

Gerben Schooneveldt[1], Debby Geijsen[1], Fasco van Ommen[1], Akke Bakker[1], Petra Kok[1], Mattias Westendarp Zanartu[2], Jean de la Rosette[2], Maarten Hulshof[1], Theo de Reijke[2], Hans Crezee[1]
[1]Dept. of Radiotherapy, Academisch Medisch Centrum, Amsterdam, The Netherlands, [2]Dept. of Urology, Academisch Medisch Centrum, Amsterdam, The Netherlands

FRI 24 Simulation of magnetic nanoparticle hyperthermia in prostate tumor models

Sri Kamal Kandala[1], Anilchandra Attaluri[2], Jianan Wang[1], Michele Wabler[2], Michael Armour[2], Haoming Zhou[2], Christine Cornejo[2], Yonggang Zhang[2], Theodore DeWeese[2], Robert Ivkov[2], Cila Herman[1]
[1]Johns Hopkins University, Baltimore, Maryland, USA, [2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

FRI 25 Design and optimization of a conformal microwave antenna for a wearable breast hyperthermia applicator

Sergio Curto[1], Manoshika Ramasamy[1], Minyoung Suh[2], Punit Prakash[1]
[1]Kansas State University, Manhattan, KS, USA, [2]North Carolina State University, Raleigh, NC, USA

FRI 26 In vivo conductivity values of cervical cancer patients reconstructed with a 3T MR system

Edmond Balidemaj[1], Peter de Boer[1], Petra Kok[1], Rob Remis[2], Nico van den Berg[3], Henrike Westerveld[1], Aart Nederveen[1], Lukas Stalpers[1], Hans Crezee[1]
[1]Academic Medical Center, Amsterdam, The Netherlands, [2]TU Delft, Delft, The Netherlands, [3]UMC Utrecht, Utrecht, The Netherlands

FRI 27 Increasing Energy Density with Polyprotic Acids and Polyamines for Use in Thermochemical Ablation

Lindsey Shea[2,3], Erik Cressman[1,2]
[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]SIR Foundation Summer Medical Student Research Internship Program, Fairfax, VA, USA, [3]University of Illinois College of Medicine at Chicago, Urbana, IL, USA

FRI 28 Destressing laboratory mice reveals new relationships between heat production, anti-tumor immunity and β-adrenergic receptor signaling

Mark Bucsek, Kathleen Kokolus, Jason Eng, Bonnie Hylander, Elizabeth Repasky
Roswell Park Cancer Institute, Buffalo, NY, USA

FRI 29 Integrated micro-thermal sensor for planning and guidance of pulmonary vein ablation

Harishankar Natesan[1], Jeunghwan Choi[1,2], Wyatt Hodges[3], Sean Lubner[3], Chris Dames[3], John Bischof[1]
[1]University of Minnesota, Minneapolis, Minnesota, USA, [2]East Carolina University, Greenville, North Carolina, USA, [3]University of California, Berkeley, California, USA

FRI 30 A novel stealth idarubicin thermosensitive liposome for ultrafast triggered release using mild hyperthermia

Tao Lu, Wouter Lokerse, Ann Seynhaeve, Gerben Koning, Timo ten Hagen
Erasmus MEdical Centre, Rotterdam, The Netherlands

FRI 31 Photothermal Ablation of Streptococcus pyogenes using Fluorescent Bio-Polymeric Nanoparticles

Nicole Levi, Sean Reid, Christie Reid, Taylor Ibelli
Wake Forest Baptist Health Medical Center, Winston-Salem, North Carolina, USA

FRI 32 External thermal therapy with concurrent radiation therapy results in rapid and durable regression of multiply-recurrent, debilitating verrucous vulgaris: a case report.

Enid Choi, James Snider, Pradip Amin, Shifeng Chen, Zeljko Vujaskovic

University of Maryland, Baltimore, MD, USA

FRI 33 Fractionated nanoparticle hyperthermia and radiation improves tumor treatment efficacy

Alicia Petryk[1], Adwiteeya Misra[1], Courtney Mazur[1,2], P. Jack Hoopes[1]
[1]Dartmouth College, Hanover, NH, USA, [2]UC Berkeley, Berkeley, CA, USA

FRI 34 Photothermal cancer therapy guided by in vivo photoacoustic flow cytometry

Mustafa Sarimollaoglu, Mazen Juratli, Dmitry Nedosekin, Ekaterina Galanzha, Vladimir Zharov
Arkansas Nanomedicine Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA

New Investigator Award Dinner

6:30pm - 9:30pm

A dinner for the 2015 New Investigator Award winners. By invite only.

Abstracts for Wednesday, April 15th

WED 1

Cancer Immunology - Tumor Microenvironment

Alexzander Asea

Deanship for Scientific Research, University of Dammam, Dammam, Saudi Arabia

The tumor microenvironment is defined as the cellular environment in which the tumor exists, including surrounding blood vessels, immunocompetent cells, fibroblasts, other cells, signaling molecules, and the extracellular matrix. There is a unique and constant interaction between the tumor and the surrounding microenvironment which determines tumor cell survival as well as modulates the host anti-tumor immune responses. The tumor influences this microenvironment by releasing bioactive mediators, inducing angiogenesis and stimulating peripheral immune tolerance. On the other hand, immunocompetent cells take part in immunoediting, a dynamic process that encompasses immunosurveillance and tumor progression, and which ultimately determines the fate of the tumor. This refresher course integrates basic and clinical aspects of cancer immunology as it pertains to the tumor microenvironment and is designed to remind the participants of the importance of the tumor microenvironment in understanding and designing safe, effective and efficacious treatment protocols for the eradication of cancer. The refresher course is also designed to stimulate interest from a wide array of investigators and students in cancer immunology.

WED 2

Evolution of nanoparticle-induced photothermal therapy; gold standards and new frontiers

Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, NC, USA

Abstract: The aim of this refresher course is to provide an up-to-date overview of nanoparticles that absorb near infrared (NIR) light for use as photothermal therapy (PTT) agents. Selective targeting of heat-generating nanoparticles is advantageous for a number of disease, including treatment of cancer or bacterial and viral infections. In addition, many nanoparticles have the advantage of also serving as agents for imaging and detection of disease. Recent advances in the synthesis of highly anisotropic novel metal nanoparticles for PTT will be described. New metals, metal oxide complexes, and current progress in the development of carbon nanoparticles, including reduced graphene oxide will be discussed. This refresher course will culminate in the recent use of electrically conductive polymer nanoparticles for hyperthermia. Mild hyperthermia, including drug delivery, versus thermal ablation will also be discussed. The advantages and unique features of contemporary nanoparticles will be highlighted. The goal of this refresher is to describe the recent evolution of nanoparticles for NIR stimulated PTT, and highlight innovations and future directions. The main objectives of this refresher course are to:

1. Provide an overview of how certain materials, when confined within nanoscale dimension, can generate heat upon light stimulation.

2. Discuss the scope of nanoparticle types and subtypes along with key advantages and disadvantages.

3. Explore how nanoparticles may be translated into clinical hyperthermia treatments.

WED 3

Integrating Imaging Mass Spectrometry with Metabolomics

Richard Yost

University of Florida, Gainesville, FL, USA

Imaging tandem mass spectrometry offers unique opportunities to combine the remarkable sensitivity and chemical selectivity of MS/MS with spatial resolution, permitting metabolites to be localized, for instance, in normal and diseased tissue from the same organ and same subject. This lecture will explore the biomedical and biological applications of imaging mass spectrometry, including the synergy between imaging MS and metabolomics, with examples from a wide variety of biomedical and metabolomic applications.

WED 4

The Power of Full Spectrum Molecular Imaging: More than Just A Pretty Picture

Darwin Asa

Waters Corporation, Milford, MA, USA

Measuring the changes in distribution of molecules involved in cellular function and physiology or monitoring drug compounds administered as part of a therapeutic regime can provide a wealth of information regarding the health and well being of patients and the efficacy of a particular therapy. Obtaining direct, definitive information about the presence or distribution of a particular molecule in tissues without resorting to the use of a limited selection of expensive labeled molecular probes has always been challenging.

Recently, many researchers have explored the possibilities of exploiting the powerful analytical and label free detection capabilities of mass spectrometry (MS) to perform molecular imaging studies to measure the distribution of molecules in tissues for a number of applications important in a clinical setting. Using MS Imaging, label free, multiplex measurements of proteins, peptides, lipids, and other small molecules as well as therapeutic drugs and their metabolites can be performed. Some laboratories have also examined using MS Imaging to discriminate healthy tissues from diseased or damaged tissue in patient biopsies or to determine the physiological state of a particular tissue or organ.

In this presentation, a basic overview of the Full Spectrum Molecular Imaging technologies and the advantages of using a multi-modal MS imaging approach for tissue imaging relative to a single imaging modality will be discussed. Comparisons of images obtained from a Full Spectrum Molecular Imaging system for the analysis of a variety of tissue samples will be compared and contrasted. Applications of this imaging technique such as tissue discrimination and drug distribution will be included in the discussion.

WED 5

MALDI Imaging MS: Visualizing Biology and Chemistry in Drug Development

Stepehn Castellino, Reid Groseclose

GSK, RTP, NC, USA

Understanding the tissue distribution of a drug and its metabolites is an essential element in the development of safe and efficacious drugs. Historically, we have relied on the use of radio-labeling methods for characterizing drug tissue distributions. However, this approach suffers from the inability to differentiate between parent drug and metabolites. Consequently, the capability to correlate the engagement of drugs or their metabolites with biological targets responsible for a pharmacological response is limited with radiographic methods. Furthermore, this approach is blind to all changes of endogenous compounds resulting from disease progression or pharmacology. Matrix-assisted laser desorption/ionization (MALDI) Imaging Mass Spectrometry (IMS) is an emerging technique which can determine the spatial distribution of a drug and its metabolites in tissue samples without the need for labeling techniques. This methodology allows for the correlation of analyte tissue distributions with histology images, thereby integrating chemical structures with tissue morphology. This imaging modality offers the potential to enhance our mechanistic understanding of disease progression and pharmacology (including toxicology). Equally important, this new tool can serve as a common platform for engaging pathologist, clinicians, biologists and chemists in addressing a wide range of biological and chemical challenges.

This presentation will focus on our efforts to couple MALDI IMS and histology in drug development to gain mechanistic insights into drug correlated toxicities and efficacy. Case studies from late stage drug development where MALDI IMS was employed to investigate the mechanisms of adverse events and guide risk assessment will be presented. The impact of MALDI IMS investigations in the early stages of drug development, where outcomes can provide insights to absorption, PK/PD relationships as well as safety, will also be included.

WED 6

Optical imaging and spectroscopy techniques and application to functional evaluation of therapeutic response

Greg Palmer

Duke University Medical Center, Durham, NC, USA

Optical methods enable non-destructive, quantitative, longitudinal functional monitoring of tissue. Intravital imaging using window chamber models allows the wide range of available optical microscopy techniques to be applied to living tissues in otherwise inaccessible sites. The acquisition and analysis of three types of functional information will be discussed: 1) hemodynamic parameters, including oxygen saturation and blood flow, 2) oxygen sensing nanoparticles for assessment of tissue hypoxia, and 3) fluorescent and luminescent reporters for cell tracking and gene expression. These enable quantitative assessment of oxygen supply and consumption, including fluctuating hypoxia in tumors. The combination of these tools facilitates a more complete characterization of tumor physiology and molecular responses, and how these interplay to influence tumor response to therapy. Such techniques have been used in the past to study a diverse range of research questions that are relevant to thermal therapy, including thermally sensitive liposomal drug delivery, alterations in perfusion following hyperthermia, and the response of tissue oxygenation following thermal therapy. This talk will provide a brief overview of the application of optical sensing techniques to characterize tissue responses to thermal therapy, as well as recent new directions in functional sensing, including snapshot hyperspectral imaging for real time assessment of tissue oxygenation and vascular function. Finally, the use of transgenic reporter animals suitable for tracking immune cell infiltration and function will be presented.

WED 7

Mass Spectrometry Imaging: An Industry Perspective

Katherine Kellersberger, PhD, Soeren-Oliver Deininger, PhD

Bruker Daltonics, Inc, Billerica, MA, USA

Mass Spectrometry Imaging (MSI) is a technique that is successfully used to directly measure compounds such as drugs, metabolites, lipids, peptides and proteins in tissue without the need for fluorescent or radiolabels, providing unparalleled insight into complex biological mechanisms by combining identification with spatial localization. Since its inception more than a decade ago, MSI has evolved to become an indispensable tool to fields such as drug discovery, metabolomics, lipidomics, and cancer research.

The popularity and utility of MSI have driven the need for innovation from instrument manufacturers in terms of enhancements to both hardware and software that have helped to fuel the exponential growth of this technique. This has in turn resulted in rapid improvements in both hardware and software tools that have helped to drive the field forward and make MSI increasingly accessible to researchers.

This presentation will focus on three key innovations that have helped to elevate MSI into the forefront of advanced medical research: the integration of traditional histopathology and MSI through improvements to laser technology and software; the application of statistics, namely hierarchal clustering, for non-targeted tissue classification; and most recently the application of ultra-high resolution mass spectrometry and isotopic fine structure matching, which provides a new dimension to molecular identification.

WED 8

Nanoheating with natural protein-nanoclusters (membrane rafts)

Gabor Andocs[1], Takashi Kondo[1], Mati Ur Rehman[1], Edina Papp[2], Tamas Vancsik[3], Oliver Szasz[4]

[1]Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Science, University of Toyama, Toyama, Japan, [2]Faculty of Information Technology and Bionics, Pazmany P. Catholic University, Budapest, Hungary, [3]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary, [4]Department of Biotechnics, St. Istvan University, Godollo, Hungary

Background

Heating by nanoparticles is a well-recognized method in hyperthermic oncology. However, the process could have numerous complications by the administration of the particles, their targeting and sometimes their post-treatment processes. Our aim is to present a possibility of selective nanoscopic heating without administration of artificial nanoparticles.

Method

The technology (called modulated electro-hyperthermia, mEHT) is impedance controlled capacitive coupling. It is impedance matched; the plane-wave radiation does not dominate the energy-transfer. The nano-selection is based on the certain deviations of the metabolic-processes of the cellular-connections and of the organizing-pattern of malignant cells from their healthy hosts. This difference is used for fine-tuned selection by electrodynamic conditions. The cell-killing mechanism is connected to the intensive but very local nano-range energy absorption which is selectively delivered. Various in-vitro measurements were performed on suspension and adherent cultures evaluated by flow-cytometry, by Buerker-cell cell-count and by microscopic observations of Ca-influx dynamics assuming the role of the TRPV cellular temperature sensor in the membrane rafts.

Results

In the first step we showed in-silico the selective and extremely large energy-absorption by membrane rafts. The thermal effects were measured by the well-known Arrhenius-plot, and conventional hyperthermia was used as reference. All kinds of measurements show definitely 3+ºC advantage of mEHT calibrated on conventional heating (cHT). This change presumed as effect of the cellular membrane which is the front-player of the electromagnetic interactions and regarded as a phenomenon which was shown in-silico models. The measured temperature shift of the effects of cell-destruction well correlates with the Ca-influx differences regarded as partial effect of the TRPV-receptors and other transmembrane proteins in the cluster of the rafts.

Conclusion

Certain cellular destruction and Ca-influx increase is reached by mEHT at least at 3ºC less than by cHT. We assume, that this difference is the consequence of the selective heating of the clusters of the transmembrane proteins, which is in fact a non-artificial nanoparticle heating.

WED 9

Temporal and spatial resolution of fiber-optic, copper-constantan and manganin-constantan thermocouple probes

Akke Bakker, Gerben Schooneveldt, Willemijn Kolff, Petra Kok, Jan Sijbrands, Geertjan van Tienhoven, Coen Rasch, Erik Schwing, Gerard van Stam, Hans Crezee

AMC, Amsterdam, The Netherlands

Introduction/Background

Accurate and real-time thermometry is essential in hyperthermia. Presently, fiber-optic probes and copper-constantan thermocouple probes (TCP) are most frequently used. Manganin-constantan TCP might be a good alternative to copper-constantan TCP as thermal conductive errors are expected to be smaller, but are presently not clinically used. We compared the temporal and spatial resolution of single sensor fiber-optic probes, multi-sensor copper-constantan TCP and multi-sensor manganin-constantan TCP to determine their clinical performance during hyperthermia treatments.

Methods

Experiments were performed using a 35°C and a 45°C waterbath separated by a thin plastic sheet (1.5 mm). 14 point TCP with a spacing of 5 mm (14/5) were compared to 7 point TCP with 10 mm spacing (7/10) (Ella CS) and to single sensor fiber-optic probes (Fiber Optic Sensor True, IPITEK). Temperatures were recorded using an in-house developed LabView program with 1 Hz sample frequency. The temporal resolution was measured by pulling the probes rapidly from the 35°C to the 45°C waterbath and vice versa. The spatial resolution (SR) was determined by slowly pulling the probes stepwise (1 mm) from the 35°C to the 45°C waterbath and vice versa. The SR is presented as the width of the 10%-90% temperature transition interval. Finally, the effect of the absence or presence of a polyurethane catheter was investigated. Each experiment was repeated at least three times.

Results

Manganin-constantan TCP showed the fastest response time, the temporal resolution was <1s for all TCP and ~30s for fiber-optic probes. The average SR without catheter was 3.4 mm for fiber-optic probes, 5.6 and 10.4 mm for 7/10 and 14/5 copper-constantan TCP, respectively, 2.9 and 4.1 mm for 7/10 and 14/5 manganin-constantan TCP, respectively. The presence of a catheter had no influence on the SR of fiber-optic probes, but increased the SR with an average of 3.5 and 0.8 mm for copper-constantan and manganin-constantan TCP ($p<0.003$), respectively. The sensor at the tip of a multi-sensor TCP has a finer SR than the proximal sensor, the difference ranging from 1.0 mm up to 7.9 mm for the 7/10 manganin-constantan and 14/5 copper-constantan TCP, respectively.

Discussion/Conclusion

Multi-sensor manganin-constantan TCP probes show a comparable SR to single-sensor fiber-optic probes, however the response time of fiber-optic probes is much slower. Therefore, we recommend to use 7 point 10 mm spacing manganin-constantan thermocouple probes for clinical use, especially in areas where large and rapid changing temperature gradients are to be expected, for example in scar tissue.

WED 10

First impressions on the performance of the new BSD2000-3D GE450W hybrid deep hyperthermia system

Gerard van Rhoon, Ali Ameziane, Daniel de Jong, Maarten Paulides, Martine Franckena

Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Introduction: End 2014, the hybrid loco-regional hyperthermia system BSD2000-3D with a GE450 wide bore MR has been installed in our department. The hybrid consists of a specially designed GE-MR-compatible S-Eye applicator integrated in the GE patient table. In this study we report the results of the first quality assurance measurements.

Material and methods: The Schottky Diode Sheet (SDS) system has been applied to measure the E-field distribution at the central plane, both in horizontal as in vertical direction. The SDS consists of 64 diodes mounted on a flexible 125 m thick polyester foil with a spatial resolution of 25 by 25 mm2. The DC-voltages of the diodes are read through high resistive wires. The phantom is a PVC tube, diameter 26 cm, filled with saline water (2g/l) and placed symmetrically in the applicator. The SAR distribution is expressed as squared voltage [V2]. Measurements are performed with the phantom outside and inside the MR-bore. Various phase settings have been applied to investigate the full 3D SAR steering features of the new applicator in the MR environment.

Results: After some additional tuning of the RF-matching network to decrease interference of the Sigma-Eye with the MR-imaging, the system performed according expectations. The SAR distributions measured for synchronic settings (i.e. zero phase difference and equal amplitude) have a normal Gaussian distribution. The area enclosed by the 50% iso-SAR contour measures in the horizontal plane 198 and 237 cm2, outside and inside the MRI respectively and for the vertical plane 226 and 215 cm2. No distinct difference was noted between the relative SAR distribution inside or outside the MR when comparing SAR distributions measured for all phase and amplitude settings . A small decrease, 10-15% in the measured squared voltage was noted when the phantom was moved from outside to inside the MR-bore. Also a small offset between the center of the SAR distribution with the phantom center was noted.

Discussion: The first SAR distributions obtained with the GE MR-compatible Sigma-Eye applicator are in line with historical values as measured using SDS for other Sigma-Eye antenna's, both MR- and non-MR compatible. Additional measurements are anticipated to compare the effective field size measured with the SDS with that measured by temperature increase using MR-thermometry.

Supported by the Dutch Cancer Foundation (KWF), EMCR 2009-4448, DDHK 2013-6072.

WED 11

A Magnetic field guiding and focusing system for pancreatic cancer treatment via MNP hyperthermia

Fridon Shubitidze, Robert Stigliano, Katsiaryna Kekalo, Ian Baker

Thayer School of Engineering at Dartmouth, Hanover, USA

Cancer is the second leading cause of death in the United States (after heart disease), and pancreatic ductal adenocarcinoma is the fourth most common cause of cancer related fatalities in the developed countries. Studies have shown that most pancreatic cancer cases occur in the 65-75 year age group and untreated metastatic pancreatic malignant stages minimizes chemo and radiation therapies curable effects. For example, in the year 2000, there were 217,000 new cases of pancreatic cancer with 213,000 deaths worldwide. Recently, magnetic nanoparticle (MNP) hyperthermia opened new possibilities for cancer treatment. A key characteristic of MNPs used for clinical hyperthermia is a high specific absorption rate (SAR), which depends on the applied magnetic field frequency and strength. The coil produces an alternating magnetic field (AMF), which penetrates inside tissue and activates MNPs in cancerous tissues. The AMF from a coil decays rapidly (as $1/R^2$); therefore, to use magnetic hyperthermia for deep tumors, such as pancreatic cancers, a high-magnitude transmitter current is required in the coil. High transmitter currents also produce eddy currents within normal tissue that cause undesirable, non-specific heating, which limits the applicability of MNP hyperthermia for pancreatic cancers. To overcome this problem, this paper investigates the applicability of a flexible ferromagnetic system for guiding and delivering transmitted magnetic fields to deep tumors, ultimately providing viable field therapies in pancreatic cancer cells. Namely, differently sized and shaped magnetic materials are modeled and investigated to determine the best locations for a flexible ferromagnetic system, relative to the AMF coil and tumor, to deliver the highest possible magnetic field to the MNPs in the tumor. The system's AMF delivery and focusing performance is modeled and measured. The numerical calculations are done using a 3D forward model based on the Method of Auxiliary Sources (MAS), a semi-analytic numerical model developed at Dartmouth College to solve various electromagnetic problems including those related to determining MNP heating mechanisms. Measured and computational results are illustrated for magnetic field at various distances from the coil. In the work presented, it is also shown that the recently developed Dartmouth MNP, with high specific absorption rate at low field, can be activated at a distance of 40 cm or more from the AMF coil and achieve clinically relevant temperatures when the flexible magnetic system is used.

WED 12

Methods for accurate simulations of microwave ablation

Mark Hagmann[1], Kent Moore[1], Garron Deshazer[2]

[1]BSD Medical Corporation, Salt lake City, Utah, USA, [2]University of Rhode Island, Kingston, Rhode Island, USA

Background: Methods for the accurate simulation of microwave ablation are being developed with the long-term objective of predicting and optimizing patient treatment.

Methods:

Determine consistent electrical and thermal properties for the tissue and the antenna because simulations with the properties at only 37ºC predict extremely high temperatures. Ji and Brace [1] corrected only the electrical properties of liver for water loss, giving more reasonable temperatures, but requiring that $\varepsilon_{r1} = 1$ and $\sigma = 0$ (vacuum) above 120ºC.

Compare “bench” and “live” simulations with the corresponding measurements.

Use multiple meshing to test for local and global convergence.

Use sensitivity studies to determine the relative significance of the parameters.

Use analytical approximations to verify and understand the results.

Extend the formalism for the near-field to lossy media to understand the results.

Multiphysics finite element software was used with axisymmetric models.

Results:

New simulations predict diameters and lengths of ablation that are within 6 and 10 percent, respectively, of our bench measurements.

The considerable effect of water loss on the specific heat of liver is introduced. The ablation debris causes a sharp rise in the thermal conductivity to increase the ablation size and limit the maximum temperature to 300ºC--consistent with our bench testing. Both water loss and the debris affect the electrical conductivity and permittivity of liver.

The treatment affects bloodflow by dilation, followed by the collapse of the vessels. Measurements of bloodflow shutdown fit the Arrhenius model for tissue damage.

The size of an ablation is more sensitive to the thermal and electrical conductivity of the liver than the other 6 parameters tested. However, a ±50% change in the frequency has no significant effect on an ablation.

Convergence is shown by comparing 9 different meshes. Surprisingly, the computer time is proportional to the number of elements N (instead of N-cubed) because the tissue properties must be updated at each time step.

Simple quasistatic approximations for the electromagnetic field are accurate close to the surface of the antenna.

Conclusions:

Accurate and computationally-efficient expressions were developed to calculate the electrical and thermal properties of liver and components of the antenna.

The rate of ablation growth by heat transfer exceeds that caused by direct microwave heating after the first 10 minutes of a simulated treatment.

Ablation in homogeneous tissue at 915 MHz is similar to that at 2.45 GHz.

[1] Ji, Z. and Brace C.L, Phys. Med. Biol. 2011;56(8):5249-5264.

WED 13

Results of cross validation from a trained model for laser induced thermal therapy

Samuel Fahrenholtz[1,2], John Hazle[1,2], Anil Shetty[3], R. Jason Stafford[1,2], David Fuentes[1,2]

[1]UT MD Anderson Cancer Center, Houston, TX, USA, [2]UT Houston Graduate School of Biomedical Sciences, Houston, TX, USA, [3]Medtronic, Inc., Houston, TX, USA

Introduction: MR-guided laser induced thermal therapy (MRgLITT) has therapeutic applications in the brain, among other sites. A primary advantage of MRgLITT is real-time monitoring. However in especially precise interventions like neurosurgery, accurate planning would behoove the procedure. Most attempts to model the procedure are rendered inaccurate due to unreliable parameter data. In this abstract, a physics-based inverse problem provided the parameter data from retrospective patients' MR temperature imaging data. In the same cohort, leave-one-out cross validation estimated the predictive accuracy of the trained model.

Methods: The training consisted of three parts: 22 MR temperature datasets, a relatively simple steady state Pennes bioheat model, and a gradient-based optimization algorithm that minimized the root mean square difference between model and observation. The optimized parameter was the effective optical attenuation, μ_{eff}—the most sensitive model parameter. The optimization creates a library of 22 optimal μ_{eff} values that can be used in prediction. The predictive accuracy of the model was estimated by using leave-one-out cross validation (LOOCV). LOOCV begins by dropping an optimal μ_{eff} from the list and makes a model prediction given the average from the remaining 21 μ_{eff} values. This procedure is permuted so that every dataset is predicted using the other μ_{eff} values. Finally, Dice similarity coefficients comparing the regions exceeding 57 ^{o}C were calculated for each LOOCV prediction to characterize the predictive performance.

Results: To three significant figures, the distribution of Dice results during LOOCV can be summarized thusly: mean, 0.643; median, 0.677; standard deviation, 0.129; minimum, 0.342; maximum, 0.848.

Conclusion: The presented train-and-predict methodology represents a general method of approaching the modeling problem. Naturally, performance can be enhanced given more data or a more sophisticated/accurate model as they become available.

WED 14

Irreversible electroporation: thermal or non-thermal, that is the question

Hans Crezee, Jantien Vogel, Gerben Schooneveldt, Akke Bakker, Petra Kok, Marc Besselink

Academic Medical Center, Amsterdam, The Netherlands

Purpose/Objective

The prognosis for patients with pancreatic cancer is dismal, most patients present with unresectable disease. These unresectable patients are now treated with palliative chemotherapy, radiotherapy or both, but with only marginal effects. For patients with locally advanced pancreatic cancer (LAPC) without metastases, local thermal ablation is used where tumors are destroyed by heat, potentially damaging surrounding structures. Secondly, cooling by blood flow may prevent effective temperatures in tumor tissue in proximity of blood vessels.

Irreversible electroporation (IRE) is a technique causing permeabilization of the cell membrane through electrical pulses, thereby destroying the tumor. IRE is thought to cause less morbidity than thermal ablative strategies. We investigated the presence of thermal effects for IRE.

Materials and Methods

A pilot-study was performed in healthy pigs with permission of the local ethical committee, where pancreas tissue was electroporated and temperatures were measured. Two to three IRE electrodes were placed in porcine pancreas in the same positions used in human clinical treatment. Four fiber optic temperature probes were placed along a line starting at the center of the ablation zone extending outward. In addition the surface temperature was measured using an infrared thermal camera. Standard IRE protocols were then performed. Simulations were performed using hyperthermia treatment planning.

Results

Electroporation was applied in the pancreas of four pigs. The IRE applications resulted in a minimum temperature rise of 1-2°C and a maximum temperature rise of 30°C in the pancreas. The temperature rise did not occur immediately and was not evenly distributed throughout the target zone. These observations were confirmed by the simulations.

Conclusions

Thermal effects are frequently present during electroporation. More research is needed to demonstrate what role thermal and non-thermal effects play in the clinical effectiveness of IRE.

WED 15

Magnetic Resonance Based Quantification of Nanoparticle Distribution and Heating in Nanoparticle Mediated Laser Interstitial Thermal Therapy (npLITT)

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Introduction: Nanoparticle Mediated Laser Interstitial Thermal Therapy (npLITT) is a technique that utilizes tumor localized optically activated nanoparticles to increase the conformality of laser ablation procedures. Temperatures in these procedures are dependent on the particle concentration which generally cannot be measured noninvasively prior to therapy. In this work we attempt to quantify particle concentration *in vivo* by estimating the increase in R2* relaxation induced by bifunctional magnetic resonance (MR)-visible gold-based nanoparticles (SPIO@Au) and relate it to the temperature increase observed during real time MR temperature imaging of laser ablation.

Methods: SPIO@Au nanoparticles (90nm) were synthesized containing a silica-iron core (for MR visibility via R2*) and gold shell (for laser induced heating via NIR absorption). Four different concentrations (saline,$1x10^{10}$, $5x10^{10}$, and $10x10^{10}$ particles/mL) were intratumorally injected into mice bearing HN5 tumor xenografts approximately 30 minutes prior to imaging. High resolution R2* maps were acquired using a 3D multi echo gradient recalled echo MR imaging sequence. An interstitial laser fiber was placed between the tumor and thigh muscle and treated at 1W for 3 minutes at 808nm. Dynamic temperature imaging was acquired using a 2D fast multi echo gradient recalled echo sequence to measure the change in the temperature dependent proton resonance frequency.

Results: The maximum temperature within the tumors increased linearly with concentration of injected particles, reaching 34.0, 37.6, 45.8, and 55.4 ^{o}C for saline,$1x10^{10}$,$5x10^{10}$ and $10x10^{10}$ particles/mL injections, respectively (R^2=.994). The highest temperatures occur at the injection site instead of the fiber or the intervening tissue, confirming that SPIO@Au nanoparticles are the primary absorber and heating source at 808nm. The differences between the median R2* measured at the injection site and the rest of the tumor were -6, 134, 111, 156 s^{-1} for the saline,$1x10^{10}$,$5x10^{10}$ and $10x10^{10}$ particles/mL injections, respectively. This R2* change is consistent with measurements made in phantom for the $1x10^{10}$ particles/mL injection. We do not observe further increases in R2* for the $5x10^{10}$ and $10x10^{10}$ particles/mL injections because accurate measurement of the expected relaxation rates requires significantly shorter echo times than can be achieved using our 3D gradient echo pulse sequence. Future experiments will focus on lower particle concentrations and include high resolution spin echo R2 mapping to better quantify the particle concentration in tumor.

Conclusion: Bifunctional SPIO@Au nanoparticles are a promising technology for providing noninvasive estimates of particle concentration via MRI and temperature increases in npLITT procedures.

WED 16

INTEGRATION OF DEEP HYPERTHERMIA WITH MR IMAGING

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Introduction- Designing a hyperthermia system that is integrated with MRI to obtain non-invasive thermometry during hyperthermia treatment involves many design constraints.

Method- The physical size and shape of the hyperthermia system must allow both the hyperthermia applicator and patient to fit inside the MR imagine opening. The equipment inserted into the MR aperture must not be magnetic materials. The equipment in the MR aperture must not create image artifacts that would distort the image quality. The hyperthermia equipment must not degrade MR receive signal to noise ratio. The receive MR coil can be integrated with of separate from the applicator. The MR should output the phase image as the proton frequency shift is temperature dependent. A suitable patient support system is needed to support the applicator and patient in the MR bore during treatments. Suitable filtering must be incorporated in the output of the hyperthermia system to reduce RF noise and signals at the MR frequency. Filtering must be added to the MR receive path to prevent the RF output power of the hyperthermia applicator from saturating or damaging the MR sensitive receiver. The magnetic field of MR systems drifts with time and may not be uniform requiring a means to detect differences in the magnetic field to enable a compensation method such as silicone gel which has a signal level that does not change with temperature but does change with magnetic field. The hyperthermia system must not emit other spurious signals that may interfere with the MR imaging process.

Results- The integration process has been successfully followed to integrate with 7 deep phased array systems. The first was at Munich with a 0.2T Siemens open Magnetom system. Four others followed that were integrated with the Siemens 1.5T Symphony system. A research configuration was completed at Duke University with a 1.5T GE MR system (60dm diameter aperture). The most recent was in Rotterdam with a GE 450W 1.5T 450W MR system. This enables the initial phase images to be subtracted from images during treatment to produce a temperature difference image. It has been discovered that resonance of the cables and the hyperthermia dipoles can also cause shadowing of the imaging if there is a resonance of the cables at the MR operating frequency.

Conclusion- Following these steps, successful integration of hyperthermia systems with MR for non-invasive thermometry during hyperthermia have been achieved.

WED 17

Polymer Dynamic Organic Theranostic Spheres (PolyDOTS) for Detection and Photothermal Ablation of Breast Cancer

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This report describes the development of donor-acceptor polymers into aqueously stable spherical nanoparticles that have the capacity to act as unique theranostic agents. We term these particles, PolyDOTS, for polymer Dynamic Organic Theranostic Spheres. In this application, PolyDOTS were created using the donor-acceptor conjugated polymer, polycyclopentadithiophene benzoselenadiazole (PCPDTBSe), which has tunable optical properties correlating to the molecular weight of the polymer. Various molecular weight fractions were combined at specific ratios to develop a hybrid nanoparticle capable of both fluorescence imaging and heat generation upon exposure to light. PolyDOTS have an approximate hydrodynamic diameter of 90nm and stable fluorescence following multiple heating/ cooling cycles, as well as minimal changes in the optical properties after a 30day exposure to ambient light. The unique fluorescence from PolyDOTS was used to observed and quantified within breast cancer cells. PolyDOTS were also observed to be excellent photoacoustic contrast agents in tissue phantoms. Upon exposure to 800nm light, PolyDOTS generated a 42 degrees Celsius temperature increase above ambient temperature. PolyDOTS were evaluated as effective photothermal agents against breast epithelial cells. Minimal cytotoxic response was observed in the absence of infrared light. In the presence of 800nm light, PolyDOTS incubated with MDA MB 231 breast cancer and MCF10A non-tumorigenic cells generate significant heating, resulting in a 90% decrease in cell viability at concentrations of 50ug/ml and higher. Fluorescence microscopy revealed that PolyDOTS localized throughout the cell but were excluded from the nucleus, and no photobleaching occurred during prolonged imaging. These results demonstrate that PolyDOTS represent a new class of theranostic nanoparticles built from the platform of conjugated polymers by selectively combining fluorescent or photoacoustic image guidance with heat generating polymers to form one stable nanoparticle that shows no fluorescence quenching and excellent photothermal capacity.

WED 18

Conjugated Nanoparticles for Detection and Thermal Therapy in Colorectal Cancer

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Metastatic colorectal cancer (CRC) has a very poor prognosis, with a five-year survival rate of ~10% compared to a 90% survival rate in localized CRC. Cytoreductive surgery and chemotherapy are the gold standards of treatment for long-term survival for patients with localized or metastatic CRC. However, detection and removal of all metastatic tumours remains one of the greatest challenges for improved survival outcome. To overcome these tasks, we have developed dual-purpose biocompatible electrically conductive polymer nanoparticles, which heat when stimulated with near infrared light and contain a fluorescent component. These nanoparticles induce photothermal ablation and can be used to detect cells *in vitro*. Recently, we have found that the folic acid receptor is expressed 200–3,000% higher in CRC lines (RKO and HCT116) as compared to a non-cancerous cell line (HEPM). We hypothesize that we can improve localized hyperthermia specific to cancer cells by targeting nanoparticles using folic acid.

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) nanoparticles synthesized using phospholipid polyethylene glycol (PL-PEG) conjugated with FITC or folic acid (FA) (PCPDTBSe-PL-PEG-FA/FITC). PCPDTBSe-PL-PEG-COOH-FITC was also synthesized and used as the control. The PCPDTBSe-PL-PEG-FA/FITC and PCPDTBSe-PL-PEG-COOH-FITC nanoparticles were characterized using transmission electron microscopy (TEM), dynamic light scattering (DLS) analysis, UV-visible spectroscopy, and fluorescence microscopy, to determine hydrodynamic diameter, zeta potential, morphology, and absorption spectra. Targeting, cytotoxicity, and thermal ablation were evaluated using 3 malignant colorectal lines (CT26, RKO, and HCT-116) and one normal bowel line (FHs 74 Int). Nanoparticle stability was investigated by the retention of heating potential over five heating and cooling cycles.

Targeted PCPDTBSe nanoparticles induce localized photothermal therapy to cancer cells and have the potential to decrease heat damage to surrounding healthy tissue. Used in conjunction with cytoreduction surgery, this regimen has the potential to improve patient outcome and survival.

WED 19

Experimental analysis of amplitude- and frequency-dependent specific loss power measurements of magnetic nanoparticles

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Magnetic nanoparticle hyperthermia is a promising cancer treatment, especially when combined with chemo and radiation therapies. Many challenges remain including a fundamental understanding of the relationship between the heating efficiency and magneto-structural properties of the magnetic nanoparticles. Heating efficiency is usually quantified by measured mass-normalized loss power, or specific loss power (SLP), as a function of magnetic field conditions, usually variable amplitude at fixed frequency.

Initial attempts to describe heating properties of magnetic nanoparticles in the presence of an alternating magnetic field (AMF) include assumptions, such as non-interacting particles exposed to low-amplitude fields, to simplify mathematical computations. As a consequence, the specific loss power is predicted to scale linearly with the frequency and quadratically with AMF amplitude. Use of these early models persists and has led to the development of prevailing paradigms of magnetic nanoparticle hysteresis heating. However, recent experimental evidence has demonstrated that nanoparticle heating at fixed frequency is often non-linear with amplitude, even at the lowest amplitudes. This suggests that frequency dependence may also be non-linear, calling into question the validity and utility of simple models. We present results of a comparative study evaluating the heating performance of several magnetic nanoparticle suspensions using a range of frequencies and amplitudes.

The SLP is experimentally determined by calorimetric measurements in non-adiabatic conditions using methods previously described by us. The resulting SLP surfaces show significant differences between heating properties of the nanoparticle suspensions under study. The differences in delayed onset and plateau in SLP with amplitude or frequency suggest that inter- and intra-particle interactions play an important role in generating measured loss power. Recent research that elucidates the magnetic domain structure of some magnetic nanoparticle formulations confirms this interpretation. Therefore, initial calculations are performed that include additional contributions to energy of interactions to assess the importance of competing energy contributions to nanoparticle interactions with external magnetic fields. In addition to its utility as a tool to compare heating efficiencies, our experimental SLP data can be used as input for more accurate modeling studies of magnetic nanoparticle hyperthermia.

WED 20

Methods to control non-target heating for iron oxide nanoparticles hyperthermia.

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Introduction: Hyperthermia sensitizes tumor cells for radiation and chemotherapy treatments in addition to having thermoablative capabilities. Due to similarities in tissue sensitivities to heat, and the large variability in blood perfusion between tumor and normal tissue, it is typically necessary to concentrate heating directly into tumor sites, and avoid heating normal tissue. Iron oxide nanoparticles (IONP) activated in an alternating magnetic field (AMF) can increase the specific absorption rate (SAR) of a tissue, resulting in a local temperature increase. An improvement in tumor targeting and injection techniques, paired with high SAR IONPs, results in an increased thermal dose, compared to surrounding tissue. However, the AMF field necessary to activate the IONPs also interacts with local tissue, depositing energy via a joule heating mechanism. This non-target heating limits the adoption of IONP hyperthermia as a viable clinical treatment.

Methods: Tissue-equivalent phantom offset and motion were manipulated using a rotating platform, while geometry, external cooling and field properties were varied to reduce non-target heating.

Results: Offsetting and rotating the phantom resulted in a 30% decrease in non-target heating without altering field strength in the target tissue. These optimized parameters, when used in conjunction with IONPs in the tumor location, showed a threefold increase in thermal dose. Although it had less effect on tissue at depth, external cooling decreased surface temperatures by nearly 50%. Inhomogeneous tissue geometry resulted in the most significant non-target heating.

Conclusion: By accounting for tissue geometry, modulating the applied field, and utilizing external cooling, IONP hyperthermia can be a viable cancer therapy.

WED 21

Toxicity and Biodistribution of Iron Oxide Nanoparticles

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Introduction: Biocompatibility and toxicity of iron oxide nanoparticles (IONPs) is dependent on the particle size, composition, and surface coating. Although significant information exists regarding IONPs with a hydrodiameter under 50 nm, there is limited knowledge relating to larger IONPs (those with a hydrodiameter of 110nm). Therefore, it is imperative to understand the short-term and long-term toxicity and biodistribution of larger IONPs prior to clinical use.

Methods: In this time-course study, 110 nm dextran-coated IONPs (NT-01) were intravenously injected into mice at 0.4, 0.6, and 1.0 mg Fe/g bodyweight (0.73, 1.10, and 1.83 mg IONP/g bodyweight respectively). Behavioural observations over a 7-day period indicated the acute toxicity levels. Mice at 0.4 mg Fe/ g bodyweight were maintained for 30 days and 90 days to evaluate the effects of long-term toxicity. Iron accumulation in organs (liver, spleen, lymph nodes, brain, heart, lungs and kidney) was ascertained using mass spectrometry and histological analysis.

Results: Acute toxicity was only noted at the highest dose of 1.0 mg Fe/ g bodyweight. At this dose, mice exhibited prolonged lethargy and delayed reflexes. Organs in the reticuloendotheilial systems (liver, spleen, and lymph nodes) demonstrated significant iron deposition within macrophages. In the kidney, heart, lungs, and brain, insufficient iron levels was detected within the organ vasculature.

Conclusion: Despite causing temporary abnormal behaviour, NT-01 nanoparticles did not induce any damage detected through histological analysis. NT-01 nanoparticles can be safely injected intravenously up to the nonlethal dose of 1.0 mg Fe/ g bodyweight.

WED 22

Nanoparticle-enhanced microwave hyperthermia: effects of nanoparticle size and shape on heating

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Background: Effective hyperthermia treatments require the delivery of sufficient therapeutic heating to the target volume, while minimizing thermal damage to non-targets. Limited electromagnetic contrast between malignant and healthy cells places a large burden on the design of devices and strategies to focus energy within the target volume. To ease this burden, nanoparticles with dielectric and/or magnetic contrast have been proposed to increase the coupling of the electric and/or magnetic field during microwave heating. Magnetic nanoparticles (MNPs) offer the potential to enhance microwave hyperthermia by increasing the electromagnetic contrast between tumor and healthy tissue. In this study, we experimentally evaluated heating enhancements offered by Fe/Fe_3O_4 nanoparticles with spherical, cubic, and hexagonal structures in aqueous solution when exposed to 2.4-2.5 GHz microwave radiation.

Methods: An experimental testbed was implemented for measuring heating of MNP solutions when exposed to microwave radiation. The testbed consisted of a glass capillary tube (1.33 mm I.D.), containing the MNP solutions, positioned in the centre of the broad wall of a WR340 waveguide. Microwave radiation (2.4-2.5 GHz, 15 W, 3 min) was injected into one waveguide port, with the other port terminated with a matched load. A fiber-optic temperature probe inserted into the capillary tube monitored temperature of MNP solutions during and after heating. The following MNPs, coated with 0.05% dopamine, were evaluated: 10 and 20 nm diameter spherical Fe/Fe_3O_4, 20 nm edge-length cubic Fe_3O_4, and 45 nm edge-length/10 nm height hexagonal Fe_3O_4. MNP heating enhancements were experimentally (n=5) evaluated at concentrations of 10 mg/ml, 5 mg/ml and 2.5 mg/ml. A 0.05 % solution of dopamine in deionized water was used as a control.

Results: The control group exhibited an average temperature rise of 23.5±1.5 °C. At a concentration of 10 mg/ml, solutions of hexagonal, cubic, 10 nm spherical, and 20 nm spherical MNPs yielded temperature increases of 24.9±1.2 °C, 25.9±2.4 °C, 38.2±0.93 °C, and 28.9±0.25 °C, respectively. At reduced concentrations of 2.5 mg/m, 10 nm and 20 nm spherical MNPs yielded temperature increases of 26.7±0.9 and 25±0.4 °C, respectively.

Conclusion: The MNPs considered in this study offer strong potential to offer heating enhancements during microwave thermal therapy procedures. Ongoing efforts are investigating the broadband complex dielectric and magnetic properties of the candidate nanoparticles in solution. Future research investigating nanoparticle delivery techniques and *in vivo* evaluation of heating is warranted.

Funding: NSF CBET 1337438 and KSU Johnson Cancer Center.

WED 23

Development of a novel cisplatin-loaded low temperature-sensitive liposome: effect on cisplatin loading/release and anti-tumor effects with hyperthermia

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Background: Liposomally encapsulating drugs have been developed over the last 30 years with promising effects on drug retention and drug delivery to target sites. However, increasing bioavailability of the encapsulated drug only at the diseased site and at controllable rates is another major challenge for this drug delivery system. We have previously developed a doxorubicin-containing low temperature-sensitive liposome (LTSL-DOX) that incorporated lysolipid to facilitate rapid content release upon reaching mild hyperthermia (40°–42°C). LTSL-DOX exhibited rapid intravascular drug release in heated tumors, resulting in significant tumor growth delay in mice, and prompting phase I-III clinical trials in chest wall recurrences of human breast and primary liver cancers. Here, we expanded this liposome formulation and developed a new cisplatin-loaded LTSL. Cisplatin was chosen because 1) it showed broad spectrum activity against a wide range of heatable cancers (i.e., those in sites such as the pancreas, colon and rectum, cervix and bladder, and 2) the same hyperthermic temperatures that enabled LTSL-drug release also enhanced cisplatin-induced cytotoxicity. Cisplatin loading/release efficiency and anti-tumor activity was investigated using this new cisplatin-LTSL in combination with hyperthermia.

Methods: A transition temperature loading method was used to encapsulate cisplatin into a LTSL formulation that contains DPPC:MSPC:DSPE-PEG2000 (85.0:9.8:5.2 mol% ratio). The stability of the cisplatin-LTSL was examined in buffer solutions and plasma. Cisplatin releasing was measured at 37°C (physiological temperature) and 41.1°C (Tm). Pharmacokinetics of cisplatin-LTSL and tumor growth control was investigated in tumor-bearing mice under normothermic and hyperthermic conditions.

Results: We demonstrated high cisplatin loading efficiency and stability using this LTSL formulation. Hyperthermic temperatures (41-42°C) increased encapsulated cisplatin release and its half-life in plasma following cisplatin-LTSL treatment compared to free cisplatin. Moreover, pre-heating the tumor for 30 min followed by cisplatin-LTSL injection and continuous heating for another 30 min significantly delayed tumor growth and increased cisplatin accumulation in the tumors as compared to mice received free cisplatin.

Conclusions: We have developed an easy and effective cisplatin-LTSL formulation. Our results demonstrated the potential effectiveness of this cisplatin-LTSL formulation on drug delivery and anti-tumor activity.

WED 24

Revisiting intracranial hyperthermia and radiation for brain tumors

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Glioblastoma is the most deadly primary brain tumor. Glioma stem cells (GSCs) are a subset of cells that contribute to tumor progression because of their high capacity for self-renewal and resistance to standard therapy. In radiation oncology, hyperthermia is known to radiosensitize cells. In a phase III clinical trial for patients with glioblastoma, the addition of interstitial hyperthermia to radiation improved survival compared to radiation alone. However, technical challenges limited its widespread acceptance. Intracranial hyperthermia using minimally invasive techniques is now re-emerging as an option for patients with glioblastoma.

Data from our laboratory using a phospho-kinase array reveal the survival kinase AKT as a critical sensitization determinant. GSCs treated with radiation alone exhibited increased AKT activation, but the addition of hyperthermia before radiotherapy reduced AKT activation and impaired GSC proliferation. Introduction of constitutively active AKT in GSCs compromised hyperthermic radiosensitization. Pharmacologic inhibition of PI3K further enhanced the radiosensitizing effects of hyperthermia. In a preclinical orthotopic transplant model of human GBM, thermoradiotherapy reduced pS6 levels, delayed tumor growth and extended animal survival. Together, our results offer a preclinical proof-of-concept for further evaluation of combined hyperthermia and radiation for GBM treatment.

WED 25

Combining thermal ablation with adjuvant therapies – current and future applications

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While focal high-temperature thermal ablation therapy has been successfully used to treat a wide range of tumors, limitations in treatment efficacy exist. A number of hyperthermia-induced secondary tissue reactions occur in and around the ablation zone that can contribute to tumor cell survival. Combining thermal ablation with adjuvant chemotherapy can potentially increase the amount and completeness of tumor destruction by targeting key mechanisms such as augmenting local cellular cytotoxicity or inhibiting reactions contributing to tumor cell survival. Methods of improved drug delivery will be reviewed including evolving use of drug-encapsulated nanoparticle delivery agents. Finally, more recently, systemic effects of thermal ablation, including stimulation of distant tumor growth or development of anti-tumor immunity are being studied. Potential opportunities to modulate these effects with combination ablation/drug therapies to improve ablation outcomes will also be discussed.

WED 26

Synergistic Effect of Thermal and Immune Response for Metastatic Cancer Therapy

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A novel cancer therapy has been developed to stimulate the whole body anti-tumor immunity by local application of thermal stress. Various types of metastatic tumor animal model were used in experimental studies. It was found that not only primary tumor could be completely destroyed through the local thermal and mechanical stresses, but also the whole body anti-tumor immunity was induced to suppress the distal metastases, and against further challenge of cancer. Significant difference was found in the survival rate by comparison made between the thermally treated and surgical resection groups. Further mechanistic studies were performed by examination of cell immune responses in blood, tissue and organs and results will be reported.

Abstracts for Thursday, April 16th

THUR 1

The Effect of Cold Temperatures on Cellular Freeze Injury

Jeunghwan Choi[1,2], Saravana Balasubramanian[2], Jing Jiang[2], John Bischof[2]

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This talk discusses the current understanding of the effects of cold on biological systems with relevance to cryosurgery. The mechanisms of cold injury to biosystems are investigated at the cellular, tissue, and systemic levels, with details concerning the related experimental methods. Cellular level studies have shown a direct relationship between biophysical changes versus freeze-thaw survival. Advances in experimental and analytical methods have resulted in qualitatively similar results for native and artificial tissue systems, with several important caveats relating to cell-cell, cell-ECM effects. While these biophysical events have informed a better understanding of immediate injury after freezing at the cell and tissue level, further understanding of delayed injury effects after cryosurgery including at the cellular (i.e. apoptosis) and host mediated (i.e. vascular and immunological) events remain important areas of research and an opportunity to improve the technique.

THUR 2

Nanocarrier-based hyperthermia-guided drug delivery to solid tumors

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Chemotherapy is one of the main treatment policies in cancer. While (acquired) resistance is a major hurdle and therefore an important subject of study, adequate and sufficient delivery to the site of action is crucial to inflict an effect of importance. Here in particular the possibilities at hand to improve drug delivery to tumors is discussed. For this purpose the focus will be on nanocarrier-based drugs (i.e. liposomes encapsulated) and the use of mild hyperthermia. Nanocarriers are used to tune pharmacokinetics and to modulate logistics in the body as well as in the target site. Hyperthermia, here mild or also called fever range, is applied to manipulate the tumor microenvironment and to control release and availability of the nanocarrier-born chemotherapeutic. By combining the beneficial characteristics of liposomes with the possibilities hyperthermia provide a better drug delivery and tumor response are anticipated.

THUR 3

Metabolic alterations in cancer

Matthew Vander Heiden

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Cells adapt metabolism to meet distinct physiological needs, and metabolic regulation influences whether a cell can proliferate. To proliferate, cancer cells must adapt metabolism to support anabolic processes and allow the accumulation of biomass. However, tumor cells also experience periods of stress, and metabolic plasticity to shift metabolism to maximize efficiency and survive nutrient limitation is also needed for tumor progression. Those nutrients with the highest consumption by cancer cells are not necessarily the fuels that contribute directly to cell mass. Glucose and serine metabolism are both critical to support nucleotide synthesis, and regulation of these pathways can impact folate/one carbon metabolism to determine whether sufficient nucleotides are available to support cell proliferation. Cancer cells catabolize a variety of nutrients, and amino acids are a major fuel source for cancer cells in vivo. Regulation of redox homeostasis is also important for cancer cell proliferation. Data from both nutrient tracing studies and mouse cancer models will be presented to clarify how metabolism impacts cancer biology.

THUR 4

Preliminary Results of the Impact of the Extent of Laser Ablation on the Median Overall Survival in patients with Glioblastoma Multiform

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Background:

Laser Interstitial Thermal Therapy has been used as a new modality by several centers across the country to enhance the outcome in patients with Difficult-to-access tumors including Glioblastoma multiform (DTA-GBM). The new modality has been used to achieve maximum extent of ablation comparable to the extent of resection done for more accessible lesions.

Methods:

Retrospective data of patients with new and recurrent glioblastoma multiform (GBM) was collected from an IRB approved database to determine the impact of the extent of ablation on the over-all survival (OS). The patients were divided into 2 groups according to the post-operative residual: Thin rim (<3mm) (group 1) and Thick rim or residual mass (group 2). The median OS was calculated in both arms.

Results:

Twenty eight cases (14 males and 14 females) with DTA-GBM were treated by Neuroblate™ in the duration from May 2011 to December 2014. Twenty six patients had KPS ≥70. Nineteen patients were newly diagnosed and 9 patients had recurrent disease. In post-operative MRI brain 19 patients had no or thin rim residual enhancement (group 1) and 9 patient had a residual mass or thick rim residual enhancement (group 2). The median OS in group 1 was 22.8 months in comparison with 8.1 months in group 2 (p-value 0.118)

Conclusion:

This initial report shows that the Extent of ablation can positively impact the overall survival. Larger sample size and prospective data analysis is needed to confirm these preliminary results.

THUR 5

Interstitial thermal therapy combined with interstitial brachytherapy after chemoradiation for pelvic local recurrence in a patient with muscle invasive bladder cancer

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Background*:* Thermal therapy in conjunction with radiotherapy has been shown to result in significant improvement in local control in a number of tumors, including transitional cell carcinoma (TCC) of the bladder. We present the case of a patient who developed a painful local only recurrence in the pelvic sidewall 7 years after undergoing neoadjuvant chemotherapy and cystectomy for a T2bN2Mx TCC of the bladder. At recurrence, he was inoperable and had small bowel adhesed near his gross tumor volume, thus precluding effective dose escalation with external beam radiotherapy (EBRT) alone. He received EBRT to 55.4 Gray concurrently with cisplatin. In an effort to improve local control while sparing late bowel toxicity, he subsequently received 2 treatments of interstitial high dose rate (HDR) brachytherapy combined with interstitial thermal therapy (ITT) as described below.

Methods: The patient underwent CT-guided placement of percutaneous 16-gauge needles by interventional radiology, with 11 catheters inserted for the first treatment and 15 catheters for the second treatment. All catheters were placed into the gross tumor volume (GTV) at 1.5 to 3cm intervals at a depth of 5.6 to 8cm from the skin. After CT simulation, the patient received HDR brachytherapy with Iridium-192 to a dose of 500cGy prescribed to the GTV for each treatment immediately followed by ITT. The BSD-500 Hyperthermia system was used with semirigid MA-251 microwave interstitial applicators consisting of small (1.1-mm diameter) coaxial microwave antennae. A total of 24 applicators were available, delivering heat through 915-MHz microwaves. Each applicator provided an ellipsoidal heating pattern along the applicator shaft from tip to about 4.5 cm. Temperatures were continuously monitored as a function of time with an accuracy of ±0.2°C. Total treatment time was 45 minutes for the first fraction and 36 minutes for the second fraction. Thermal sensor ranges were 38-42.5°C. The treatment was started with the power set at 2 watts per antennae and was varied differentially in each antenna to final values ranging from 1.4 to 4.3 watts. Treatment times were 36 and 45 minutes, respectively.

Results: The patient tolerated treatment well, and has no evidence of tumor growth 7 months after completing treatment.

Conclusion: ITT combined with interstitial brachytherapy can be considered as a means

of maximizing local control in patients with pelvic sidewall malignancies.

THUR 6

Hyperthermia And Radiation For Recurrent Breast Cancer

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Background/Purpose: Recurrent breast cancer within a previously irradiated field poses a challenge because the benefits in local control must be weighed against the increased side effects from repeat radiation. For these patients, hyperthermia has emerged as an adjunct treatment that can improve the radiosensitivity of cancer cells. The primary objective of this retrospective study is to evaluate local control with hyperthermia and radiation for breast cancer. The secondary objective is to evaluate acute and long-term toxicity of treatment.
Methods: This retrospective study is comprised of thirty patients (median age 59) who received concurrent hyperthermia treatment with radiation for recurrent breast cancer from 2/2011 to 1/2015 (median time to recurrence 6.1 years). These patients underwent multiple prior treatments. Patients then received salvage hyperthermia, weekly or twice weekly, with radiation (median 35.5 Gy).
Results: Twenty-six (87%) patients received prior radiation therapy (median 60.4 Gy). Average follow-up was 7.7 months. Complete response (CR) was observed in 15 patients (50%), partial response (PR) in 4 patients (13%), and stable disease (SD) in 11 patients (37%). Twenty-two patients experienced acute grade 1 and 2 toxicities, primarily pain and erythema, and twenty-two experienced long-term grade 1 and 2 toxicities, mainly lymphedema and hyperpigmentation.
Conclusions: Hyperthermia and radiation provide good local control with a favorable side effect profile in heavily pretreated patients. Thermoradiotherapy should be considered for patients with locally recurrent breast cancer.

THUR 7

Concurrent External Beam Radiotherapy and External Thermal Therapy for the Treatment of Extramedullary Plasmacytomas: A Case Report.

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Background: Multiple myeloma is a relatively rare malignancy of plasma cells that most commonly arises as painful lytic bone lesions and is managed by chemotherapy followed by hematopoietic stem cell transplantation. Targeted radiation therapy (RT) usually accompanies this regimen only for symptomatic lesions causing significant morbidity. Extramedullary disease is uncommon and is underreported in the literature. In our clinic, we have coupled external thermal therapy (ETT) with RT for the treatment of a patient with multiple refractory soft-tissue extramedullary plasmacytomas. To our knowledge, this represents the first report of hyperthermia used concurrently with external beam radiotherapy for an extramedullary plasmacytoma, of the chest wall.

Methods: The patient was a 50 year-old female who initially presented with multiple myeloma and symptomatic sacral involvement that was managed with chemotherapy followed by RT with excellent clinical response. Unfortunately, she had a local and distant recurrence requiring further systemic therapy and reirradiation to the sacrum. Upon presenting for stem cell transplant evaluation, she had developed biopsy-proven bilateral breast and chest wall plasmacytomas each measuring 3-4 cm in greatest dimension. She was treated with a single electron beam fraction of 5 Gy prescribed to the 90% isodose line, to each lesion, with a 1 cm bolus. This resulted in minimal response. Therefore, two additional fractions of 3 Gy each were delivered in conjunction with ETT two days later. She received one hour of ETT with the temperature maintained at 40 to 43 C by the BSD-500 unit after each RT fraction. These additional 2 fractions of RT and ETT were delivered in conjunction with the patient's conditioning regimen for stem cell transplant of total body irradiation to 12 Gy in 2 Gy per fraction, twice daily.

Results: The patient experienced a complete clinical response and a complete radiographic response by PET/CT in both breast lesions. The patient had minimal side effects with only minor scarring and skin erythema at the sites of disease. This regimen successfully reduced her burden of disease, which may portend for a better response to bone marrow transplant.

Conclusion: In this case report of a patient with refractory extramedullary plasmacytomas, concurrent ETT and RT resulted in a complete clinical and radiographic response with minimal toxicity. Further investigation regarding concurrent ETT and RT for extramedullary plasmacytoma is warranted.

THUR 8

Focal laser ablation of prostate cancer—technique and outcomes in 85 patients.

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Focal laser ablation of prostate cancer (FLA) is a new technique to treat organ-confined tumors using magnetic resonance (MR) guidance and thermometry.

We treated 85 patients with FLA since June of 2013. Patients included in this group had

focal lesions (1-3) visible by MRI that were biopsy-proven prostate cancer graded less than Gleason 8. Ineligible patients had large lesions (over 2 cm), extracapsular tumor spread, metastases or absolute contraindications to MRI.

All patients in this study filled out pre-treatment sexual health in men (SHIM) score sheets as well as the international prostate symptom score sheet (IPSS) to obtain baseline erectile and urinary function. Men repeated such scoring at 6 and 12 months, then yearly.

The FLA procedure involved insertion of an endorectal needle guide and imaging in a 3 tesla MRI. After the probe was calibrated to the MRI sequences, we guided a 13g plastic cooling cannula through each lesion. Typically, FLA involved irradiation with 65-70% of 24 watt diode laser energy for 2-3 minutes per ablation MRI thermometry projected color-coded maps showing cell death as it occurred during the FLA process. . Patients were discharged after they voided clear urine. MR and PSA follow up occurred at 6 months, one year and then yearly after the FLA procedure.

All procedures were technically successful. One major complication occurred with development of a rectourethral fistula post FLA. Minor side effects included urgency for 1-5 days (n=4), groin pain for 1-2 weeks (n=4), and epididymitis (n=1). Only two patients had new erectile dysfunction after FLA: both had bilateral FLA procedures. Of the 85 patients, 6 (7%) required a second FLA procedure. Tests of urinary and sexual function did not differ at 6 months (25 patients with SHIM scores averaging 21.6 pre FLA and 20.4 post FLA p=0.66 and IPSS scores averaging 7.6 pre FLA and 7.2 post FLA, p=0.58) nor at 12 months for a limited group of 7 patients (SHIM scores averaging 19 pre FLA and 20.6 one year post FLA, p=0.43 and IPSS scores averaging 8.9 pre FLA and 8.9 one year post FLA, p=0.47).

In conclusion, FLA for low or intermediate risk prostate cancer is safe and requires few retreatments (about 7%). FLA has no significant impact on a man's sexual or urinary function although bilateral disease should be treated with caution. In selected cases, focal therapy of prostate cancer can be considered as primary therapy, as it is already in many other organ systems.

THUR 9

EMF hyperthermia in Childhood Cancer

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Background: Cisplatin-based chemotherapy plus regional deep hyperthermia (RHT) can be utilized successfully to render children with dismal prognosis due to local tumor progression eligible for curative treatment strategies. To further control the local application of hyperthermia, we recently introduced 3-dimensional magnetic resonance imaging (MRI) as tool for non-invasive temperature monitoring. This was achieved by combining radiofrequency applicators with annular phased array antennas with a standard Magnetom 1.5T Siemens machine (BSD 2000 3D MRI hybrid system). We analyzed our clinical treatments whether 1) this novel non-invasive approach was feasible and comparable to the results achieved with standard invasive Bowman temperature probes and 2) the non-invasive approach can define a patient specific temperature profile in the tumor or surrounding tissue that can be utilized for non-invasive temperature.

Patients and methods: Most hyperthermia patients, aged 1-20 years, were heated using the BSD2000-3D hyperthermia system equipped with a range of phased array applicators (Sigma-30, Sigma-40, Sigma-60, Sigma-Eye) all emitting electromagnetic energy and using the constructive interference to heat tumors located deeply in the body according to the Hyper-PEI protocol: 4x1800 ifosfamide/qm, 4x100mg etoposide/qm, 2x40mg cisplatin/qm plus 2xhyperthermia (42-43°C,1h). In this study we only report the heating performance of the Sigma-40 used for young children. All treatments were performed using SOP as recently published as ESHO-guidelines for RHT.

Results: The Sigma-40 applicator operates at 100 MHz and has eight antennas that are pair-wise connected to four RF-amplifiers. The absorbed electromagnetic energy distribution in the child's body has been calculated using the SemcadX FDTD (Finite Difference in Time Domain) solver for a typical clinical indication. Using this advanced hyperthermia treatment modeling platform it is shown that heating using the Sigma-40 applicator a relative homogenous heating across the lower abdomen is obtained for small body sizes common with young children. Using a particle-swarm optimization in combination with a line-search optimization the optimal energy distribution was calculated for the

following applicator settings: Amplitude [top, bottom, left, right] = [1, 0.89, 0.87, 0.59], phase = [15, 25, 10, 0]. This leads to a HTQ value of 3.83, with a TC25 of 97%.

Conclusions: By multimodality therapy with regional hyperthermia local tumor control rate and long term survival can be improved in children with high-risk tumors with dismal prognosis. Multiple channel heat applicators and non-invasive MR temperature monitoring for childhood cancer can produce precise target volumes with substantial sparing of normal tissue.

Support: Deutsche Krebshilfe e.V., Elterninitivative Kinderkrebsklinik e.V.

THUR 10

EARLY EXPERIENCE WITH INTERSTITIAL LASER THERMAL ABLATION IN GRADE 2 AND 3 GLIOMAS.

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Aims:

To report our early experience of stereotactic laser ablation of grade 2 and 3 gliomas using the Neuroblate system.

Background:

There is an emerging trend of utilizing laser thermal ablation in grade 2 and 3 gliomas with effective outcomes.

Methods:

Retrospective review of pathologically confirmed grade 2 and 3 glioma patients who underwent laser ablation. Demographic data, tumor parameters &technical details were noted. Correlation of various factors with progression free survival (PFS) and overall survival (OS) was attempted.

Results:

22 patients were treated;8 had grade 2(4-oligodendroglioma,2-oligoastrocytoma,1-astrocytoma and 1 uncharacterized) and 14 had grade 3(10-anaplastic astrocytoma,3-anaplastic oligodendroglioma and 1 mixed) tumors. There were 12 males and 10 females. Mean preoperative tumor volumes was 11.71cc (range 0.39 to 65.18cc). Mean duration was 7.2 hours (range 3-12 hours) and average blood loss was 68cc (range 5-300cc). Average post ablation rim thickness was 3.44mm (range 0-7.9mm) and was categorized into thin (<=3mm) and thick (>3mm).. The overall median PFS for grade 3 glioma patients was 9.8 months (thick rim 14.1mo, thin 2.9mo; p=0.253) and for grade 2 patients was 7.9 months (thick 7.9mo, thin 5.7mo; p=0.692). The median OS for grade 3 patients was 40mo for those with post op thick rim and 30.50 for those with thin rim (p=0.364). There was a trend towards higher PFS in grade 3 patients with thin post-ablation rim.

Conclusion:

Laser ablation therapy appears to be an effective modality in management of patients with grade 2 and grade 3 patients.

THUR 11

The Immune Checkpoint Inhibitors: A mounting excitement with an imperative to combine with Hyperthermia

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Background: Over the past year two types of checkpoint inhibitors, the anti-CTLA-4, and the PDL inhibitors have been approved for therapy of advanced melanoma. Each acts by a diverse mechanism. **Methods**: This presentation is a review of new information and how hyperthermia should be combined with these potentially powerful new immune agents.

Results: Responses to these agents are notable because they occur in bulky disease that has failed to respond to prior therapies, and for the durability of their induced cancer response. Importantly, these two types of immune inhibitors, as well as anti PDL-1, and anti-PDL-2 drugs are in active phase I and II trials to treat other resistant epithelial neoplasms such as lung (including squamous cell), pancreas, colon, and gastric cancers. These trials show early but startling anti-tumor efficacy. The agents have also shown surprising responses in lymphoma, particularly resistant Hodgkin's disease, and also promise in glioblastoma.

Response rates are relatively high given disease bulk and tumor resistance to chemo-and targeted therapies, however their response rate cannot as yet be termed "hit runs" as they do not induce complete responses in most patients, and many patients' tumors do not respond at all.

Fever is an evolutionarily evolved mechanism to increase host immune response to viral, bacterial, and fungal infections. All in the field of hyperthermia recognize that hyperthermia, in virtually all its forms of delivery, also enhances the host immune response against infection, but also against cancer.

Conclusion: It would seem to be intuitive to combine hyperthermia with the immune checkpoint inhibitors. To date, research using this obvious combination has not been published. Why not?

THUR 12

Hyperthermia treatment overcomes temozolomide resistance in glioma cells by downregulating MGMT expression and increasing temozolomide uptake

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Background: Glioblastoma multiforme (GBM) is the most common and malignant brain tumor. Current standard treatment for GBM following maximum safe resection includes temozolomide (TMZ) with concurrent radiotherapy. Despite the improvement of survival by TMZ and radiation, the overall prognosis remains poor for GBM patients. This is partially attributed to drug resistance. Expression of the DNA repair protein O6-methylguanine methyltransferase (MGMT) in gliomas confers TMZ resistance and a worse prognosis. Therefore, development of novel therapy to suppress MGMT expression and overcome TMZ resistance is highly desired. Hyperthermia has been shown to increase TMZ sensitivity in melanoma. This provides a good rationale to extend the study and evaluate whether hyperthermia overcomes TMZ resistance in glioblastoma cells. In this study, we investigated the effect of hyperthermia treatment (43°C) on TMZ sensitivity in glioblastoma cells and the underlying molecular mechanisms.

Methods: Human glioblastoma cell lines (two TMZ sensitive and two TMZ resistant cells) were treated with TMZ under normothermic and hyperthermic conditions. TMZ sensitivity was determined using clonogenic assay. MGMT expression and TMZ uptake was determined by Western blotting and liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis.

Results: Our results showed that hyperthermia increased TMZ-induced cell death in TMZ-resistant glioma cells, but had no additional beneficial effect in the TMZ-sensitive cells. Hyperthermia in combination with radiation further overcame TMZ resistance. To study molecular targets, we found that hyperthermia downregulated MGMT expression through increasing proteasome-mediated MGMT degradation, which can be reversed by the proteasome inhibitor bortezomib. Hyperthermia had no effects on p53 expression and MGMT promoter methylation which was responsible for *MGMT* gene silencing. In addition, LC-MS/MS analysis showed an increase of TMZ and its downstream product 5-aminoimidazole-4-carboxamide (AIC) in hyperthermia-treated cells, indicating an increase of TMZ drug uptake and breakdown.

Conclusions: These results suggest that hyperthermia overcomes MGMT-mediated resistance of glioblastoma cell lines to TMZ and increases TMZ drug uptake. This study suggests a potential benefit of using hyperthermia in the treatment of GBM, particularly those with more adverse prognosis.

THUR 13

Self-assembling viral-like nanoparticles for tumor immunotherapy by in situ vaccination

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Tumors are recognized by the immune system, but tumors that reach clinically relevant size have established mechanisms to suppress the immune response and protect themselves from immune attack. One approach to enable effective immune response is to change the immunosuppressive tumor microenvironment into an immunostimulatory environment by introducing immunostimulatory reagents directly into tumors. This is essentially an antitumor therapeutic vaccination, because the tumors provide the antigens and the adjuvants are the immunostimulatory reagents. The overall goal of the approach is to not only stimulate an anti-tumor immune response against the directly treated tumor, but more importantly to stimulate a systemic anti-tumor response to treat unseen metastases. 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 resistance to metastatic tumors. The treatment is immune-mediated since it requires IFN-γ, IL-12, and adaptive immunity. Tumor reduction or elimination occurs in many anatomic locations and with multiple tumor types. 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 and very versatile avenue of cancer immunotherapy.

THUR 14

Myeloid-Derived Suppressor Cells Subvert the Immunostimulatory Activity of Thermal Therapy by Blocking T cell Trafficking in the Tumor Microenvironment

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The success of T cell-based cancer immunotherapy and, unexpectedly, thermal therapy, standard chemotherapy and radiation hinges on cytotoxic T cells gaining access to tumor targets. These observations have prompted interest in strategies to improve T cell trafficking to tumors although the mechanisms that positively or negatively regulate lymphocyte extravasation at tumor vascular checkpoints are poorly understood. Our laboratory has previously demonstrated that mild and ablative thermal therapies such as systemic thermal therapy (STT; 39.5 ± 0.5°C for 6 h) or radiofrequency ablation (RFA; 90°C for 1 min) convert tumor vessels from T cell-low to –high recruitment sites in multiple murine tumor models (i.e., EMT6 mammary carcinoma, CT26 colorectal carcinoma, B16 melanoma, and RIP-Tag5 pancreatic cancer). Enhanced T cell trafficking required induction of the prototypical trafficking molecule intercellular adhesion molecule-1 (ICAM-1) on tumor vessels. Here we report on a subset of tumor models (4T1 mammary, Polyoma Middle T-transgenic mammary, and Pan02 pancreatic tumors) in which thermal therapies failed to boost trafficking of cytotoxic T cells. A unifying characteristic of these thermally-refractive tumors is the expansion of a population of immunosuppressive immature myeloid cells called myeloid-derived suppressor cells (MDSC). Further analysis revealed that resistance to thermal therapy is temporally and inversely related to the expansion of intratumoral MDSC. Moreover, acute depletion of MDSC sensitizes tumor vessels to thermal modalities. To investigate whether MDSC contribute to poor effector T cell trafficking, thermally-sensitive tumor cells (EMT6, CT26 or B16) were co-implanted with syngeneic $CD11b^{+}Gr\text{-}1^{+}$ MDSC isolated from spleens of tumor-bearing mice at a ratio of 2:1, mimicking the high MDSC burden detected in thermally-refractive tumors. The frequency of $CD11b^{+}Gr\text{-}1^{+}$ MDSC remained elevated during outgrowth of tumors co-implanted with MDSC and tumor vessels became refractory to ICAM-1 induction by thermal therapy. Taken together, these findings identify a novel role of MDSC in subverting the immunostimulatory effects of thermal therapy by limiting T cell trafficking at the tumor vascular loci. These results lay the foundation for future studies to identify novel mechanisms to overcome resistance to thermal modalities in tumors with high MDSC burden. Supported by NIH (CA79765, AI082039, CA085183) and the Mark Diamond Research Fund.

THUR 15

Defining immunological impact and therapeutic benefit of mild heating in a murine model of arthritis

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Background: Traditional treatments, including a variety of thermal therapies have been known since ancient times to provide relief from rheumatoid arthritis (RA) symptoms. However, a general absence of information on how heating affects molecular or immunological targets relevant to RA has limited heat treatment (HT) as an "alternative therapy". In this study, we evaluated the effectiveness of mild HT in a murine model for collagen-induced arthritis (CIA) which has been used in many previous studies to evaluate newer pharmacological approaches for the treatment of RA. We tested whether inflammatory immune activity was altered following HT. We also compared the effect of HT to methotrexate, a well characterized pharmacological treatment for RA.

Methods: CIA mice were treated with either a single HT for several hours or daily 30 minute HT with or with methotrexate. Disease progression and macrophage infiltration were evaluated. Disease-specific cellular and humoral responses were detected by ELISA. Tissue pro- and anti-inflammatory cytokine and other molecular targets were detected by ELISA and Western blotting.

Results: We found that both HT regimens significantly reduced arthritis disease severity and macrophage infiltration into inflamed joints. Surprisingly, HT was as efficient as methotrexate in controlling disease progression. At the molecular level, HT suppressed TNF-α while increasing production of IL-10. We also observed an induction of HSP70 and a reduction in both NF-κB and HIF-1α in inflamed tissues. Additionally, using activated macrophages in vitro, we found that HT reduced production of pro-inflammatory cytokines, an effect which is correlated to induction of HSF-1 and HSP70 and inhibition of NF-κB and STAT activation.

Conclusions: Our findings demonstrate a significant therapeutic benefit for HT in controlling arthritis progression in a clinically relevant mouse model, with an efficacy similar to methotrexate. Mechanistically, HT targets highly relevant anti-inflammatory pathways which strongly support its increased study for use in clinical trials for RA.

THUR 16

Housing Temperature-induced Stress in Laboratory Mice drives Therapeutic Resistance Through β2-adrenergic Receptor Activation

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Pre-clinical evaluation of therapies relies on mouse models, but promising therapies often do not achieve the predicted results in patients. There are likely many reasons for this disparity, but recent evidence suggests that several housing factors can lead to metabolic abnormalities which can directly affect experimental outcomes in models of diseases such as obesity. We are interested in how housing temperature affects mouse tumor models. IACUC guidelines mandate that mice be housed between 20-26˚C (standard temperature, ST) even though the thermoneutral temperature (TT) is 29-31˚C. At ST, mice must generate heat through adaptive thermogenesis, a norepinephrine (NE) driven process. Data from several labs documents the tumor promoting effects of NE and epinephrine. We recently reported that the anti-tumor immune response is severely suppressed at ST; at TT there are more tumor specific CD8 T-cells, and fewer suppressor cells (MDSC, Tregs), correlating with significantly improved tumor control. Now we have found that ST induces therapeutic resistance in tumors in SCID mice which lack T and B lymphocytes. Murine (Pan02) and human cell lines (MiaPaca2, BxPC3) and patient xenografts were sensitized to cisplatin, Abraxane and Apo2L/TRAIL when mice were placed at TT compared to ST. We found that NE levels were lower in tumors of mice housed at TT than at ST while expression of anti-apoptotic molecules Bcl-2, Bcl-x_L, Mcl-1 and phosphorylated BAD^{112} was also decreased at TT compared to ST. Tumor cells were found to express β1,2 adrenergic receptors and *in vitro* treatment demonstrated that adrenergic signaling can directly induce the expression of anti-apoptotic signalling molecules in a time dependent manner in human pancreatic tumor cell lines, correlating with increased resistance to both chemotherapeutic and death receptor-mediated apoptosis. *In vivo*, tumors in mice at ST could be sensitized to Apo2L/TRAIL by the β1, 2-blocker propranolol. Prevention of adrenergic signalling by shRNA knock down of β2-AR (MiaPaca2) also resulted in sensitization of cells to therapy. Together, these results indicate that mice at ST are under chronic cold stress and support a critical role for β2-AR signalling in environmentally induced therapeutic resistance. Therefore, adrenergic signalling results in both resistance of tumor cells to apoptosis and immunosuppression which are sufficient to impact the outcome of experiments evaluating the efficacy of immunotherapy and other novel therapies.
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THUR 17

Radiation enhancement by tumor stromal thermotolerance

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Here we studied the changes in vascular thermotolerance on tumor physiology and the effects of multiple clinically relevant mild temperature hyperthermia (MTH) treatments on tumor oxygenation and corresponding radiation responses. The vascular thermoresponse was monitored by daily one-hour 41.5°C heatings in two murine solid tumor models, SCK murine mammary carcinoma and B16F10 melanoma. A transient thermotolerance was seen by an increase in overall tumor oxygenation for 2-3 days, followed by a progressive decline in tumor pO(2) upon continued daily heatings. This vascular thermotolerance was further studied by treating tumors with different heating strategies, i.e. (1) a single 60 min 41.5°C treatment; (2) two consecutive daily treatments of 41.5°C for 60 min; (3) a single 60 min 43°C treatment or (4) two days of 41.5°C for 60 min followed by treatment with 43°C for 60 min on the third day. Pre-heating tumors with mild temperature hyperthermia induced vascular thermotolerance, which was accompanied by evidence of vessel normalizsation, i.e. a decrease in microvessel density and an increase in pericyte coverage. By employing these heat-induced increases in tumor oxygen levels with rational scheduling of fractionated radiation, we were able to significantly and synergistically inhibit tumor growth. *In vitro* clonogenic survival responses indicated only a direct cellular thermotolerance effect in endothelial cells as compared to the other cell types associated (i.e. fibroblasts, pericytes and tumor cells). Overall, this suggests that a major part of *in vivo* tumor thermotolerance is a physiological phenomenon mediated through improvement of functional vasculature. We are currently assessing the baseline changes in vascular hypoxia as another potential factor in the improved radiation response.

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THUR 18

A Novel High Throughput Model to Study Islet Amyloid Aggregation and β-Cell Death in Type 2 Diabetes Mellitus: Role of Hsp70 (HSPA1A)

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Type 2 diabetes mellitus (T2DM) is characterized by reduced β-cell mass resulting from misfolded islet amyloid polypeptide (h-IAPP) that forms toxic aggregates and destroys β-cells. Heat shock proteins (HSP) combat unwanted self-association of unfolded proteins. To explore h-IAPP-mediated intracellular toxicity, we generated a transgenic Caenorhabditis Elegans model that expresses h-IAPP in body wall muscles and pharynx. Tissue-specific plasmids containing h-IAPP:YFP were injected into pha-1(e2123); him-5(e1490); lite-1(ce314) hermaphrodites. Human Hsp72 tissue-specific plasmids were co-injected with h-IAPP:YFP plasmids expressed in the same tissues. We demonstrate that thermal stress significantly upregulates expression of Hsp72 and Hsp25, and subsequently reduces h-IAPP toxicity ($p<0.001$). The transgenic C. elegans model shows h-IAPP aggregates in body wall muscles and pharynx. Phenotypically, this model shows developmental retardation, however, co-transfection with human Hsp72 reduces h-IAPP aggregates and improves the phenotype. Taken together, our studies suggest that use of thermal stress to offset detrimental effects of islet amyloid deposition and prevent β-cell death is a feasible approach to manage T2DM.

THUR 19

NIH and NCI Grant-Related Changes During Fiscal Years 2014/2015

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The 2014 fiscal year continues to be challenging for all federal agencies despite the Congressional strategies proposed to address the U.S. budget deficit. The Bipartisan Budget Act of 2013 passed by the House and Senate in December 2013 approved a two-year spending bill cancelling the proposed sequester cuts (i.e., 4-5% NIH/NCI budget reductions) required in 2014 and 2015, but extending the sequestration period through 2023. What impact this passage will have on the final NIH/NCI appropriations for 2014 and subsequent number of NIH/NCI grants funded in 2014 remains to be seen.

The overall success rate and funding paylines for NIH/NCI applications in all areas of research besides the Hyperthermia and Thermal Therapy research field will be provided for the past few years. Information on new initiatives and funding opportunities including Dr. Varmus' Provocative Question initiative during the past two years will also be discussed.

The new NIH grant-related policy changes implemented in 2014 and those proposed for 2015 will be highlighted. These changes could impact the grant application and award process for STM applicants and their academic institutions. Information on various NIH resources available for grant applicants and their institutions will also be provided.

In September 2014, Congress passed a Continuing Resolution to keep the government operational until December 11, 2014 and finally passed the NIH FY2015 budget on December 16, 2014 with overall funding similar to FY2014. While inflation continues to erode into the NIH and NCI budget for the past 10 years since the doubling of the NIH budget ended in 2003, NIH and NCI is committed to fund the best research showing the highest impact within the field of research being proposed. Basic mechanistic research projects are important, but those having clinical translational applicability will continue to be valued as having high impact and more likelihood of being funded in these critical budget periods.

THUR 20

Is There an Advantage to Combinatorial Cryo/Thermal Therapy?

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The adoption of combinatorial therapeutic strategies to ablate cancerous targets is developing as a major clinical trend especially when faced with recurrent disease. While many of these treatment approaches are considered experimental and primarily of salvage benefit, the question arises within the context of thermal therapies whether heat/freeze sequences can positively alter outcomes. We addressed this question in a pancreatic cancer *in vitro* model with a focus on tumor margin exposures with the objective of optimizing cell death following the application of paired, but individually suboptimal, thermal excursions.

Two human pancreatic cancer cell line (Panc-1 and BxPC-3) were exposed to individual and paired thermal conditions (-10, -15, -20, +45 and +50 ^{o}C) for 5 minutes to simulate a clinical dose at a tumor's margin. While each individual thermal dose yielded significant levels of cell death (range = 40-75%), only the dual combinations yielded complete ablation. The combination of +50 and -10 ^{o}C yielded complete death in BxPC-3 by 24 hours post-thaw while the +50 and -15 ^{o}C combination resulted in 98% death in Panc-1 cells. These data provide preliminary evidence to support further study of the role of dual thermal stressors in cancer ablation.

THUR 21

Focal Cryoablative Technologies 2015

Aaron E. Katz

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Since the era of prostate specific antigen (PSA) testing, there has been a stage and grade migration seen with prostate cancer along with a reduction in mortality. Subsequently, concerns have been raised about the over treatment of patients following the diagnosis of localized prostate cancers. Cryotherapy, in which extremely low temperatures induce cell death via multiple mechanisms, has seen a drastic improvement in its technology since the 1800s. Such advances have improved oncological outcomes while reducing complication rates. Furthermore, technological advances have allowed the development of focal cryotherapy which aims to reduce morbidity associated with more radical whole-gland therapies. In this forum the recent technical advances using cryotherapy will be discussed as well as the role of HIFU, electroporation and laser-guided therapy.

There is growing evidence that focal ablation provides good oncological and morbidity rates when compared with traditional radical/whole-gland therapies. One of the main reasons for this shift has been an effort to decrease side-effects and improve quality of life in men who are diagnosed with early stage prostate cancer. Functional results indicate short-term effects on urinary and sexual function are frequent but seem to be less severe than whole gland or conventional treatments. Interest in this form of focal treatment has developed following encouraging initial reports suggesting feasibility, safety and favorable quality of life. In this lecture there will be a discussion on the follow up monitoring for the patients. Recently the use of multiparametric MRI has been shown to be the optimal imaging modality for follow-up after focal therapy in addition to PSA and biopsy.

More specific data to understand the long-term outcomes, goals and expectations for functional recovery that may be specific to each treatment modality are needed and the pitfalls of the current investigations will be discussed.

THUR 22

Patient Selection and Oncological Outcomes of Focal Cryoablation of the Prostate

Thomas Polascik

Duke Cancer Institute, Durham, NC, USA

Focal cryoablation of prostate cancer promises effective disease control while maximizing functional outcomes in eligible patients. By reducing the burden of significant disease, more men may be kept on active surveillance, thus sparing them the morbidity of whole gland treatments such as radical prostatectomy or radiation.

Appropriate patient selection is critical to a successful focal cryoablation. The three-dimensional location of the cancer within the prostate, its volume and biological potential dictate suitability for focal treatment as well as treatment margins. Focal prostate cryoablation has, thus far, been practiced only in trial settings. While it is generally accepted that it may be an option in low stage disease, there are no guidelines for patient selection based on traditional parameters such as prostate specific antigen (PSA) or Gleason score. When applied as a hemi-ablation strategy, patients are often selected based on the occurrence of unilateral disease only. Because of limited sampling, standard extended sextant biopsies are not sufficient to exclude bilateral disease. 3-D prostate mapping biopsies, which require anaesthesia and have higher rates of post-procedure urinary retention, are often needed to assess disease laterality. An even finer resolution is needed if more selective focal ablation such as quadrant-ablations or lesion-specific ablation is being considered.

Multiparametric MRI (mpMRI) has been shown to have promising results in identifying and localizing significant disease. MRI-TRUS fusion biopsies may thus identify truly aggressive foci to guide focal therapy of prostate cancer. However, the data on the accuracy of MRI-TRUS fusion biopsy has yet to mature, especially with regards to its false negative rate. There is also a limit to the size of the lesion that can be detected and biopsied by MRI-TRUS fusion even though it may contain significant disease.

This presentation will focus on current available data on patient selection for focal cryoablation and its impact on oncological outcomes.

THUR 23

Multiparametric Prostatic Ultrasound, targeted biopsy individualized ablation of the prostate

Daniel Rukstalis

Wake Forest School of Medicine, Winston-Salem, NC, USA

Learning Objectives:

1. Understand the appearance of prostate cancer on the various parameters of ultrasound imaging.

2. Learn to use Doppler ultrasound to guide ablation of the prostate. Describe the risk of residual cancer following an individual ablation.

Abstracts for Poster Session: Thursday, April 16th 5:00pm-7:00pm

POS 1

Thermal Profile of Acetic Acid Analogues for Potential Use in Thermochemical Ablation

Travis Miles, Erik Cressman

Department of Interventional Radiology, MD Anderson Cancer Center, Houston, Texas, USA

Purpose: To evaluate the exotherms of the reactions between the acetic acid analogs triflouroacetic acid (TFA), dichloroacetic acid (DCA), and glacial acetic acid (AcOH) with the strong base sodium hydroxide (NaOH) for potential use in thermochemical ablation.

Materials and Methods: Aliquots of acetic acid analog and NaOH solutions were injected sequentially into a gel phantom in triplicate. A thermocouple was used to measure the temperature change for the reaction over a 5 minute time span at increasing concentrations 1M, 5M, and 10M. Temperature curves were plotted from the data.

Results: Peak temperatures were reached immediately following injection. Incremental increases in concentrations brought about an increase in peak temperatures for all derivatives. Peak temperatures reached an average 86°C in TFA trials, 51°C in DCA trials, and 44°C in AcOH trials. The higher concentrations of NaOH were viscous and difficult to mix completely with the acids, making 10M trials inconsistent.

Conclusions: The neutralization of AcOH and its analogs with NaOH releases substantial energy in the form of heat with the highest concentrations yielding the largest temperature changes. Stronger acidity correlated with higher peak temperatures, which in all analogs were seen to reach the range suitable for tissue coagulation. Further studies as thermochemical ablation reagents are warranted for TFA and DCA due to their imaging and pharmacologic properties.

POS 2

Analysis of Exotherms of Ethanolamine Derivatives in Reactions with Acetic Acid

Travis Miles, Erik Cressman

Department of Interventional Radiology, MD Anderson Cancer Center, Houston, Texas, USA

Purpose: To evaluate the reactions of ethanolomine and derivatives in neutralization reactions with acetic acid (AcOH).

Materials and Methods: The bases were injected in triplicate into a gel phantom containing equivalent volumes and concentrations of acetic acid. A thermocouple temperature monitoring device recorded temperature data for the reaction for 5 minutes over a concentration range from 1M to 10M. Plots of averaged temperature as a function of concentration for each condition were created.

Results: Peak temperatures were seen to increase with increased concentrations for all derivatives and occurred almost instantly. Peak temperatures at 10 M were highest in the aminoethylethanolamine (85°C), followed by morpholine (75°C), ethanolamine (73°C), and n-methylethanolamine (66°C). The peak temperatures for the 5M solutions fell in a range between 40-45°C. Differences among reagents at 1M concentrations were negligible.

Conclusion: All of the ethanolamine derivatives at 10M concentrations exceed the threshold temperature value recognized by hyperthermia studies as sufficient for cell death. The exothermic profiles measured for these reactions warrant further study for use in ablation techniques.

POS 3

A robust power deposition scheme for large counter-current blood vessels in tumor during hyperthermia treatment

Huang-Wen Huang

Tamkang University, I-Lan county, Taiwan

In local hyperthermia, to raise target tumor temperatures to a uniform therapeutic temperature (i.e. 43~45 ℃) with minimal injury to normal tissues is the key treating process. However, existing thermally significant blood vessels within or near a small tumor area makes hyperthermia treatment very difficult as the traditional 1st-order iterative adaptive power scheme is unable to heat the area fast during treatment[1]. Strong convective heat transfer by large blood vessels is the main reason. The objective of this paper is to investigate a new proposed fast adaptive power scheme when a pair of counter-current blood vessels (artery-vein) flowing in a treated tumor area. The new scheme with features of controlling parameters: sentinel convergence value (SCV), internal scheme shifts and high temperature residual terms, attempts to reach uniform therapeutic temperature fast in tumor during hyperthermia treatment planning (HTP). Convergence value (CV) represents normalized root-mean-square deviation (NRMSD) of temperatures and is used in the study to search optimal power density deposition. Higher order power deposition schemes (up to the 7^{th} order), two counter-current blood vessels, and various distances between large artery and vein have been proposed and tested in computer simulations. The results show the new scheme is robust with more than one large blood vessel under considerations. The scheme is capable of estimating power density deposition with accuracy in a short time and reveals "scheme mismatch" which could speed up the convergence process. And, the higher order temperature-based term acts as amplification of small-scale temperature residuals that gives us a way to resolve some application issues dealing with small-scale temperatures. Finally, a more general procedure to obtain a robust power deposition scheme offered readers a good reference to solve similar (i.e. nonlinear convective effect) issues in thermal engineering.

POS 4

Fabulous neurological recovery in spinal cord compression from solitary fibrous tumor of pleura with concurrent thermoradiotherapy : A case report.

Poompis Pattaranutaporn

Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Purpose : To report a case with spinal cord compression from solitary fibrous tumor whom had a fabulous neurological recovery after concurrent thermoradiotherapy.

Materials and Methods : A 51-year-old woman with spinal cord compression from solitary fibrous tumor of pleura failed to recovery after radiotherapy. Her motor power at consultation was grade 0. Concurrent radiotherapy and hyperthermia was given to her. Radiotherapy was 5Gy per fraction, once a week for 5 fractions. Hyperthermia of 42 Celsius for 50 minutes was performed weekly in conjunct with radiotherapy.

Results: After radiation for 25Gy and hyperthermia for 5 session with 2 additional hyperthermia alone, significant improvement on her sensation and motor power of lower limbs were observed. Motor strength of her both legs returned to grade IV. Her pain at chest wall was dramatically subsided.

Conclusions: Radiotherapy concurrent with hyperthermia showed a favorable response in solitary fibrous tumor. Its effect on neurological recovery is promising but need further study to verify this findings.

POS 5

NF-κB is involved in regulating the microRNA generating enzyme dicer during fever range hyperthermia

Anand Devasthanam[1], Thomas Tomasi[1,2]

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Dicer is a type III endoribonuclease pivotal for microRNA biogenesis, a process resulting in the generation of mature microRNAs ~22nt in length which are capable of post-transcriptionally regulating the proteome. MicroRNAs modulate multiple aspect of eukaryotic cell biology and are active players in tuning the cellular response to extrinsic stresses such as hypoxia, nutrient deprivation, viral infection, UV radiation and heat. Our previous work has suggested that fever range hyperthermia (39.5°C) induces cyclic changes in dicer protein abundance that represents a biological oscillatory phenomenon. However, little is known of the mechanism(s) involved in the oscillation responses of dicer following a mild heat stress delivered over a 24h period**.** Using western blotting and qRT-PCR analyses, we demonstrate that the oscillatory response is characterized by two distinct phases: an earlier phase (2-7h) where dicer levels are transcriptionally regulated and a latter phase (8-24h) where dicer levels are post-transcriptionally regulated. Using computational methods, we explore whether the ER stress factors NF-kB, XBP-1, ATF4, ATF6f as well as Heat Shock Factor 1 have binding sites in the *DICER1* gene promoter. We identify NF-kB as a strong candidate. Furthermore, we show that NF-κB, a well-known mediator of inflammation, interacts with a kB binding site in the *DICER1* gene promoter during the earlier phase of fever range hyperthermia treatment. This work has implications in microRNA biogenesis and gene regulation during disorders which induce elevations of core body temperature, such as those experienced during fever, certain arthritic events as well as battlefield conditions in which heat may be one of several stresses.

POS 6

Combining electromagnetic, thermal and human virtual models for MNP hyperthermia treatment planning and optimization

Fridon Shubitidze[1], Robert Stigliano[1], Levan Shoshiashvili[2], Alicia Petryk[1], P. Jack Hoopes[1]

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A key characteristic of magnetic nanoparticles (MNP) used for clinical hyperthermia is a high specific absorption rate (SAR), which depends on the applied magnetic field frequency and strength. The coil produces an alternating magnetic field (AMF), which penetrates inside tissue and not only activates MNPs in cancerous tissues, but also generates unwanted eddy currents in the normal tissues. These induced eddy currents can result in significant heating of normal tissue, thus imposing limitations on the product of magnetic field and frequency for hyperthermia treatment. In addition, recent theoretical and experimental studies have shown that the induced current's distribution (directions and magnitude) is significantly affected by biological tissue's heterogeneous electrical conductivity. Thus, in order to achieve effective and safe MNP hyperthermia, one must monitor and avoid/minimize unwanted eddy currents in normal tissues. In this work electromagnetic, thermal and human virtual models are combined for MNP hyperthermia optimization and treatment planning. Namely, a 3D alternating direction implicit finite-difference time-domain method is used to solve the coupled EM and heat transfer equations for virtual human models. The high-resolution human virtual models, together with accurate electromagnetic and bio-heat equations solvers, provide the ability to estimate and optimize eddy current distributions during MNP AMF hyperthermia treatments. The virtual human models, which were developed for evaluation of high frequency electromagnetic exposure, are based on high-resolution magnetic resonance images and have more than 80 different tissue types. Each organ's electromagnetic, thermal, and blood flow parameters are provided. Thus, our model considers realistic conditions that include blood flow and heat exchange for different biological organs. Namely, the combined model: 1) calculates and maps alternated electromagnetic field from a coil, 2) uses realistic virtual human models and estimates electromagnetic fields and eddy currents at every point in the region of interest (ROI), 3) calculates the SAR due to eddy currents and MNP in the ROI, 4) solves bio-heat equation and provides temperature and its gradient at every point in the ROI, 5) identifies best locations for temperature probes for monitoring, 6) guides eddy current mitigation and estimates AMF power values for safe treatment in clinical setting. The presented work demonstrates comparisons between modeled and actual data for various conducting, heterogeneous phantoms, and will illustrate the applicability and accuracy of the combined model for MNP hyperthermia treatment planning and optimization.

POS 7

Use of Waterbolus to Adjust Heating Patterns from Microwave Waveguide Applicators

Paul Stauffer, Dario Rodrigues, Dairu He, Mark Hurwitz

Thomas Jefferson University, Philadelphia PA, USA

Background

Superficial hyperthermia (i.e. raising tissue temperature <3cm deep to 40-45□C) has been shown in clinical trials to increase the effectiveness of radiation and chemotherapy for cancer. Although conformal heat applicators that provide better coupling to contoured anatomy are under development, the most widely used applicator for superficial heating is the microwave waveguide. With only a single power input, the user must be innovative to adjust heat treatment to accommodate variable size, shape, and depth of tumors spreading across contoured tissue surfaces. Although not well characterized at this time, it is well known that waveguide heating patterns are modified significantly via changes in waterbolus shape, thickness and temperature, as well as power and position of the applicator over tumor.

Methods

We use coupled electromagnetic and thermal simulation software (Ansys HFSS and COMSOL Multiphysics) to simulate heating patterns in superficial tumors from commercially available microwave waveguide applicators. Temperature distributions are calculated inside layered fat/muscle/tumor tissue loads for a typical range of parameters for waterbolus shape, thickness and temperature. Variable thickness waterbolus is also simulated to model coupling of a planar waveguide aperture to contoured anatomy.

Results

We demonstrate a wide range of power deposition patterns possible from commercially available waveguide antennas by controllably varying the size, thickness (0.5-4cm) and temperature (38-43□C) of the waterbolus coupling layer. Results of parametric studies provide useful guidance on use of a waterbolus to adjust heating patterns under a waveguide antenna to maintain tissue temperatures between 40-45□C.

Conclusion

Lateral and depth heating characteristics of 915MHz waveguide antennas can be adjusted over a wide range by controlled adjustment of waterbolus thickness and temperature to shift hot spot locations proactively and avoid patient pain. This approach provides higher average temperature in the tumor target and leads to more homogeneous thermal dose over a 60 min hyperthermia treatment. These treatment planning results should facilitate improved quality of treatment with commercially available hyperthermia systems in current use.

POS 8

A motion phantom for ex vivo experiments of MRgFUS in moving organs

Caroline v. Dresky[1], Florian Hagen[3], Richard Rascher-Friesenhausen[3], Daniel Demedts[1], Joachim Georgii[1], Christian Schumann[1], Tobias Preusser[1,2]

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Introduction

We focus on MRgFUS treatment of moving organs like the liver. A model based software prototype has been developed that assists in the planning and execution of the treatment. For its ex vivo evaluation we present an experimental setting, which allows for FUS sonication during controlled motion of the target tissue. The construction is suited for the simultaneous operation with an ultrasound transducer system by Image Guided Therapy (IGT) in the bore of a Siemens MAGNETOM Skyra MRI scanner.

Methods

For the realization of motion we developed a cost-efficient system based on linear actuators controlled by a microcontroller board (Arduino). It consists of two components. The motion apparatus is placed on top of the IGT positioning system such that the phantom holder is centered above the ultrasound transducer. It allows for moving the phantom in the horizontal and vertical direction. The second component holding two linear actuators is placed at the end of the MRI patient table. Two aluminum bars transmit the horizontal displacement realized by the actuators to the motion apparatus where a scissor-type jack converts one displacement into a vertical movement of the phantom holder. Due to the independent motion of both actuators objects can be moved along arbitrary 2D trajectories. MR compatibility is achieved using non-ferromagnetic materials such as brass, aluminum and engineering plastics.

Results

The motion system has been successfully tested for MR compatibility. MR images have been analyzed with respect to changes of noise and artefacts as a result of inappropriate material properties or electrical interferences. Satisfactory accuracy of the motion could be proven using an optical tracking system.

The motion system has been used to evaluate the capability of the software prototype to steer the ultrasound beam in real-time according to tracked motion. The target's position is predicted by an extrapolation of the actuators' potentiometer feedback. The position is translated into phase shift values for the transducer's elements in order to refocus to the desired position. Thermometry results show that without motion compensation the heated area forms a line, while motion compensation reduces the heated area to a spot.

Conclusion

Using the developed construction ex vivo MRgFUS experiments during controlled motion can be performed. In particular the system allows for the approximation of liver movement during respiration. Hence it enables the evaluation of software for assistance in FUS liver therapy. So far motion compensation based on tracking information has successfully been validated.

POS 9

The impact of the water bolus temperature during locoregional hyperthermia

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Introduction: Hyperthermia is a proven radio and chemosensitizer, which significantly improves clinical outcome for several tumor sites. Deep seated tumors are usually heated with radiative locoregional hyperthermia systems. These systems use a water bolus between the antennas and the patient. The function of this water bolus is twofold; it provides coupling of the electromagnetic fields into the body and it prevents hot spots at the skin by cooling. Currently, there is no univocal policy about which water temperature should be used for optimal heating. The purpose of this study was to investigate the impact of the water bolus temperature on the quality of locoregional heating by use of treatment planning.

Methods: Hyperthermia treatment planning for heating with the 70 MHz AMC-8 system was performed for five cervical cancer patients. To compare 2D and 3D steering both a single ring (4 antennas) as well as a double ring (8 antennas) were simulated. Tissue segmentation was based on Hounsfield Units and the tumor was outlined manually. Literature-based tissue properties were assigned and the electromagnetic field distribution was calculated using the finite difference time domain method. Temperature-based optimization was performed to determine phase-amplitude settings for optimal target heating by minimizing the tumor volume with a temperature below 43°C, subject to normal tissue temperature constraints of 45°C. Bolus temperatures of 10, 15, 20, 25, 30 and 35°C were considered. Optimized settings were compared and the heating quality was analyzed by comparing indexed tumor temperatures and the volume of normal tissue exceeding 43°C.

Results: Optimal phase-amplitude settings varied substantially with the water temperature. After optimization adequate tumor heating was attainable for all bolus temperatures, although slightly higher tumor temperatures could be achieved with lower bolus temperatures. For both 2D and 3D steering the T90 was on average 0.2°C higher with a water temperature of 10°C, compared to a water temperature of 35°C. For the T10 this difference was about 0.3°C and 0.2°C with 2D and 3D steering, respectively. The bolus temperature yielding the lowest volume of normal tissue exceeding 43°C varied between patients and no clear relation between bolus temperature and normal tissue heating was observed.

Conclusion: Phase-amplitude optimization allows adequate tumor heating with a tumor temperature that is not strongly dependent on the water bolus temperature in a range between 10°C and 35°C. Generally, slightly higher tumor temperatures can be achieved with a low water bolus temperature of about 10°C.

POS 10

Effects of hyperglycemia on lonidamine-induced acidification and deenergization of human melanoma xenografts

Kavindra Nath[1], David Nelson[1], Rong Zhou[1], Ronald Coss[2], Jerry Glickson[1], Dennis Leeper[2]

[1]University of Pennsylvania, Philadlphia, PA, USA, [2]Thomas Jefferson University, Philadelphia, PA, USA

Introduction: It has been long known that administration of excess glucose leads to extracellular acidification of tumors by lactate production. Acute acidification sensitizes tumors to mild hyperthermia. However, tumor acidification by glucose is limited and only mild sensitization is induced. Respiratory inhibitors such as metaiodobenzylguanidine (MIBG) will significantly increase tumor acidification but only when combined with excess glucose. In this study we sought to evaluate whether the induction of hyperglycemia (26 mM) could enhance the effects of lonidamine (LND). LND inhibits the monocarboxylate transporters 1 and 4 (MCT1 and 4) and inhibits the mitochondrial pyruvate carrier (MPC).

Methods: Lonidamine, 100 mg/kg, i.p. in glycine buffer, induces intracellular acidification, bioenergetic decline and potentiation of the activity of melphalan (LPAM) against DB-1 human melanoma xenografts in male nude mice. Hyperglycemia (26 mM) was induced for 2 hr by i.v. infusion. Magnetic resonance spectroscopy was used to determine pH, bioenergetics and lactate concentration.

Results: Intracellular pH (pHi), extracellular pH (pHe) and bioenergetics (**β**-nucleoside triphosphate to inorganic phosphate ratio, **β**-NTP/Pi) were reduced by 0.7 unit ($p<0.001$), 0.3 unit ($p<0.05$) and 51% ($p<0.05$), respectively, by LND in the presence or absence of hyperglycemia. The therapeutic response to LPAM (7.5 mg/kg, i.v.) + LND under normoglycemic conditions was a tumor growth delay (TGD) of 18 days. Under hyperglycemia, the TGD was reduced by about a factor of two relative to normoglycemia, producing a TGD of 8 da (tumor doubling time, 5 da) compared with LND alone of 1.7 da and LPAM alone of 0.3 days. The effect of LND on hyperthermia response of DB-1 melanoma xenografts is underway. LND produced little or no effect with or without glucose infusion in normal tissues: skeletal muscle, liver, brain.

Conclusion: The decreased tumor growth delay under hyperglycemic conditions correlated with an increase in tumor ATP levels resulting from increased glycolytic activity. However, hyperglycemia substantially increased lactic acid production in tumors by a factor of approximately six ($p < 0.05$), but hyperglycemia did not increase the effects of LND on acidification of the tumor, most probably because of the strong buffering action of carbon dioxide (pKa of carbonic acid = 6.4). Therefore, this study demonstrates that, unlike MIBG, the addition of glucose during treatment with LND diminishes the activity of this agent. (Supported in part by NIH R01 grants CA129544 and CA172820.)

POS 11

Photoacoustic Ultrasound-Guided Real-Time Imaging of Thermochemical Ablation in Ex Vivo Porcine Liver

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Background

Thermochemical ablation (TCA) is a novel technique for treatment of solid tumors such as hepatocellular carcinoma (HCC). Much remains unknown regarding the mechanism of ablation. Photoacoustic ultrasound-guided (PA-US) imaging detects alterations in tissue viability secondary to changes in endogenous photoacoustically active agents, such as hemoglobin, known to be rich in liver tissue due to filtration of blood. In this study, goals were twofold: (1) assess the feasibility of using PA-US imaging as a method for monitoring TCA; (2) observe TCA in real time to gain insight as to how tissue is ablated.

Materials and Methods

Ex vivo porcine liver samples were suspended in a potato dextrose agar matrix to minimize motion artifacts during imaging and subsequently covered with sterile saline. Images were acquired using Vevo 2100 LAZR (FUJIFILM VisualSonics Inc., Toronto, Ontario) PA-US small-animal imaging system (21 MHz central frequency transducer) operating at 710 nm, with B-mode ultrasonography. Three trials were run - two injecting 5 M acetic acid and 5 M sodium hydroxide simultaneously (goal ablation size 5 mm in 2 x 2 x 2 cm cubes) and one with normal saline to control for volume washout. Injections were performed through an angiocatheter. Pre- and post-ablation images were taken, as well as real-time recording of the injection itself. Data were analyzed for change in signal intensity. Gross pathology of ablated samples was observed to assess the correlation with PA-US imaging findings.

Results

In the ablated sample, local signal was seen to decrease markedly; this did not occur with the saline control and so likely is a result of TCA. Interestingly, previous studies by collaborators using high intensity focused ultrasound (HIFU) for ablation with PA-US imaging demonstrated an increase in the signal of endogenous hemoglobin; this phenomenon was putatively attributed to heat denaturation of hemoglobin, though has not yet been fully characterized. These experiments suggest that a different mechanism of action may be responsible for ablation in TCA than is in HIFU ablation.

Conclusion

TCA was successfully visualized in real-time by PA-US imaging, with zones of ablation clearly seen on both photoacoustic and ultrasound modalities. Therefore, this may be a method by which ablation can be monitored in real time. This experiment also suggests that the mechanism of TCA differs from that of HIFU. Further experiments will be needed to characterize the mechanism of ablation, such as by determining the relative contributions of thermal, pH, and concentration components.

POS 12

Use of E-field measurements in the Sigma-60 water bolus for antenna feed point correction

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In hyperthermia treatment planning, accurate translation of the predicted SAR distribution from monitor to patient is still a critical aspect. Mismatch between predicted and actual applied SAR distribution can be reduced substantially by minimizing positioning errors and apply correct phase & amplitude settings at the feed point of the antennas. Integration of an ultrasound detector at the central plane of the applicator is a straight forward approach to reduce positioning errors. Alternatively, in a hybrid BSD2000-3D-MRI system a partial body MR-scan at start of treatment can provide accurate information on the exact position of the patient.

Gellermann et al [Med. Phys. 2006] demonstrated that applying feed point correction can halve the mismatch between “Hyperplan” predicted and MRI measured SAR distribution in phantoms. Phase displacement as high as 30-45° were reported. Additional amplitude correction in the feed point further reduced the error between planning and measurement to below 10%. It is still unclear, whether this methods can be applied during patient settings as SAR measurement during treatment is more complicated.

In this study, we theoretically demonstrate that a similar effect of phase & amplitude feed point correction can be obtained by matching the E-field distribution as measured by a distinct number of fiber optic (FO) E-field sensors in the water bolus of the Sigma-60 applicator. The distortion of the E-field distribution investigated is due to a more inward curvature of the water bolus compared by the anticipated predicted set-up. In our approach we considered measurement of the actual E-field at 8 virtual FO-E-field sensors in the water bolus of the Sigma-60 applicator, equally circular distributed around the patient. From subsequent matching of measured and predicted E-fields at these 8 locations, using an earlier obtained “calibration” E-field distribution matrix, we could calculate corrected phase & amplitude settings in the antenna feed points for the set-up with the inward curved water bolus. The resulting SAR distribution with the corrected feed point setting is in close agreement with the standard water bolus, i.e. the 25% iso-SAR contour coverage difference is below 5%. As the cost of this FO_E-field sensor is relatively low, it is possible to integrate multiple FO_E-field sensors in the water bolus to continuously measure the actual E-field distribution and enable fast automatic correction of phase and amplitude settings in the antenna feed points.

Supported by the Dutch Cancer Foundation (KWF), EMCR 2009-4448, DDHK 2013-6072.

POS 13

Accurate Modelling of Laser Induced Thermal Therapy in Presence of Heterogeneous Tissue

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MR guided laser induced thermal therapy (LITT) is a safe and effective technique for heat mediated cancerous tissue destruction. Precise modelling of thermal ablation procedure is important for treatment planning and allows accurate risk assessment of the temperature fluctuations within critical structures such as brain.

The availability of heterogeneous tissue property information is the limiting factor in precise modelling of thermal ablation procedure for mathematical models of the bioheat transfer. The temperature state within a tissue critically depends on spatially varying tissue properties like thermal conductivity and optical attenuation coefficient.

In this research, the effect of the tissue heterogeneity in modelling the thermal ablation procedure is studied. In detail, the sensitivity of different tissue types and properties (thermal conductivity and optical attenuation) on modelling the thermal ablation procedure is considered. An inverse problem scheme is utilized to estimate the most suitable tissue properties by comparing the model predictions and MR thermometry data acquired during LITT in brain tumours. Estimated tissue properties are then used in the model to predict the temperature field. Results show the proposed technique leads to realistic model predictions that achieve patient specific prediction accuracy and may be useful in therapy planning.

POS 14

THERMAL-STABLE IMMUNOGLOBULIN G ANTIBODY EPITOPES IN BIOFLUIDS OF PATIENTS WITH MULTIPLE SCLEROSIS

Michael Graner, Xiaoli Yu

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

Background

A characteristic feature of the central nervous system (CNS) inflammatory response in patients with Multiple Sclerosis (MS) is the increased intrathecal synthesis of immunoglobulin G (IgG), and the presence of oligoclonal immunoglobulin bands (OCBs) in the serum, in the brain, and in cerebrospinal fluid (CSF). MS patients with the most malignant courses had raised CSF IgG levels more frequently than that of patients with a benign course (Stendahl-Brodin and Link, 1980), indicating that the intrathecal IgG may play a critical role in disease pathogenesis. Recent studies showed that B cells in the peripheral blood of patients with MS participate in OCB production, suggesting that the activation of disease-associated B cells and their secreted antibodies operate both in the periphery and in the CNS. Our objective is to identify the unique features of IgG antibodies in MS and of the protein complexes in MS patient biofluids, and the effects of high stress conditions on those proteins/complexes.

Methods

We investigated the thermal stability of IgG antibody epitopes in 11 patients with MS and 7 patients with other neurological disorders (OND). Sera and CSF samples were heated at increasing temperatures up to 95°C for 10 minutes, and a serial 5-fold dilutions (starting with 200 ng/spot) were loaded onto nitrocellulose membranes, along with the unheated sera and CSF as controls (spot blot). The membranes were probed with a 1:2000 dilution of anti-human IgG antibody (recognizing heavy and light chains) conjugated with alkaline phosphatase, followed by color detection with NBT/BCIP. We also examined heat shock protein content of the samples, and have identified scFvs that react with heat shock-related molecules screened on MS patient CSF.

Results

Heat-resistant IgG antibody epitopes were maintained in 100% (5/5) of the CSF and 42% (5/12) of the sera of MS patients. Samples from patients with OND contained heat-resistant IgG (100%, 3/3) in the CSF, but not in the paired sera (n=7). Elevated levels of HSPs were found in both groups compared to healthy donor control samples

Conclusions

Our data demonstrate the presence of thermal-stable IgG epitopes in patients with MS in their biofluids, and such antibodies are significantly enriched in the CSF. We speculate that this outcome may be due to complex formation, with initial preservation by HSPs

POS 15

A new method for triggered release of hydrophobic drugs from heat-sensitive imageable liposome

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Purpose: Low temperature sensitive liposomes can be triggered to rapidly release hydrophilic drugs (e.g. doxorubicin, DOX) at elevated temperatures (40–43 °C). However, the application of LTSL for triggered release and delivery of hydrophobic drugs (e.g. docetaxel, DTX) under image guidance to cancerous tissues remains a challenge. There is a critical need to develop a reliable encapsulation and trigger method that can limit side effects and enhance drug targeting of hydrophobic drug agents. Objectives of this study were to: 1) formulate a library of ultrasound imageable LTSLs containing DOX (D1-LTSL) or DTX (D2-LTSL), 2) characterize triggered release of drug in combination with mild hyperthermia (40-42°C) in vitro, and 3) confirm in vivo ultrasound imageability in a mouse tumor model.

Methods: D1- and D2-LTSLs were formulated with a phase changing perfluoropentane (PFP)-based ultrasound contrast agent (n-PFP (bp: 29°C) and H-PFP (bp: 42°C). Drug encapsulation and release in physiological buffer was quantified by spectroscopy. Imageability of D1- and D2-LTSL was determined in mouse tumor via ultrasound in combination with mild hyperthermia (40-42°C).

Results: D1- and D2-LTSLs encapsulated >95% of added drugs. PFP loaded D1-LTSLs showed <5% DOX release at baseline (25°C) and body temperatures (37°C), but >99% release with hyperthermia (~41°C), whereas n-PFP loaded D2-LTSL demonstrated ~80-90% release of encapsulated DTX at both 37°C & 42°C. In contrast, H-PFP loaded D2-LTSLs demonstrated <30% release at body temperatures (37°C), but >70% release with hyperthermia (~41°C). Systemic injection of PFP-loaded LTSLs in mouse while heating tumor showed an increase in ultrasound contrast as a function of temperature, lasting up to ~ 25 minutes, with maximum contrast occurring ~10 min after injection.

Conclusion: An imageable heat sensitive liposome co-loaded with DOX or DTX and US contrast agent was developed. DOX release from LTSL at 37°C and 42°C was independent of PFP-loading. In contrast, hyperthermia-mediated DTX release from LTSLs demonstrated strong correlation with PFP loading, and its boiling point. We speculate that hyperthermia-triggered release of drugs from ultrasound imageable LTSL is a function of drug chemistry (hydrophilic vs hydrophobic), and its localization (bilayer vs aqueous core). Studies using US-guided HIFU to determine image guided drug delivery from D1- and D2-LTSLs are currently in progress. Our initial data suggests that this novel technology to trigger release of hydrophobic drugs from LTSLs has great potential for clinical translation.

POS 16

Evaluation of Deep Heating Characteristics of 13.56 MHz Radio-frequency Hyperthermia Device in Phantom Models

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Oncothermia is an improved hyperthermia treatment technique, which uses modulated radio-frequency (RF) electric field to heat and destroy deeply located tumor cells without harming normal cells. In this study, we evaluated deep heating characteristics of 13.56 MHz RF oncothermia device as well as selectivity of the heating in phantom models. A homogeneous porcine meat phantom was used to observe the temperature distribution at different depths during RF heating with oncothermia device. Moreover, materials with different electrical conductivities (distilled water, egg white and saline) were used to study the selection efficacy of the heating mechanism in experimental and numerical simulation approaches in phantom models. Numerical simulation was performed using SEMCAD X software. Experimental results demonstrated high temperature increase of about 20°C even at the deepest part (20 cm) of the porcine meat phantom. Temperature increase of about 5-10°C in 20 min of time was observed, which is enough to destroy deeply seated tumor cells in clinical treatment. In the water-egg white phantom model, the temperature of the egg white increased selectively because of higher electrical conductivity while the water around it remained nearly at room temperature. This study elucidated deep heating mechanism in homogeneous phantom experiment. Moreover, selectivity of heating in different electrically conductive materials was also observed in phantom models. Although human body is more complicated than phantom models, due to the high electrical conductive behavior of tumor cells than normal cells, the possibility of absorbing more energy in tumor cells could be expected on the basis of the results of these phantom studies on the oncothermia treatment technique.

POS 17

Study on the heating characteristics of Oncothermia heating devices

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Oncothermia EHY-2000, a capacitive-type heating devise utilizing 13.56MHz RF, is widely used throughout the world for treating various types of cancer. It has been reported that this device is capable of selectively heating tumor cells because RF current is preferentially absorbed near cell surface due to the high ion concentration around the cancer cells caused by high metabolic activity of cancer cells. It is further suggested that the large temperature gradient between the intra- and extracellular temperature leads to flow of extracellular heat to cytosol, thereby causing various molecular changes in the cell membrane including activation of signaling for apoptosis. In this regard, it was reported that whereas 1 h heating of cancer cells in culture at 42°C with water-bath induced apoptosis in 4% of the cells, that with a Oncothermia device caused apoptosis in 45% of the cells. It is technically impossible to determine such microscopical temperature gradients in tissues. Nevertheless, there have been numerous studies on the heating capability of Oncothermia EHY-2000 in vitro and animal and human tumors. The purpose of the present study was to review previous reports on the heating characteristics of Oncothermia EHY-2000 and compare with our results obtained with the Oncothermia EHY-2000 in our institute. We used cylindrical agar phantom (4% agar gel containing 0.2% NaCl) of 25 cm diameter and 25 cm high. The phantom was placed on the electrode plate and coupled with a 20 cm diameter electrode placed on the top of the phantom. When heated with 150 W output power, the temperature at 5 cm deep from the top of phantom increased by almost 8°C in 60 min. The temperature in mouse tumors grown s.c. in the legs could be increased by more than 6°C in 10 min by heating with a small electrode specially made for mouse tumors. Further study on the heating characteristics of Oncothermia heating devices is in progress in our laboratory.

POS 18

Triple-Negative Breast Cancer Stem Cells (TNBC-CSC) Exhibits an Aggressive Phenotype: Role of HSPA1A-Containing Exosomes

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Triple-negative breast cancer (TNBC) is quite distinct from triple-positive breast cancer (TPBC), which is a much more aggressive disease without tumor-specific treatment options. TNBC is more difficult to treat and generally insensitive to most available hormonal or targeted therapeutic agents. We constructed a population of TNBC and TPBC by stable transfection of 4T1 cells with the rat HER2 gene, ER gene and PgR gene to avoid non-specific immune responses, and sorting using flow cytometry. Cells were injected into mice and HT was achieved using gold nanoshells, and live animal imaging was used to non-invasively measure tumor growth. We uncovered two phenotypically distinct populations of cancer stem cells (CSC) based on the expression of CD24+/ALDH-1+/CD44high cells, and demonstrated that they proliferate significantly faster than CD24-/ALDH-1-/CD44low cells or wild type controls. Exposure of TNBC-CSC and TPBC-CSC to HT, RT or HT+RT result in significantly different levels of released Hsp72. Under all conditions tested, TPBC-CSC released significantly more Hsp72 than TNBC-CSC. Western blot analysis of the 1.17 g/ml density exosome fraction (obtained from sucrose gradient ultracentrifugation) revealed that TPBC-CSC contained significantly more Hsp72 within the exosomes than TNBC-CSC. Our study suggests that the use of combined HT+RT in combination with current anti-breast cancer chemotherapeutic, known as the triple modality will be beneficial to patients with TNBC.

POS 19

Approaches for improved spatial control of microwave ablation with interstitial applicators

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Background: Currently available microwave ablation systems operate at 915 MHz and 2.45 GHz, and have been systems largely optimized towards yielding large ablation zones in highly perfused organs like the liver and kidney. Antennas in current use with clinical systems typically have cylindrically symmetric radiation patterns, offering limited spatial control of power deposition. The objective of this study was to design and evaluate two approaches for improved localization of microwave heating with percutaneous applicators.

Methods: First, we designed and characterized a 2.45 GHz microwave antenna offering directional control of heating. To achieve a directional device, a coaxial monopole antenna was augmented with a hemi-cylindrical metallic reflector positioned to limit radiation to a preferred direction. A coupled electromagnetic-bioheat transfer model was employed to optimize the antenna design. A water-cooled designed was implemented to restrict applicator diameter, and actively cool the coaxial feedline. Fabricated antennas were characterized with 10 min, 50-80 W ablations in *ex vivo* tissue. Second, we investigated the feasibility of microwave ablation at 4.75 GHz. It was hypothesized that increased electromagnetic energy absorption and lower wavelengths at 4.75 GHz would yield more rapid heating to greater temperatures and shorter antenna lengths affording improved control of heating along the antenna axis. Computational models and experiments in *ex vivo* tissue were employed to characterize a proof-of-concept 4.75 GHz ablation system.

Results: Computational models yielded an optimized 2.45 GHz directional antenna (3 mm OD) with radial penetration of the ablation zone extending to 21 mm in the forward direction, and backward heating limited to 5 mm. Experimentally measured peak temperatures in the forward and reverse directions were 92 °C and 44 °C, respectively, indicating good directional control. Experimental ablation zones (n=6) were 17.6 ± 0.5 mm in the forward direction, and 5.2 ± 2 mm in the reverse direction. Experiments with a prototype 4.75 GHz system limited to 10 W yielded ablation zones measuring 2.8 x 2.9 cm^2 after 10 min, compared to 2.5 x 4.0 cm^2 with an equivalent 2.45 GHz system. Peak temperatures measured 5 mm from the antenna were 98.1 °C and 80 °C for the 4.75 GHz and 2.45 GHz systems, respectively. These results suggest 4.75 GHz microwave ablation systems produce equivalently sized, but more spherical ablation zones than 2.45 GHz systems.

Conclusion: Microwave antennas affording improved control of spatial energy deposition patterns may serve as practical applicators for thermal ablation of targets in proximity to critical structures.

POS 20

Retrospective analysis of nerve sparing technique used in cyrotherapy of the prostate

Gary Kalser

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This study reviews an innovative technique in an attempt to reduce the incidence of impotence in post prostate cyrotherapy patients. This technique uses normal saline along with an anaesthetic to create a buffer zone between the ice ball and the neurovascular bundle. Hydodisection is performed using trans rectal Doppler ultrasound prior to the cyroablation. Preoperative and postoperative shim scores are used to analyse sexual function. Inclusion criteria preoperative are shim scores greater than 16 and patients without prior radiation or cyrotherapy. Exclusion criteria are preoperative shim scores less than 16 and patients with prior cancer treatment. Also patients that are not sexual active were excluded. Follow up is 6 months to one year

Abstracts for Friday, April 17th

FRI 1

Refresher Course: "Biological Heat Transfer Modeling Including Perfusion, Hyperthermia, and Ablation"

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The standard approach in commercial finite element modelling (FEM) packages includes the Pennes model for perfusion in addition to thermal conduction and surface convection processes. After a brief review of classical conduction and convection heat transfer the intricacies of perfusion modelling will be summarized. Ablation processes at elevated temperatures often involve significant water boiling. The course will address boiling thermodynamics and underline the errors involved in using a simple variable-specific heat approach to modelling them. If time permits, some discussion of including thermal damage models will be included.

The Pennes model of perfusion is simple to implement in both finite element and finite difference formats, but widely understood to be inaccurate: Blood may well leave control volumes of tissue at the local C.V. temperature, but almost certainly does not enter at a constant arterial temperature, especially in the majority volume fraction of all tumor-bearing tissue, which is dominated by capillary flow. In very highly perfused tissues, such as liver, representing the perfusion heat near major vessels is a delicate undertaking. Other approaches that have been used to address this issue include: 1) an "equivalent thermal conductivity" approach, which can be implemented in finite difference format, but not in finite element models, 2) a vector perfusion flux approach, and 3) the Weinbaum-Jiji approach, which is rigorous but requires extensive detailed anatomical data to implement.

At higher temperatures, water is the most thermodynamically-active tissue constituent. While variable-specific heat models are useful for solidification phase change processes, they fail to incorporate the mass defect created by vaporization of tissue water. This is important because the thermal properties of tissues are often dominantly-determined by the local mass fraction of water. The course will address the usefulness of Trezek and Cooper models in representing the residual effects of boiling processes.

Reaction kinetics, in the form of Arrhenius models, can be easily included in commercial FEM models. Time permiting, some examples will be included in the refresher course.

FRI 2

A HOT MESS: STRESS, HEAT SHOCK PROTEINS, AND EXTRACELLULAR VESICLES

Michael Graner

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Extracellular vesicles (EVs) such as exosomes and microvesicles are nano-sized, membrane-enclosed particles that are utilized in extracellular communication. EVs are released extracellularly either via "budding" directly off the cell surface, or upon the fusion of endosomally-derived multivesicular bodies with the plasma membrane. These are information-dense packages, and as a population contain thousands of proteins, assorted bioactive lipids, and an extraordinary bevy of nucleic acid species, all within viral-sized dimensions. As EVs garner increasing attention in all aspects of cell science and medicine, we find that their functions are progressively variable and interesting. However, the study of EVs released under cellular stress conditions is relatively unexplored, but likely to be an area of great importance. Cells, tissues, and organisms face stressful situations including ischemia, hypoxia, inflammation, hyperthermia, and oxidative stress, as well as metabolic, proteomic, genetic, and even psychological stress. Often, heat shock proteins are EV components that are likely prominent players in recognition of, and response to, the aforementioned stresses. This talk will discuss heat shock proteins as packaged responders to stress that can be transferred locally or systemically in the form of EVs, and will suggest potential therapeutic roles for EVs in certain pathologies.

FRI 3

Polymeric Micelles – A Transformative Technology at the Clinical Stage

Alexander Kabanov

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Polymeric micelle drug carriers were invented a quarter of century ago. Today this technology has reached a clinical stage. Nearly a dozen of drug candidates based on polymeric micelles undergo clinical trials and one product, Genexol-PM, a polymeric micelle paclitaxel, was approved for cancer therapy in South Korea. The value proposition of currently developed polymeric micelle drugs include increased drug solubility, increased extravasation and targeting to disease sites (e.g. tumors) as well as increased drug activity with respect to multidrug resistant cancers and cancer stem cells (CSC). One class of polymeric micelles is small aggregates (10 to 100 nm) formed by amphiphilic block copolymers. Hydrophobic drug molecules incorporate in polymeric micelles through cleavable covalent bonds or non-covalent interactions. Latest developments in this field include poly(2-oxazoline)-based polymeric micelles that can carry unprecedented high loading of hydrophobic drugs, such as paclitaxel, as well as blends of several insoluble drugs. Such formulations have much lower toxicity compared to conventional formulations, which use high amounts of unsafe excipients to dissolve poorly soluble drugs. Consequently, novel polymeric micelle formulations can be administered at much greater doses and are more efficient in killing cancer cells. Another class of polymeric micelles incorporates charged drug molecules and macromolecules by forming electrostatic complex with ionic block copolymers. In this format the incorporated molecules entrap into the polyion complex cores of micelles where they are protected from the biological environment by non-ionic water-soluble polymeric micelle shell. Upon reaching the target destination the micelles disintegrate and released their payload. This technology originally developed for antisense oligonucleotides, is now being used with chemotherapeutic agents, pDNA, *si*RNA and proteins. For example, extensive studies focus on the use of such systems for delivery of therapeutic enzymes (nanozymes) to the brain and other disease sites. In selected cases the nanozymes or are loaded into macrophages, which safely transport them, release at the sites of inflammation during disease. Moreover, the macrophages were shown to transduce the nanozyme particles as well as deliver genes into the host cells at the disease site. The proof of the principle has been obtained using animal models of stroke, hypertension, Parkinson's disease, eye inflammation, influenza virus infection, spinal cord injury, and other diseases. Recent work was supported by NIH (U01 CA151806, R01CA184088, R01 CA89225, R01 NS051334, P20 RR021937), NC TraCS (4DR11404), DoD (W81XWH-09-1-0386, W81XWH-10-1-0806, W81XWH-11-1-0700), Rettsyndrome.org (HeART Award #3112) and Ministry of Education and Science of Russian Federation (11.G34.31.0004).

FRI 4

Echogenic thermosensitive liposomes for image-guided drug delivery and real-time nanothermometry

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Purpose: Co-encapsulation of a chemotherapeutic agent, such as doxorubicin (Dox), and an ultrasound contrast agent into thermosensitive liposomes has the potential to reduce systemic toxicity and provide reliable means to track and induce drug release upon mild hyperthermia (~41-42°C). Objectives of this study were to: 1) develop and characterize E-LTSL, an echogenic low temperature sensitive liposome co-loaded with ultrasound (US) contrast agent (perfluoropentane, PFP) and Dox 2) compare Dox drug release, stability and imageability of PFP in E-LTSL with echogenic non-thermosensitive liposomes (E-NTSL) 3) investigate the ability of E-LTSL to report on real-time Dox release and tissue temperature in both tissue mimicking physiological phantoms and in *in vivo* mouse tumor model in combination with US-guided hyperthermia.

Methods: Dox was actively loaded into E-LTSL using a pH gradient method, while PFP was passively loaded using an innovative 1-step sonoporation method. Dox release and PFP imageability from E-LTSL was quantified by fluorescence spectroscopy, ultrasound imaging and transmission electron microscopy (TEM). Imageability of E-LTSL in mouse tumor was assessed via ultrasound in combination with mild hyperthermia (40-42°C). Comprehensive in vitro comparisons were made with E-NTSL.

Results: TEM confirmed that PFP emulsion is contained within E-LTSL. Temperature vs. size increase and drug release kinetics of E-LTSL demonstrated no difference with LTSL alone. Dox release in physiological buffer was <5% at baseline (25°C) and body temperatures (37°C), but >99% release with hyperthermia (~41°C), whereas E-NTSL showed only ~5% drug release at 42°C. E-LTSL showed a marked increase in US contrast as a function of temperature relative to E-NTSL in tissue mimicking phantom. Intensity of observed ultrasound images with respect to temperature in the range of 31-40°C correlated strongly to the formation of gas bubbles in E-LTSL, and stabilized to a fixed intensity up to the transition temperature. After the transition temperature of E-LTSL was reached, the US intensity increased again similar to Dox drug release. Systemic injection of E-LTSL in mouse while heating tumor showed an increase in US contrast as a function of temperature, lasting up to ~25 minutes, with maximum contrast occurring ~10 min after injection.

Conclusion: An US imageable heat sensitive liposome co-loaded with Dox and US contrast agent was developed. Stability, imageability, US monitoring of contrast agent, and Dox release suggest that US-guided drug delivery from E-LTSL may assist physicians in real-time tumor drug delivery mapping and nanothermometry. Studies using US-guided HIFU to determine image guided drug delivery using our E-LTSL are currently in progress. This technology has great potential for clinical translation.

FRI 5

Preliminary clinical experience of magnetic resonance guided focused ultrasound surgery for bone metastasis in Taiwan.

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Background/Introduction: Bone metastasis is one of the major causes responsible for cancer related pain worldwide. Recently, magnetic resonance guided focused ultrasound surgery (MRgFUS) has been approved as a treatment strategy for pain palliation of bone metastasis by US FDA. Herein we report the first clinical experience in Taiwan.

Methods: Between May 26th and Nov 29th in 2014, total 20 patients with painful bone metastases were evaluated and treated by MRgFUS at Taipei Cancer Center, Taipei Medical University in Taiwan. The MRgFUS treatment was conducted using the ExAblate 2000 system (InSightec Ltd., Israel), which integrates a focused ultrasound phased array therapeutic compartment with a GE 1.5T magnetic resonance (MR) imaging scanner. Therapeutic ultrasound waves were targeted to the painful bone metastatic sites while monitoring the accumulated heat using real-time MR images. The treatment response of MRgFUS was evaluated by the interval change of numerical rating scale (NRS) before treatment, at 1 and 3 days; 1 and 2 weeks and 1 and 3 months after treatment. Pain relief is defined as a reduction of 2 points or more on NRS pain scoring system.

Results and Conclusions: The median age of the 20 treated patients (14 male and 6 female) was 56 years old (range, 40–83). Each patient underwent MRgFUS treatment for a single lesion. The majority of treatments were aimed at lesions located in the pelvis (14 sacroiliac joints and 2 ilium), two at the limbs and two at the sternum. None of the patients experienced any procedure related adverse events and the treatment was tolerated well by all. At a median follow-up duration of 198.5 days, significant pain relief ($p < 0.01$ by pair t-test) is observed between each time point (Pre-treatment, Day 1, Day 3, Week 1, Week 2 and Month 1). At day 1 post-treatment, 80% of patients experienced pain relief (median 3.6 points reduction on NRS) from median baseline NRS of 6.55 (range, 4–8). On the second week, 85% of patients reported pain relief (median 2.98 points reduction on NRS). By the first month after treatment, the median NRS decreased to 1.5 (range, 0-5, P=0.001) and 30% of the patients declared complete response (pain score decreased to 0). The median length of the procedure (patient walk-in to walk-out) was 01:42 hours (01:05 to 02:20 hours), of which the median treatment time was 47 minutes.

FRI 6

TRANS-FUSIMO – Software support for clinical application of MRgFUS in the liver

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Treating liver tumors with MR-guided focused ultrasound (MRgFUS) presents tremendous technological challenges due to target displacement by breathing motion and shielding effect of the ribcage. We aim at a software system that assists in planning and conducting FUS procedures in moving abdominal targets like the liver, with the goal an efficient, effective and safe treatment. In the EU project FUSIMO (2011-2013) a software demonstrator for the patient specific planning of FUS in the liver has been developed. The EU project TRANS-FUSIMO (2014-2018, www.trans-fusimo.eu) translates this software into a system that is fully integrated with imaging and FUS hardware and that allows for planning, conducting and assessing a FUS treatment of the liver. The key-technology behind the FUSIMO software demonstrator is a set of dynamic organ models for the physical and biophysical processes involved in FUS treatment: (i) an abdominal motion model simulates the patient specific deformation of the organ and relevant anatomical structures during breathing; (ii) a patient specific tissue model represents the ultrasound propagation, the energy deposition as well as the tissue heating and cooling; (iii) an organ/tumour model captures the patient specific tissue's response to the therapy. The proposed software system orchestrates the interplay between the model components. In particular it parameterizes the model components with patient specific data that is extracted from patient specific pre- and intra-interventional imaging data like MRI and/or US imaging data. The system including the dynamic organ model is being validated in phantom and ex vivo experiments as well as in Thiel soft embalmed cadavers. In TRANS-FUSIMO an in-vivo animal trial will be conducted to show safety, efficacy and efficiency of the software system. The last stage of the project will be a human patient study showing the applicability of the TRANS-FUSIMO system in the clinical setting. In conclusion, the resulting integrated TRANS-FUSIMO software system shall support patient specific planning, conducting and monitoring of an abdominal FUS treatment. Our ex vivo experiments show that the demonstrator is capable of compensating organ motion through real-time motion detection using US-tracking, motion modelling and real-time beam steering. The fully integrated system will be evaluated by in-vivo animal studies and a first patient study that shall show that MRgFUS in moving organs can be performed safely, efficaciously and effectively. Acknowledgements: The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreements no. 270186 (FUSIMO) and no. 611889 (TRANS-FUSIMO).

FRI 7

In-vitro evaluation of thermal dose accuracy for high intensity focused ultrasound hyperthermia therapy: MRgFUS experience.

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Background/Introduction:

High intensity focused ultrasound (HIFU) has performed its non-invasive heating capability for tumour treatment. Magnetic resonance image (MRI) guided HIFU surgery has been initially proved for uterine fibroid. ExAblate MRgFUS system (Insightec, Israel) recently demonstrated hyperthermia application for malignant bone metastasis palliation and been certificated by US FDA. HIFU beam projects ultrasound power at precise local bone cortex. In order to protect nearby critical organs, thermal dose should be delivered correctly to treatment area within a short period. Over 56°C/sec heat shock theoretically creates thermo necrosis in human tissue. MRgFUS system embedded proton resonance frequency (PRF) algorithm to monitor real time temperatures. Hence, we reported heating calibration protocols and thermal dose, which integrates true temperature measurement and PRF readout at target spots.

Methods:

ExAblate 2000 system (Insightec, Israel) installed in Taipei Medical University and was used to treat bone metastasis for severe pain patients. This system contented a 1.5T GE magnetic resonance system and a phase array transducer with 208 independent HIFU elements. During entire evaluation processes, each sonication spot was delivered ultrasound energy (from 433J to 960J) in 20 seconds at daily quality assurance (DQA) phantom. We simultaneously used an insulated thermocouple wire (Thermoway co., Taiwan) to detect true temperature and compared with PRF temperature. Base on these data, thermal dose was calculated by Sapareto's TD43 equivalent minutes. Statistical analysis distinguished significant differences for various sonication duration, energy, depth spot position and transducer angle. Moreover, multiple regression and Matlab models validated correlation of dose bias.

Results and Conclusions:

This report has demonstrated a further evaluation to assure temperature accuracy for MRgFUS treatment. In order to investigate the reliability of thermal dose, this method mimicked similar condition of bone cortex treatment by DQA phantom and thermal couple grid. Both PRF values and thermal couple readouts showed a consistent trend during modulating sonication energy. Sonication trend and thermal dose also showed a significant correlation by Pearson's correlation coefficient. These results indicated that PRF imagine thermometry remained acceptable accuracy to endorse treatment safety. However, transducer movements created projection bias in deeper targets, which may need to be

considered as a confounding factor for treatment planning. Furthermore, this method also demonstrated potentials to improve treatment accuracy and convenience.

FRI 8

MR-HIFU hyperthermia for drug delivery: translation to a clinical platform for pediatric applications

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Introduction: Previous studies have demonstrated the feasibility of using MR-HIFU to trigger drug release from thermosensitive liposomes (TSLs). Translation to humans requires robust hyperthermia algorithms on commercial MR-HIFU systems, as well as indication-specific heating strategies and dose levels. Our goal is to apply MR-HIFU hyperthermia-mediated doxorubicin (DOX) release from TSLs as a neoadjuvant therapy for pediatric sarcoma. Localized high-dose DOX delivery and reduced drug deposition in critical sites of long-term toxicity such as the heart could improve outcomes. To determine heating and drug administration protocols for human trials, we are conducting large animal studies to identify the effects of heating duration and injected dose on the therapeutic index between DOX concentrations in targeted tumors vs. the heart. Here we evaluate the ability to use a clinical MR-HIFU system to achieve mild hyperthermia in rabbit Vx2 tumors for fixed durations of 10, 20, and 40 minutes.

Methods: Rabbits had Vx2 cells injected into each thigh 12 days before therapy. For each rabbit, one tumor was heated using the Philips Sonalleve MR-HIFU system with modified software designed for mild hyperthermia. Automatic control of heating was based on MR thermometry acquired in 6 slices every 3.2 seconds. The feedback control algorithm aimed to maintain 42°C in a 10 mm diameter region centered on the tumor, switching power off if temperature above 43°C was observed on any slice across the beam. MR-HIFU hyperthermia was delivered to one tumor in each rabbit for 10, 20, or 40 minutes. During heating, TSL-DOX (Thermodox, Celsion Corporation) was administered intravenously at 2.5 mg/kg over 5-6 minutes. Rabbits were sacrificed and perfused with saline 30 minutes post heating, and tissue samples were harvested for DOX quantification

Results: Treated Vx2 tumors (n=10) had diameters of 17.2±3.1 mm. During hyperthermia, mean temperature in the 10 mm diameter target region was 42.4±0.3°C, with T90 and T10 of 41.3±0.5°C and 43.4±0.2°C. Temperature outside the heated region was 36.0±0.5°C, with a temporal SD of 0.4±0.05°C. The region exposed to 41-45°C for at least 10 minutes had a diameter of 12.2±0.9 mm and length of 34.5±14.0 mm. For planned sonication durations of 10, 20 and 40 minutes, the target region had a mean time in the 41-45°C range of 10.7, 19.9, and 40.4 min.

Conclusions

Mild hyperthermia was consistently achieved in rabbit Vx2 tumors for durations of 10, 20 and 40 minutes using a clinical MR-HIFU system. This capability will be used in studies of hyperthermia-mediated drug delivery.

FRI 9

MR-HIFU mild hyperthermia as an adjuvant to radiotherapy and chemotherapy for recurrent rectal cancer: preliminary validation studies and clinical trial design

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OBJECTIVES: Our goal is to conduct a clinical trial investigating the safety of MR-HIFU mild hyperthermia as an adjuvant to radiation and chemotherapy for recurrent rectal cancer. Here we present results from a preclinical evaluation of MR-HIFU mild hyperthermia in pelvic locations typical of recurrent rectal cancer, and a prospective imaging-only study in volunteers with rectal cancer...

METHODS: The safety and performance of MR-HIFU mild hyperthermia was evaluated in a preclinical study, in normal muscle targets close to locations of recurrent rectal cancer. Mild hyperthermia was performed in pig thigh muscle (9 sonications, 6 pigs) using the MR-HIFU system. Thermal maps were used to automatically control sonications in 18mm diameter treatment regions to achieve temperatures of 42-42.5°C for 10-60 minutes. Heating accuracy in targets near the rectal wall and deep thigh were evaluated.

RESULTS: In pigs, mean target temperature accuracy and precision were 0.2°C and 0.5°C. No evidence of tissue changes was observed on contrast-enhanced imaging or at necropsy. MR temperature measurements made in human volunteers showed adequate precision and stability, especially with rectal filling. Temperature precision and stability without rectum filling were 7.25°C and 2.95°C. With rectum filling, precision and stability were 0.85 and 0.48°C.

MR-HIFU accessibility and MR thermometry quality near the rectum was evaluated by a prospective imaging study in volunteers with rectal cancer. Anatomical and MR thermometry images were acquired in 6 consenting volunteers with rectal cancer. Subjects were positioned on the MR-HIFU tabletop (Sonalleve, Philips Healthcare) in the MRI scanner (Achieva 3T, Philips Healthcare). In 4/6 subjects, rectal filling with saline was used to reduce motion-related artefacts. Thermal maps were obtained in 6 planes every 3.2s. The quality of thermometry was assessed based on its stability and precision.

CONCLUSIONS: In pigs, MR-HIFU can safely deliver mild hyperthermia (41-43°C) to a targeted volume for 30 minutes. Careful patient selection and preparation enable adequate targeting depth for recurrent rectal cancers, with sufficient MR temperature mapping stability to control mild hyperthermia. These results support the initiation of a pilot human trial assessing acute toxicities and treatment feasibility of MR-HIFU hyperthermia given in addition to radiation and chemotherapy. The primary objectives of the planned prospective, single-arm clinical trial will be to assess acute toxicities and treatment feasibility in

20 patients. Secondary objectives will include assessment of late toxicities, pain reduction, quality of life, and radiologic response, plus evaluation of treatment workflow, thermally-induced tissue changes, and accuracy of treatment delivery.

FRI 10

Engineered Prussian blue nanoparticles for photothermal therapy of tumors

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Photothermal therapy (PTT) using nanoparticles is an attractive and minimally invasive thermal treatment option for tumors. In this treatment modality, near infrared absorbing (NIR) nanoparticles that accumulate within tumors (or are intratumorally injected) are irradiated with a low power NIR laser resulting in rapid heating and ablation of the tumors. Since heating is minimal in the absence of the nanoparticles, nanoparticle-based PTT serves as a precise, activatable method for tumor ablation with minimal bystander effect resulting in more favourable tumor treatment outcomes.

In this work, we describe the novel use of Prussian blue nanoparticles, a dye first synthesized in the early 18th century, for PTT of tumors. The Prussian blue nanoparticles, which are comprised of mixed valence iron hexacyanoferrate, were synthesized using a modified, facile, one-step synthesis scheme. The resultant nanoparticles were ~70 nm in hydrodynamic size and were stable in both water and physiological media as measured by dynamic light scattering. The Prussian blue nanoparticles exhibited an absorbance peak at NIR wavelengths (650 – 900 nm), and had a photothermal conversion efficiency of 20.5% at 808 nm.

As proof-of-concept, the PTT capabilities of the Prussian blue nanoparticles were tested in a mouse model of neuroblastoma. Neuroblastoma is the most common type of extracranial solid tumor of childhood constituting roughly 7% of all newly diagnosed cases of childhood cancer. About 60% of neuroblastoma patients present with advanced disease at diagnosis making it one of the most difficult tumors to treat. The various treatment options used to treat advanced neuroblastomas including surgery, chemotherapy, retinoid therapy, radiation therapy, high-dose radiation therapy/chemotherapy with stem cell transplant, and immunotherapy have made incremental but limited progress for this patient population. Therefore, a less invasive and more precise means for debulking advanced neuroblastomas would be a major step forward in the management of this disease.

In the neuroblastoma mouse model studies, the Prussian blue nanoparticles were intratumorally injected and irradiated with an 808 nm NIR laser. PTT using the Prussian blue nanoparticles resulted in rapid and marked tumor debulking relative to controls. The treatment also resulted in decreased tumor growth rates, and increased survival in PTT-treated mice relative to control mice. These results demonstrate the potential of the Prussian blue nanoparticles as an effective treatment option for tumors.

FRI 11

Evaluation of Exotherms of the Polyamine Spermine Analog, Diethylenetriamine With Partial to Complete Neutralization by Acetic Acid

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Purpose: To evaluate the exothermic potential of the polyamine diethylenetriamine (DETA) in reactions with one, two, and three equivalents of acetic acid (AcOH).

Materials and Methods: Aqueous DETA (200µL, 1-3M) was injected into a gel phantom containing an equal volume of AcOH with up to 3 equivalents of acid corresponding to full neutralization of the triamine. Temperature change was measured with a thermocouple probe and results from triplicate runs were averaged.

Results: Peak temperatures were reached within 10-15 seconds of injection in most cases, with higher concentrations reaching 60-70°C. As the concentrations of base increased, so did the temperature. Peak temperatures increased further with increased equivalents of available AcOH with the highest temperature change seen with full neutralization using 3 concentrations of DETA.

Conclusion: DETA neutralization releases more heat energy with increased equivalences of AcOH, releasing the most energy with full neutralization. The elevated temperatures associated with the higher concentrations of DETA and AcOH and the pharmacologic activity of DETA support further study for potential use in the thermochemical ablation of tumors.

FRI 12

Investigating Thresholds and Mechanisms of Injury in Multiple Cell Types after Cryo, Heat and Electroporation Focal Therapies.

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Cryotherapy, heat and irreversible electroporation (IRE) are minimally invasive focal therapies increasingly used in cardiovascular, cancer and neural disease. We present here an initial comparative study of the mechanism and thresholds of one therapy vs. another in three cell types: HL-1 (cardiac), LNCaP (prostate), and CLU-172 (neural). For freezing experiments, the cooling rate (CR, 0.5 - 130 ^{o}C/min), end temperature (ET, 0 - -60 ^{o}C), and hold time (HT, 0 - 5 min) were varied while all samples were subsequently thawed rapidly at 130 ^{o}C/min. The peak post-thaw survival rates using a Hoechst-PI (HPI) dye exclusion assay at ET = -20 ^{o}C (n=6) were HL-1 = 31%, LNCaP = 31%, CLU-172 = 72%, at CR = 5 ^{o}C/min. Additionally, survival rates at ET = -60 ^{o}C with CR = 5 ^{o}C/min were HL-1 = 4% and LNCaP = 7%. For heating experiments, the cells were heated at 5 ^{o}C/min to various ET (40 - 70 ^{o}C) then cooled rapidly (130 ^{o}C/min) back to 25 ^{o}C to insure that the major injury occurred during heating. For instance, the temperatures at which the majority of cells (% viability value in parenthesis) had been destroyed (by HPI assay) were HL-1 = 60 ^{o}C (97%), LNCaP = 65 ^{o}C (95%), and CLU-172 = 60 ^{o}C (98%). Using Differential Scanning Calorimetry (DSC) we were able to measure the protein denaturation during the same heating protocols, and correlate it to cellular destruction. For instance, the % total cellular denaturation was 35% at 60 ^{o}C for HL-1, 23% at 65 ^{o}C for LNCaP, and 24% at 60 ^{o}C for CLU-172. Thus, only a minority of protein denaturation needs to occur before complete cell death in all cells, although somewhat more was needed in HL-1. For electroporation experiments, the electric field (250 - 2500 V/cm), pulse duration (10 - 100 us), and number of applied pulses (10 - 99 times) were varied with the pulse frequency set at 10 Hz. Based on viability assays (HPI) the initial injury threshold where viability was first observed to be less than 90% was determined to be 750 V/cm with 99 50-us pulses for all cells (HL-1 = 76%, LNCaP = 86%, CLU-172 = 75%), while the complete injury threshold where viability was first observed to be less than 10% was determined to be 1250 V/cm with 99 50-us pulses for all cells (HL-1 = 4%, LNCaP = 10%, CLU-172 = 6%). Interestingly, while previous work has demonstrated that lipids are important in defining IRE thresholds, we demonstrate here that IRE also dramatically reduces viable native protein using a novel DSC protocol. In summary, viability reduces below 50% for cryotherapy for both LNCaP and HL-1, but not CLU-172 at -20 °C by dehydration and IIF mechanisms. Heat was able to destroy HL-1 and CLU-172 at 60°C although LNCaP required 65°C by mechanisms correlated to protein denaturation. Finally, IRE demonstrated that for all cell types 1250 V/cm was required to induce more than 90% of cell destruction under pulse conditions of 50 us duration, 99 repeats, at 10Hz. While very preliminary, this study begins to probe the relative mechanisms and thresholds for each therapy in three key target cell types. This study therefore provides a beginning framework for comparison and selection of one therapy over another for a given cell type, and by future extension, disease.

FRI 13

The effect of heat treatment in Sarcoma 180 cells: Comparison between *in vitro* and *in vivo*studies

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It is well known that heat develops an independent cytotoxic effect on cultured cells in vitro at temperatures around 43 °C, at least human ones. In order to Investigate the effect of heat in Sarcoma-180 cells *in vitro*, the murine sarcoma-180 tumor cells (S180) (ATCC # TIB-66) were cultured in suspension in RPMI 1640 medium respectively, supplemented with 10% fetal calf serum, 100 mg/mL penicillin, and 100 mg / ml streptomycin. The cultures were incubated in a humidified incubator at 37 °C with 5% CO_2. After 24 hours, the cell culture was quantified in 5 x 10^5 and mesured by flow cytometry. The cells were heated for 30 min by thermal bath in 41ºC, 42ºC, 43ºC, 45ºC, 46ºC, 48ºC, 50ºC and 60 °C. After each treatment, the cells were analysed by flow cytometry. Further, other experiments with distinct heating times at 48 °C for up to 60 min were evaluated. After the period of treatment, the assay of viability was performed to detect the cell death by apoptosis and necrosis through flow cytometry analysis. The data were analized by Cell Quest software. Within 60 min, there was no reduction in the amount of viable cells in any group treated with temperatures from 41 to 46oC when compared to the negative control. Only in the temperature range from 48 to 50 °C observes a statistically significant reduction in the number of viable cells. There was also a significant increase in early and late apoptosis in three temperatures, namely 48, 50 and 60 °C. In particular, the temperature of 60^{o}C showed 1.26% initial apoptosis and 86.32% of late apoptosis and 10.02% of necroses and only 1.2% of viable cells in comparison to the negative control. There was a statistically significant increase also in the treatment of late apoptosis at 48 and 60^{o}C, with 28.48% and 28.77%, respectively and with a minimal increase in the amount of necrotic cells for the same temperatures, compared with the negative control. In addition, the analysis of the data suggests the possibility of a more complex death pathway, as for instance parthanatos and netoses. Although other tests should be carried out in order to confirm this mechanism. Finally, all the in vitro data gives support to our *in vivo* studies, which showed total tumor regression response for temperatures around 48C after magnetic nanoparticle hyperthermia procedure.

FRI 14

Bacterial Lipopolysaccharide (LPS) Augments Expression and Extracellular Release of HSP70 in Cells Exposed to Febrile Range Hyperthermia (FRH)

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Sepsis, SIRS (systemic inflammatory response syndrome) and ARDS (acute respiratory distress syndrome), often lethal complications of severe infection, account for more that a quarter million deaths and about 15 billion dollars in hospital expenses annually in the US alone. Generally characterized by fever and persistent dysregulated inflammation, SIRS and sepsis progress into multi-organ injury and death despite clearance of invading pathogens by antibiotics. While infections activate the inflammatory response in part through Toll-like receptors (TLRs), fever activates the heat shock (HS) response and induction of heat shock protein (HSP)-70 and the combination further augments the expression and extracellular release of HSP70. Using differentiated human THP1 cells we found that concurrent exposure to febrile range hyperthermia (FRH; 39.5°C) and bacterial lipopolysaccharide (LPS) as well as TLR2 and TLR3 agonists synergized to activate expression of inducible HSP72 (HSPA1A) mRNA and protein via a p38 MAP kinase-requiring mechanism. Co-exposure to FRH and LPS also increased extracellular release of HSP70 roughly paralleling the increase in intracellular levels in the FRH/LPS-co-exposed cells. Release of extracellular HSP70 in FRH/LPS-co-exposed THP1 cells was sensitive to inhibition by glibenclamide, but not brefeldin, indicating mediation of non-classical protein secretory mechanisms. Furthermore, co-exposure to FRH and LPS also increased the secretion of exosomal vesicles in the cell culture media. To determine whether extracellular HSP70 was secreted via the exosomal route we analyzed HSP70 levels in exosome-depleted culture supernatants from FRH/LPS co-exposed THP1 cells and found that HSP70 levels in un-fractionated and exosome-depleted culture supernatants were comparable indicating that LPS-stimulated HSP70 release did not occur via the exosome pathway. Immunoblot analysis of the exosome fraction of culture supernatants from these cells showed constitutive HSC70 (HSPA8) to be the predominant HSP70 family member present in exosomes. Thus LPS, in synergy with FRH, increases both intracellular expression and extracellular secretion of HSP70 that is mediated via a non-classical, non-exosomal pathway for protein secretion. The impact of increased macrophage intracellular HSP70 levels and augmented secretion of proinflammatory extracellular HSP70 in the febrile, infected patient remains to be elucidated.

FRI 15

Synergistic cytotoxic effects of combined thermal and osmotic stress are consistent across multiple cell lines.

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Background

The cell response mechanisms to simultaneous thermal and osmotic stress as generated in thermochemical ablation (TCA), the potential for synergistic cytotoxic effects, and how the combination treatment leads to cell death are unknown. In one variant of the TCA platform, using acetic acid neutralized with sodium hydroxide, the product is sodium acetate (NaOAc) along with release of heat energy. At the margins of a TCA lesion, the concentration of the salt would be low and the hyperthermia would be both mild and relatively short in duration. We report on the assessment of the relationships between exposure times, osmotic stress from salt exposure, and thermal dose on liver cancer cells in vitro.

Methods

Viability and clonogenicity of human and rat liver cancer cell lines, specifically Hep3B, HepG2, and McA-RH7777 cells, respectively, were assessed after exposure to increasing concentrations of NaOAc (0-800mM), at 37°C or 43°C, for time periods of 1h or 3h. Triplicate samples were run in each case and experiments were repeated three times.

Results

Cytotoxic effects without thermal stress were generally apparent between 200 and 400 mM added NaOAc. Cells in all cases were very sensitive to combined thermal and osmotic stress and, as expected, were more sensitive with longer exposure times. In both HepG2 and McA-RH7777 cells toxicity was observed with as low as 100 mM added NaOAc for 1 h a 37°C. Hep3B cells appeared most robust, although at 3h and 43°C all but controls fared poorly. Clonogenic assays likewise demonstrated added toxic effects with combined stresses.

Conclusion

Combined thermal and osmotic stresses show evidence of synergy. This suggests that the marginal zone would be expected to be cytotoxic even in areas subject to heat sink in normal ablations. Thus TCA may prove effective in lowering local recurrences rates in tumors such as hepatocellular carcinoma. Further work to clearly define more specifically the mechanisms and thresholds for effects is warranted.

FRI 16

Tumor specific drug uptake prediction for Temperature sensitive liposomes

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Introduction:

A considerable number of interrelated transport properties depending on drug, drug delivery system (DDS), and tumor physiology determine amount of drug taken up by a tumor. Computational model could aid in examining and explaining drug delivery kinetics, and serve as tool for optimizing DDS for a particular drug and tumor.

Methods:

Intravital fluorescence microscopy studies were performed in a window chamber mouse model, where tumors based on the Lewis Lung Carcinoma cell line were grown. In each mouse (n=7), a 1x1 mm tumor segment was imaged. Images were obtained at 1/s rate following bolus administration of unencapsulated carboxyfluorescin (CF). Several tumor transport properties were calculated from these data, including vascular fraction, permeability-surface area, perfusion, and clearance. After the dye has cleared, temperature sensitive liposomes (TSL) filled with CF were administered, and the same segment was imaged every 10 s while hyperthermia at 42 ºC was applied for 10 min. Intra- and extra-vascular fluorescence time course was determined from these data. Based on the tumor transport properties and considering in vitro measured TSL release kinetics, multi-compartment computer models were employed to predict amount of drug delivered to this tumor, and results compared to measured fluorescence.

Results:

The observed differences in dye delivered to tumor segments could be explained by variations in tumor transport properties between different tumor segments. Tumor segment transit time was the most important factor affecting amount of dye delivered to a particular tumor segment. There was good correlation between computer model predictions and experimental data (R^2=0.7).

Discussion:

Computer models could predict amount of drug delivered to a particular tumor segment based on tumor transport properties of that segment, and on TSL release kinetics. Such models may have application in design and optimization of TSL and other DDS, and for tumor specific prediction of drug delivery.

FRI 17

Hyperthermia mediated change in biofilm matrix microenvironment in combination with antimicrobial loaded Thermally Sensitive liposomes improves bactericidal activity

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Purpose: Bacterial biofilms found in soft tissue wounds and prosthetic implants are complex structural communities of one or more species of drug-resistant bacteria embedded in an extracellular polymeric substance (EPS). Current methods of treatment are limited in killing biofilm bacteria due to protection the EPS offers and toxicity associated with antimicrobial therapy. Objectives of this study were to: 1) develop antimicrobial (e.g. ciprofloxacin) encapsulated low temperature sensitive liposomes (LTSLs), 2) determine stability of ciprofloxacin encapsulation and characterize its release from LTSL in physiological media and 3) investigate the ability of mild hyperthermia (41-42°C) and LTSL combination in inducing EPS structural change and bacterial killing.

Methods: LTSL was actively loaded using a pH gradient loading with ciprofloxacin, a broad spectrum antibiotic and characterised for size using dynamic light scattering (DLS) and release in physiological media (PBS) by fluorescence spectroscopy. Therapeutic efficacy of LTSL in combination with hyperthermia was determined by establishing a high throughput MBEC screening of Staphylococcus aureus. The mechanism of EPS structural change in the presence and absence of LTSL & hyperthermia was determined by scanning electron microscopy (SEM). Treatment groups were compared for differences in mean bacterial killing using ANOVA followed by Tukey's multiple comparisons using GraphPad Prism 6 ($p<0.05$).

Results: The hydrodynamic diameter of LTSLs measured by DLS was ~160 nm. Active loading of Ciprofloxacin in LTSL yielded an encapsulation efficiency of > 95%. Ciprofloxacin release in physiological buffer was <5% in 1 hr at baseline (25°C) and body temperatures (37°C), vs. >99% release with hyperthermia (~41°C) in PBS. Efficacy determination using MBEC assay showed LTSLs in combination with mild hyperthermia resulted in significant reductions of S. aureus (~90%) compared to LTSL or free ciprofloxacin at 37°C (~60-70%). SEM demonstrated significant structural change (e.g granularity and roughness) in the EPS of biofilms exposed to hyperthermia plus LTSL. Additionally, the coccus S. aureus bacteria appeared deformed and possibly damaged, and was less than uniformly spherical.

Conclusion: An antimicrobial loaded LTSL with high stability and >95% encapsulation efficiency was developed. Efficacy of the synthesised LTSLs in combination with hyperthermia significant improved killing of biofilm causing bacteria. Adding hyperthermia to biofilm therapy can induced EPS structure change and can sensitize pathogens to respond favourable to chemotherapy. More detailed in vivo to determine the therapeutic efficacy of LTSL-hyperthermia combination technology against hard-to-treat chronic wounds is currently in progress. This novel technology has potential for clinical translation.

FRI 18

Body Warming to Alter [thermo]Regulation and the Microenvironment [B-WARM] Therapy: A Pilot Study

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Thermoregulation in normal tissues is a rapidly reversible process that is mediated by the presence of a structurally mature (covered by smooth muscle cells) vascular network with autonomic innervation. In contrast, tumors possess defective blood vessels that often lack a smooth muscle, so they can't effectively control heat distribution. Our published murine data demonstrates that body warming to alter [thermo]regulation and the microenvironment [B-WARM] normalizes interstitial fluid pressure, reduces tumor hypoxia, and enhances radiation sensitivity up to 24 hours post heating.

Herein, we report initial results from a pilot clinical study to determine the feasibility and efficacy the B-WARM regimen (39°C for 2 hours) on altering tumor blood flow in patients with a variety of malignancies. The primary objective is to determine the extent and duration of effects of B-WARM on blood flow in a variety of tumors with CT angiography (CTA). The secondary objective is to investigate whether thermal imaging of the skin, in tumor region, correlates with changes in blood flow in the tumor.

Initial results suggest that B-WARM increases the rate of blood flow and volume in the tumor, and it remained nearly double for 5 days, compared to baseline. The thermal imaging data suggest that changes in skin temperature are associated with changes in blood volume in the tumor.

These encouraging results indicate that B-WARM may be effective in sensitizing tumors to radiation therapy, and thermal imaging could be useful in monitoring the changes in blood flow and volume, during B-WARM.

FRI 19

Magic Bubbles: Sensitizing Nanoparticles for Targeted Enhancement of Tumor Thermal Ablation and Radiotherapy

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Introduction: Thermal ablation and radiotherapy are frequently utilized for treatment of solid tumors that are otherwise unresectable or untreatable. While effective in initial reduction of the tumor burden, these loco-regional approaches often result in incomplete destruction of larger tumors and are thus associated with local recurrence. We have developed a simple self-assembled therapeutic nanoparticle that can augment treatment volumes and reduce local recurrence associated with these approaches to improve therapeutic outcomes.

Methods: The foundation of the nanoparticle is the nonionic surfactant, Pluronic. Pluronics, also known as poloxamers, are a family of triblock copolymers of polyethylene oxide (PEO) and polypropylene oxide (PPO), following the general structure of EO_x-PO_y-EO_x where x and y vary and subsequently lead to a wide range of bioactivity. Pluronics have been extensively studied for their chemosensitizng activity in multidrug resistant cancers and comprised the first micelles evaluated in clinical trials for delivery of chemotherapy in pioneering work done by Kabanov *et al*. In addition to the structural and chemosensitizing functions, our group has shown certain Pluronics to be potent and cancer-selective thermal and radiation sensitizers, potentially through modulation of heat shock protein 70 and 90 expression [Int J Hypertherm 2011;27(7):672-681, Int J Rad Bio 2013; 89(10):801-812]. To fully utilize these far-reaching capabilities, we incorporated Pluronic into the membrane of gas bubbles which are similar in structure to clinically-utilized ultrasound contrast agents (microbubbles).

Results: The resulting lipid and Pluronic-stabilized perfluoropropane gas nanobubbles are approximately 100 nm in size yet highly echogenic at clinically relevant frequencies (3-12 MHz), carry the bioactive thermal and radiation sensitizer in their membrane, and are susceptible to ultrasound-mediated activation at the tumor site. These unique features make Pluronic nanobubbles ideal for ultrasound-guided administration and deployment. When Pluronic nanobubbles were used in conjunction with radiofrequency ablation of human LS174T colorectal tumors in mice, the combination approach was significantly more effective than ablation alone [Pharm Res 2014;31(6):1407-1417].

Conclusion: We are currently working on expanding the capabilities of the nanoububbles by functionalizing them to facilitate early tumor detection via ultrasound molecular imaging and by developing constructs with enhanced stability and cargo space for better on demand drug delivery. Taking advantage of the excellent safety profile, broad accessibility and low cost of ultrasound and the remarkable qualities of Pluronic, the multifaceted theranostic nanobubbles can considerably broaden the reach of ultrasound in future applications focused on the diagnosis and treatment of cancer.

FRI 20

Biodegradable plasmonic nanoparticles for cancer imaging and therapy

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Many inorganic nanoparticles such as gold are intrinsically multimodal and, therefore, are of great interest in a number of critical clinical applications in cancer healthcare including early detection, diagnosis, image guided therapy, therapy monitoring, externally triggered drug delivery and enhancement of cancer immunotherapy. Presently, gold nanoparticles with a strong NIR absorbance are typically larger than ca. 30 nm that is above the threshold size of ca. 5 nm required for efficient renal clearance. As these gold nanoparticles are not biodegradable, concerns about long-term toxicity have restricted their translation into the clinic. Here, we present a strategy to development of biodegradable plasmonic nanoparticles (BPNs) with controllable size from ca. 20 to 100 nm and a strong NIR absorbance that covers the first (650-950nm) and the second (1000-1350nm) NIR windows. We showed that BPNs biodegrade in live cells such as macrophages to primary ca. 5 nm components which are highly favorable for body excretion. Furthermore, we demonstrated that BNPs do not cause any acute or liver toxicity in live mice and are excreted from the liver over time. We used directional conjugation chemistry to synthetize molecularly targeted BPNs and demonstrated their utility in highly sensitive imaging of cancer cells in animal cancer models in vivo. In addition, BNPs showed more than 4-fold increase in signal strength and superior photostability in PA imaging as compared to gold nanorods that is associated with cluster morphology of BPNs. We have specifically focused on biodegradable gold nanoparticles with plasmon resonances in the NIR region. However, our platform can be easily extended to other inorganic nanomaterials. The nanoparticles degrade to easily clearable components in the body and, therefore, can provide a crucial missing link between the enormous potential of metal nanoparticles for cancer imaging and therapy and translation into clinical practice.

FRI 21

Localized hyperthermia in rodent models for targeted delivery of antibiotic agents

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Introduction: Chronic bone infections require extended length antibiotic therapy and are often limited by the delivery of drugs to the site of infection. The use of temperature-sensitive drug carriers allows a rapid release of drugs within a region of localized heating. Magnetic resonance guided high-intensity focused ultrasound (MR-HIFU) can create controlled heating within tissue and bone using active temperature feedback. The hypothesis of this study is that targeted release of antibiotics (ciprofloxacin) could be achieved in heated tissues using MR-HIFU hyperthermia and thermosensitive liposomes.

Methods: The hyperthermia platform consisted of an MRI-compatible small animal HIFU system (RK100, FUS Instruments, Canada), a custom-made receive coil for high signal to noise (Clinical MR Solutions, USA), and a 3T MR imager (Ingenia, Philips Healthcare, Netherlands). Custom software was processed images acquired during heating into temperature maps, and adjusted power based on a proportional-integral-derivative (PID) feedback control algorithm. Preliminary studies were performed in a tissue-mimicking phantom with implanted fiberoptic temperature sensors (Neoptix, Canada) to verify the accuracy of the temperature maps calculated by the software. In a second set of experiments, single point hyperthermia was performed in the thigh of Sprague Dawley rats (n=3, male, 300-350g). All in-vivo experiments were approved by the Institutional Animal Care and Use Committee. A target temperature of 42°C was set and 30 minutes of hyperthermia was delivered followed by a 5-10 min cooling procedure. During the treatment, a temperature-sensitive liposome containing ciprofloxacin (TSL-Cipro) was infused IV at a dose of 10mg/kg b. wt. using a power injector. After heating the muscle was extracted and the quantity of ciprofloxacin was measured in the heated muscle using fluorescence spectrophotometry. Two rats received HT+TSL-Cipro, and one rat received HT alone.

Results: Greater than 95% loading efficiency of Cipro into the TSL was observed in this initial study. Excellent agreement (≤1°C) between the MR-derived temperatures and the fiberoptic sensors was observed. A mean temperature of 42.2±0.3°C was achieved over the 30 minutes heating session with a T90 of 41±0.7°C and T10 of 43.4±0.5°C. The cooling rate after heating was approximately 0.8°C/min. An increase of Ciprofloxacin (4x) was measured in the muscle of rats that received HT+TSL-Cipro.

Conclusions: The small animal platform is capable of precise hyperthermia in a rodent model. TSL-Cipro is capable of efficient loading of antibiotic agents for targeted drug delivery. Localized delivery of ciprofloxacin can be achieved in the thigh of rodents using hyperthermia generated with MR-HIFU and TSL-Cipro.

FRI 22

Theranostic Polymer Nanoparticles for Photothermal Ablation and Fluorescent Imaging of the Breast Cancer *In Vitro* and *In Vivo*

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Nanoparticle mediated photothermal ablation of cancer is a promising technique that utilizes light energy to destroy cancer cells. Specifically, nanoparticles that absorb in the near infrared (NIR) region, 700 - 900 nm, are optimal because these wavelengths are an absorption minima for water and hemoglobin. As these wavelengths are where tissues are most transparent, NIR photothermal therapies allow for efficacious localized hyperthermia. Our lab has recently used 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), a donor-acceptor electrically conductive polymer, to form NPs capable of generating heat when stimulated by 800 nm light.

Non-invasive visualization of nanoparticles is invaluable for better understanding nanoparticle behavior *in vitro* and *in vivo*. Among imaging modalities, fluorescence is one of the most common as it is safe and cost-effective. Conjugated polymer-based probes are attracting significant attention due to their increased Stoke's shifts, improved photostability, and decreased susceptibility to enzymes or pH changes. One such conjugated polymer is poly(9,9-dihexylfluorene)-co-2,1,3-benzothiadiazole-co-4,7-dithiophen-2-yl)-2,1,3-benzothiadiazole (PFBTDBT10) which absorbs at 464 nm and fluoresces at 700 nm. We combined PFBTDBT10 and PCPDTBSe polymers to generate an optimal theranostic nanoparticle capable of both NIR photothermal ablation and NIR fluorescent imaging.

PCPDTBSe and PFBTDBT10 were used to form a hybrid nanoparticle and were collected by centrifugation. Nanoparticles were characterized by ultraviolet visible spectroscopy, transmission electron microscopy, and dynamic light scattering. Nanoparticles were evaluated *in vitro* by cytotoxicity assay, clonogenic assay, and photothermal ablation assay in murine breast cancer cell lines 4T1 and EO771 and murine non-cancerous fibroblast cell line Tib80. Fluorescent microscopy was also performed after 24 hour incubation with PolyDOTS to investigate *in vitro* uptake. *In vivo* photothermal efficacy and imaging was investigated in orthotopic 4T1 breast cancer model in Balb/c mice.

This theranostic hybrid nanoparticle offers great promise as an effective imaging and photothermal agent both *in vitro* and *in vivo*.

FRI 23

Thermophysical fluid modelling for loco-regional hyperthermia treatment of Non-Muscle Invasive Bladder Cancer

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Purpose/Objective

Intravesical instillation of Mitomycin C (MMC) combined with loco-regional hyperthermia (HT) is a promising adjuvant treatment of intermediate risk Non-Muscle Invasive Bladder Cancer (NMIBC). Recently, a multi-centre phase III randomized clinical trial comparing adjuvant MMC therapy with and without HT has started. For optimal treatment and quality control, reliable thermometry as provided by multi-sensor probe measurements and an accurate HT treatment planning system are needed. Therefore, we have developed a high resolution treatment planning system capable of modelling convective heat transport inside the bladder and compared it to the currently clinically used HT treatment planning system.

Materials and Methods

We created a convective thermophysical model and set up a phantom experiment to test its accuracy. A porcine bladder filled with 60 ml 0.9 % NaCl solution was placed in tissue equivalent gel (wallpaper paste with 0.3 % NaCl). The phantom was heated with the AMC-4 70 MHz deep HT device for 900 s at 400 W to reach a clinical temperature rise. This was repeated with 120 ml bladder volume to cover the clinically relevant volume range. Inside the bladder, temperatures were measured using the umbrella probe, a novel multi-sensor temperature probe measuring the temperature of both the bladder wall and the fluid inside; on the exterior we used copper-constantan thermocouple probes. We simulated this experiment using both the clinically used treatment planning system and the new convective model using the OpenFOAM toolkit.

Results

The temperature distribution computed by the convective model was in much closer agreement with the measurements than that by the current treatment planning system. The temperature measurements in the 60 ml case were practically identical to those in the 120 ml case. Comparison of the temperature distribution between the new convective model and the current treatment planning system showed good agreement within the solid regions of the phantom; however, the models differed significantly inside the fluid and in the immediately surrounding tissue, *i.c.* the bladder wall. Temperature differences exceeded ±1 °C, demonstrating the need for the new model. The clinically used treatment planning system generally underestimated the bladder wall temperature and overestimated the temperature at the bladder centre.

Conclusions

The new convective model is a marked improvement over the clinically used treatment planning system. Explicit modelling of convective heat transport in fluids is particularly important when the bladder or its direct surroundings are part of the treatment target area.

FRI 24

Simulation of magnetic nanoparticle hyperthermia in prostate tumor models

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Background: Magnetic nanoparticle hyperthermia (MNPH) is heating tumors using magnetic iron oxide nanoparticles (MIONs) in the presence of an alternating magnetic field (AMF). Understanding the role of intra-tumor nanoparticle distribution in tumor heating is essential for effective treatment planning. In this study, we simulate magnetic nanoparticle heating in model tumors using various constructs for nanoparticle distribution. **Methods:** Six models representing nanoparticle distribution were studied – three were idealized representations, and three were generated from images obtained from mouse models. Three human prostate cancer xenograft tumors (PC3, DU145 and LAPC4; n=40) grown in nude mice having volume of 0.15±0.02cm^3 were injected with commercially available BNF IONPs (5.5 mgFe/cc of tumor) or PBS. Twenty-four hours after injection the tumors were harvested and assessed for nanoparticle distribution using Prussian blue staining. Prussian blue stained tissue sections were digitized and were then converted to binary images using MATLAB's image processing toolbox. In these binary images, the dark pixels represent the stained nanoparticles, thus giving the nanoparticle distribution in each of the tumor models. For comparison among the tumor models, the number of nanoparticles in each of the tumor models was made equal. Three reference distribution models, viz. uniform, concentrated, and Gaussian having same number of nanoparticles were generated for additional comparison. The distributions were imported into COMSOL for 2D heat transfer analysis using the Pennes' bioheat equation. The tumors and surrounding healthy tissue were modeled as ellipses. Two perfusion models: 1) constant perfusion, 2) varied perfusion – depending on local tissue damage modeled using the Arrhenius equation, were considered. The heating power required to obtain a clinically relevant thermal dose (CEM43 >= 60min in 90% of tumor area) was calculated and compared. **Results:** PC3, DU145, and LAPC4 exhibit varied nanoparticle distributions, with LAPC4 exhibiting more uniform distribution than the others. The calculated heating power required to target thermal dose was the highest for DU145 model, whereas that required for all other models was comparable. When temperature-dependent perfusion based upon tissue damage is considered, differences among nanoparticle distributions on required heating power to achieve target thermal dose are minimized. **Conclusions:** For the 2D models studied, intratumor nanoparticle distribution plays a minimal role to determine total thermal dose when temperature-dependent tissue perfusion is considered. This is a stark contrast to prevailing conceptions of nanoparticle-mediated hyperthermia.

FRI 25

DESIGN AND OPTIMIZATION OF A CONFORMAL MICROWAVE ANTENNA FOR A WEARABLE BREAST HYPERTHERMIA APPLICATOR

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INTRODUCTION. Clinical trials have shown that hyperthermia can significantly improve the effectiveness of radiotherapy and chemotherapy cancer treatments. Currently available clinical systems for hyperthermia treatment cancer consist of bulky, inflexible radiofrequency waveguides that do not conform to the breast. A conformal and wearable hyperthermia system can improve the heating performance, reduce power requirements, and improve comfort, thereby facilitating treatment delivery and patient treatment persistency. Systems incorporating multiple antennas positioned within configurations optimized for individual patient anatomies may enhance power deposition within target volumes. Ink jet printing technology presents a novel approach to develop a patient-specific applicator within a quick, simple and fairly low manufacturing cost. The objective of this work is to design, optimize, and assess the feasibility of a microwave hyperthermia system integrated in a wearable garment with a conformal patch antenna. Varying groundplane geometry and ink jet printing technology which would enable printing the antennas on conformal surfaces allowing customized patient-specific devices is evaluated.

METHODOLOGY. A 3D electromagnetic-bioheat transfer model was used to optimize a conformal 915 MHz patch antenna element for a wearable hyperthermia applicator. Optimization objectives were device miniaturization, impedance matching, and maximizing the treatment volume (41 °C iso-therm). The antenna performance was evaluated with conical, hemispherical and flat groundplanes. Optimized prototypes were built and impedance matching and heating performance was measured. Computational models incorporating multiple-antenna strategies for focusing energy within patient-specific target models are under development.

RESULTS. The optimized conformal antennas yielded a -10 dB bandwidth of 90 MHz (±3%) centred at 915 MHz with a miniaturized patch dimensions of 13.7 mm × 3.9 mm. The antennas were capable of creating treatment volumes of 11.32 cm^3, 13.75 cm^3, and 1.36 cm^3 for the hemispherical, conical and flat groundplane configurations with an input power of 15 W. Variations of 50% in the blood perfusion yielded variations in the treatment volume up to 12%. E-field back-radiation reduced more 79% for the hemispherical and conical groundplane compared to the flat groundplane configuration.

CONCLUSION. The proposed patch antenna with hemispherical and conical groundplane shows encouraging performance to be integrated in a clinical array system. Printing antennas on flexible polymeric substrate presents a promising novel approach for customized patient-specific wearable hyperthermia devices. Prototype experimental characterization is in progress and will be presented at the conference.

FRI 26

In vivo conductivity values of cervical cancer patients reconstructed with a 3T MR system

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Background: Reliable tissue electrical conductivity (σ) values are required to determine the RF energy absorption for Hyperthermia Treatment Planning (HTP) as conductivity uncertainties can lead to treatment limiting hot spots and up to 2°C lower tumor temperatures. Currently used σ-values are mostly based on ex vivo measurements, and tumor σ is mostly unknown. Our aim is to acquire in vivo pelvic tissue conductivity for muscle, bladder and cervical tumor using 3T MRI.

Methods: Conductivity values were reconstructed using Electric Properties Tomography (EPT) which is based on B_1^+ field. Earlier we have validated this method for the pelvic region using phantom experiments and in vivo simulations. In this study, MR measurements of 12 cervical (squamous cell) carcinoma patients and one uterine adenocarcinoma patient were used to reconstruct σ-values in tumor, muscle and bladder. For a reliable σ-reconstruction the composition of a particular tissue should be relatively homogenous and sufficiently large (>3cm). Thus the σ of 9 tumors and 7 bladder fillings could be reconstructed. Results were compared to literature data.

Results: The reconstructed σ-values of muscle tissue were up to 35% elevated compared to literature values. Moreover, the reconstructed σ-values of the bladder were up to 10 times higher than values currently used in human models for HTP. Finally, for 75% of the squamous cell carcinomas the σ-values were 5-12% higher than the σ of muscle tissue found in this study. The reconstructed σ of the adenocarcinoma was 22% higher compared to muscle tissue.

Discussion & Conclusions: This study demonstrated the feasibility to measure the σ of healthy tissue and tumors in vivo. The measured conductivities were higher than reported in literature, which could probably be explained by the higher blood and water content during in vivo conditions. A decrease of σ after death has been reported for (human) liver, (animal) brain and (animal) muscle tissue. The present study showed that the commonly unknown tumor σ is 5-12% higher compared to the σ of muscle. The σ-value reported in the literature for bladder corresponds to bladder wall tissue, the volume percentage of which is lower than that of urine. However, this study shows that urine σ is much higher and shows a large inter-subject variation. Future studies will determine to which extent the reliability of HTP improves when using these patient-specific σ-values. These results are further interesting for applications such as MR safety and RF coil design for MR systems.

FRI 27

Increasing Energy Density with Polyprotic Acids and Polyamines for Use in Thermochemical Ablation

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Background

Thermochemical ablation has previously been described as a novel method to induce localized changes in temperature of tissues for ablation of solid tumors. Previous studies have centered around single equivalent acids and bases, which are limited by concentration and volume considerations. In this investigation, the potential of polyprotic acids and polyamine compounds as more energetically dense compounds for thermochemical ablation was explored, particularly with respect to ratio of molar equivalents, as well as order and method of addition.

Materials and Methods

Solutions of trifluoroacetic acid (TFA), dichloroacetic acid (DCA), sulfuric acid, phosphoric acid, aminoethylethanolamine (AEEA), N-methylethanolamine (NMEA), hexamethylenediamine (HMDA), diethylenetriamine (DETA), and tetramethylethylenediamine (TMEDA) were prepared at molar equivalents of 1, 2, and 3 N. In a baby oil gel matrix, solutions were combined to a total volume of 400 uL with logging of temperatures at 3 s intervals over a period of 5 min. Reactions were carried out in triplicate. All permutations of molar equivalent combinations (e.g. 1 N acid with 1 N base, 1 N acid with 2 N base, 2 N acid with 1 N base, etc.) were tested, as well as methods/order of addition including: 200 uL base added in a single aliquot to 200 uL acid; 200 uL base added in two 100-uL aliquots to 200 uL acid; and 200 uL acid added in two 100-uL aliquots to 200 uL base. Reaction exotherms were plotted, with maximum changes in temperature noted for each.

Results

Greater energies were liberated with higher mole equivalents and concentrations. High variability in temperature change was present, particularly during higher concentration runs likely secondary to localized pockets of solution that did not readily mix. Additions of compounds in two separate injections almost always demonstrated a second surge of thermal energy released, regardless of the stoichiometry.

Conclusion

Polyprotic acids, such as phosphoric and sulfuric, as well as polyamine bases have increased energy density secondary to their chemical structures containing multiple reactive moieties, yielding larger changes in temperature. This lends the possibility of using smaller volumes of lower concentrations to

generate changes in thermal energy comparable to those produced by larger volumes and higher concentrations of mono-reactive compounds, minimizing volume effects and toxicity that have previously been described with chemical ablation.

FRI 28

Destressing laboratory mice reveals new relationships between heat production, anti-tumor immunity and β-adrenergic receptor signaling

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Several studies have raised concerns with the accuracy and reliability of modeling diseases in laboratory mice. For instance, our laboratory has demonstrated that housing temperature can significantly affect the incidence and growth of tumors in murine models. In particular, we have found that maintaining mice at thermoneutral temperatures (TT, 30°C), or the temperature at which basal metabolism is sufficient to maintain body temperature, significantly delayed tumor growth compared to that seen in laboratory mice housed at standard, cool housing temperatures (ST, 22°C). (Kokolus et al., PNAS, 2013). However, the mechanisms underlying the enhanced anti-tumor control at TT compared to ST are not clear. Under cool conditions, mammals maintain a constant body temperature by producing heat via adaptive thermogenesis, a process driven by signaling of the stress hormone, norepinephrine (NE) through β-adrenergic receptors (β-ARs). NE has many other physiologic effects, such as immune suppression when it binds to β-ARs on immune cells. Our new data show that tumor-bearing mice housed at ST have elevated levels of NE in both plasma and tumors compared to mice housed at TT. Moreover, we have shown that the rate-limiting enzyme in NE production, tyrosine hydroxylase, is present within tumor tissue suggesting that NE is being synthesized both locally and systemically. From these data, we hypothesized that the detrimental effect of standard housing temperatures on the anti-tumor immune response is due to chronic cold stress induced production of NE and the resulting activation of β-adrenergic signaling pathways in immune cells. To test this hypothesis, we utilized β-AR antagonists (i.e., β-blockers) to block β-AR signaling in mice bearing 4T1 mammary tumors. Pharmacologic blockade of β-ARs in ST-housed mice bearing 4T1 tumors recapitulated the increased tumor control seen at TT. Further, we were able to show that the improved tumor control was a result of specifically blocking the β_2-AR which is the predominant adrenergic receptor on immune cells. However, β-AR blockade did not further improve control of tumor growth in mice housed at TT. These data demonstrate that baseline NE-mediated stress signalling in laboratory mice can significantly influence the outcome of anti-tumor immune control. These data also suggest that more attention be given to the production of NE in cancer patients, who may experience both physical and psychological stressors, since it may play a role in determining the outcome of cancer therapies. This work was supported by the Peter T. Rowley Breast Cancer Research Grant and the Harry J. Lloyd Charitable Trust.

FRI 29

Integrated micro-thermal sensor for planning and guidance of pulmonary vein ablation

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Atrial fibrillation (AF), which affects millions of people every year is commonly treated by focal therapy of pulmonary vein (PV). These focal treatments require improved monitoring of probe contact, tissue thickness, and freeze completion through the wall for optimal outcomes. Unfortunately, clinical imaging such as Ultrasound (US), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT) have resolutions similar in scale (~ 1 - 2 mm) to PV. In contrast, optimal treatments will require resolution much finer than this. Thus, alternatives are urgently needed to improve monitoring of cryoablation within PV at the sub-mm level. Here then we present a new, micro- thermal sensor based on the "3ω" technique (Cahill et al. *Physical Review B 1987*) modified for thin, anisotropic and composite biological systems. This "supported" 3ω sensor comprises a gold heater line (3 mm X 30 µm X 200 nm) deposited on a glass substrate, and measures the *k* of a sample placed in contact. Our initial experiments using this sensor demonstrate accuracy of more than 95% in *k* measurements for sample thicknesses down to 100 micron in water and liver tissue (Lubner et al. *Rev. Sci. Instruments 2015*). Here we expand this data set to include samples of porcine PV < 2 mm thick and surrounding esophageal tissues <3 mm thick. The *k* of PV was measured to be 0.41 to 0.55 ± 0.02 W/mK in the suprazero temperature regime (14.4 to 36±0.6°C) and 1.14 to 1.44±0.08 W/m.K in the frozen sub-zero temperature regime (-10 to -30.9±1.3^{0}C) for N = 3. Similarly, *k* of esophageal tissues was measured to be 0.48 to 0.55±0.04 W/m.K in the supra-zero temperature regime (14.0 to 35.6±0.4^{0}C) and 1.1 to 1.58±0.13 W/m.K in the frozen sub-zero temperature regime (-8.7 to -25.6±0.8^{0}C) for N=3. Finally, we provide proof of principle that such a sensor mounted on a probe can monitor important dynamic aspects of PV cryoablation and other probe based therapies. For instance, we demonstrate the ability to sense tissue contact vs. fluid contact without flow vs fluid contact with flow. We also demonstrate for the first time the ability to measure tissue thickness and the initiation and completion of tissue freezing with accuracy better than 0.1 mm in water and PV. In total, we demonstrate that our sensor can measure k, tissue contact, thickness, and phase change, all of which can help in sub-mm monitoring of cryo and other focal therapies in thin tissues.

FRI 30

A novel stealth idarubicin thermosensitive liposome for ultrafast triggered release using mild hyperthermia

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Previous research on doxorubicin-loaded thermosensitive liposomes shows improved chemotherapeutic efficacy in combination with mild hyperthermia. Idarubicin (IDA), another anthracycline chemotherapeutic drug, is generally believed to have less cardiotoxicity and stronger anti-cancer activity (in some tumors) than doxorubicin. IDA may have better characteristics because of its more lipophilic nature and higher potency. These features may improve its release from liposomes, subsequent cellular uptake and tumor cell killing when combined mild hyperthermia.

The aim of the study is to develop a novel thermosensitive liposome encapsulating the lipophilic drug idarubicin (IDA-TSL). Here, we investigated a series of parameters, including loading buffer, lipid composition, internal buffer pH, liposome size and drug to lipid ratio, to optimize IDA-TSL formulation. Optimized IDA-TSL formulation was composed of DPPC/DSPC/DSPE-PEG (6/3.5/0.5 mol%) with ammonium EDTA as loading buffer, possessing a ultrafast triggered release under mild hyperthermia.

In *in vitro* studies, the optimal IDA-TSL formulation displayed a minimal leakage of ~20% in whole serum at 37 °C for 1 h; while an ultrafast, complete and triggered release of IDA was observed in a few seconds at 42 °C. In cytotoxicity assays with murine B16BL6 melanoma cells, human BLM melanoma cells and murine C26 colon carcinoma cells, IDA-TSL showed comparable cytotoxicity to free IDA at 42 °C, but 3- to 11-fold reduced cytotoxicity to cells at 37 °C.

In vivo studies were performed in dorsal skin flap window chamber-bearing mice implanted with murine B16BL6 tumor. Intravital microscopy imaging demonstrated an efficient intravascular triggered drug release from IDA-TSL under mild hyperthermia, and a subsequent massive IDA uptake by tumor cells. These results suggest beneficial potential of IDA-TSL for further development in combination with hyperthermia.

Further studies are currently performed to unravel the underlying IDA ultrafast release mechanism at 42 °C and on the therapeutic efficacy of IDA-TSL in solid tumors.

FRI 31

Photothermal Ablation of *Streptococcus pyogenes* using Fluorescent Bio-Polymeric Nanoparticles

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Photothermal Ablation (PTA) may be able to locally generate heat in order to destroy an active site of infection. In the present study, we compared the effects of conjugated polymer nanoparticles on Gram-positive *Streptococcus pyogenes* (Group A Streptococcus or GAS). Hybrid polymer nanoparticles (NP) comprised of Poly(3-hexylthiophene-2,5-diyl) (P3HT) with 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 synthesized using Pluronic F127. The P3HT/PCPDTBSe NP's were coated with either O-carboxymethyl chitosan (O-CMC) with attachment of GAS antibody (GAS AB) or bare chitosan without antibody attachment. GAS AB loaded O-CMC coated P3HT/PCPDTBSe NP's were characterized using a Bicinchoninic assay (BCA), to determine effectiveness of the antibody conjugation to the NP's. The NP's were characterized using Fourier transform infrared spectroscopy (FTIR), dynamic light scattering (DLS) and transmission electron microscopy (TEM). Confocal microscopy was used to observe the fluorescence of the nanoparticles. A heat curve was generated comparing change in temperature versus concentration of nanoparticles, exposed to 5W of 800 nm of light for 1 minute. Nanoparticles were then separately incubated with GAS for one hour and photothermally ablated using a K-Laser (5 W, 800 nm, 1 minute). Colony forming units were counted after ablation to evaluate the effectiveness of killing of the O-CMC and chitosan coated P3HT/PCPDTBSe NP. Our results ultimately showed that chitosan coated P3HT/PCPDTBSe NP's had higher killing of GAS compared to the GAS AB loaded O-CMC coated P3HT/PCPDTBSe NP's in GAS because of a low loading of the GAS AB onto the nanoparticles. PTA using the chitosan coating was effective at eradicating GAS. As a result, this comparative study suggests that chitosan coating may offer enhanced binding of the nanoparticle to bacteria compared to the GAS AB loaded O-CMC coating.

FRI 32

External thermal therapy with concurrent radiation therapy results in rapid and durable regression of multiply-recurrent, debilitating verrucous vulgaris: a case report.

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Background: Verrucous vulgaris (VV), or the common wart, often results from HPV skin infection. A typically mild condition, VV may generally be managed with topical medications or minor surgery. In a subpopulation of patients, such as the immunocompromised, VV disseminates widely and greatly affects quality of life; these severe cases merit aggressive treatment with surgery, chemotherapy, external thermal therapy (ETT), and/or radiation therapy (RT). The safety and efficacy of concurrent ETT+RT, while reported in oncologic therapy, have not been described for VV. We present the first case report of response to ETT+RT for severe VV of the bilateral thumbs refractory to multiple therapies, including previous irradiation.

Methods: BM was a 48 year old female with lupus, rheumatoid arthritis, immunodeficiency disorder, and a 12-year history of worsening VV involving the groin, lower abdomen, arms, and multiple digits of each hand. Her bilateral thumbs were particularly symptomatic with pain, bleeding, and disability. She had previously undergone surgery, topical acids, steroid injections, cryotherapy, topical imiquimod and fluorouracil, laser treatments, ultraviolet therapy, and intravenous cidofovir requiring multiple inpatient admissions. She also previously received RT to the left thumb at an outside facility totaling 20 Gray in 5 fractions. The RT resulted in near complete resolution of the thumb lesions, but they recurred within a few weeks. She elected to undergo reirradiation of this thumb and primary RT of the contralateral, each totaling 30 Gray in 10 fractions over 2 weeks. ETT was delivered concurrently with the BSD 500 hyperthermia device using superficial thermometry for 4 treatments, one hour each to 40 degrees Celsius.

Results: BM tolerated treatment well with only minor irritation and pruritus at the end of therapy. One week later, she reported worsening pain and dry desquamation of the thumbs which was managed conservatively. By one month post-therapy, there was complete regression of the treated VV lesions and her acute side effects were largely resolved. At most recent follow-up (7 months), there was no clear evidence of recurrence. Response to ETT+RT has proven much more durable than the previous, approximately bioequivalent RT without ETT. RM has subsequently undergone ETT+RT to other hand lesions with similar outcome.

Conclusion: Concurrent therapy with ETT+RT for VV resulted in rapid, complete, and more durable response in this patient than many other modalities, including RT alone. ETT+RT may be safely administered for refractory, clinically significant VV lesions.

FRI 33

Fractionated nanoparticle hyperthermia and radiation improves tumor treatment efficacy

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Introduction: Iron oxide nanoparticle (IONP) hyperthermia, combined with ionizing radiation, demonstrates an improved therapeutic ratio, when compared to either monotherapy. The majority of published studies using these techniques have employed single doses. While the single dose approach is experimentally efficient, it does not reflect clinical practice.

Methods: These studies utilized a mouse mammary adenocarcinoma flank tumor model (C3H/MTGB), and dextran coated IONP (110nm hydrodynamic radius). IONP hyperthermia (CEM 30) was induced with an alternating magnetic field (AMF) on the second and fourth day of a five day, 3 Gy radiation plan.

Results: When used alone, the small radiation and hyperthermia doses used in these studies resulted in little, if any treatment effect as compared to the control. However, when IONP were injected prior to irradiation, with no AMF activation/hyperthermia, significant efficacy/regrowth delay was observed (2X). This regrowth delay was further increased when IONP were activated, following irradiation, and hyperthermia induced (2.5X).

Conclusion: These data demonstrate the potential of IONP as a stand-alone radiation sensitizer and cell-specific hyperthermia sensitizer of radiation.

FRI 34

PHOTOTHERMAL CANCER THERAPY GUIDED BY IN VIVO PHOTOACOUSTIC FLOW CYTOMETRY

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Background: Photothermal (PT) therapy demonstrated tremendous potential to treat cancer. It is based on energy conversion from light into heat leading to destruction of tumor cells. However, PT therapy can trigger cancer cell release from primary tumor into the blood circulation. These circulating tumor cells (CTCs) start metastasis by spreading the tumor to distant organs. Since majority of the cancer-related deaths are associated to metastasis, it is essential to not provoke CTC release during diagnostic and therapeutic procedures. In order to optimize the treatment parameters for minimal CTC release, *in vivo* monitoring of the CTCs is needed. We propose to use photoacoustic flow cytometry (PAFC) for real-time quantification of CTC release during PT therapy. PAFC is based on PT conversion of absorbed energy into acoustic waves. Therefore, melanoma cells with intrinsic melanin pigments or other cancer cells labelled with PT contrast agents (e.g., gold nanoparticles) are ideal candidates for PAFC detection.

Methods: Three groups of nude mice were used: Group 1 were cancer-free control; Group 2 were inoculated with mouse melanoma; and Group 3 were inoculated with breast cancer cells. Cell lines were also expressing green fluorescent protein. When the tumor volume reached ~220 mm^3, anesthetized mice were monitored using integrated photoacoustic and fluorescent flow cytometry, on a vessel distant from the tumor site. The monitoring started one hour before the procedure, and continued during and after the procedure. Incisional biopsy was conducted on group two by cutting through the tumor with a scalpel. PT therapy was performed on group three by irradiating (488 nm, 50 mW) the tumors for 30 minutes. Same procedures were repeated on control mice.

Results: No signals were detected in control mice, before, during, or after the procedures. CTC detection rates (number of CTC per 10 minutes) for the incisional biopsy were 1.3, 75.1, 44.3, and 7.7 for before, during, first hour after, and second hour after the biopsy, respectively. CTC rates for PT therapy were 1.9, 9.3, and 2.8 for before, during, and first hour after the therapy, respectively.

Conclusion: PT therapy dramatically (5-fold) increases CTC release into the circulation, potentially increasing the risk of metastasis. These results suggest the careful optimization of PT therapy to maximize treatment of primary tumor while simultaneously reducing CTC release. We also propose the use of anti-CTC therapies during tumor interventions. PAFC monitoring makes it possible to quantify CTC release and adjust treatment parameters.

ABSTRACT

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Making a Difference
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AUTHOR INDEX
(by day, Posters are Thursday evening)

Notes

Notes

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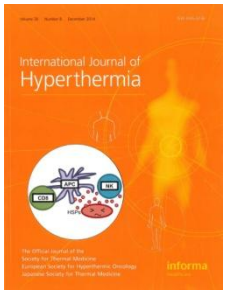

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