35TH ANNUAL MEETING OF THE SOCIETY FOR THERMAL MEDICINE

TEMPERATURE MATTERS

MAY 7–MAY 10, 2018 • TUCSON, ARIZONA

2018 PROGRAM & ABSTRACT BOOK

SAVE THE DATE

APRIL 28 – MAY 2, 2019!

TradeWinds Island Resorts on St. Pete Beach Welcomes

The Society for Thermal Medicine

2019 STM 36th Annual Meeting

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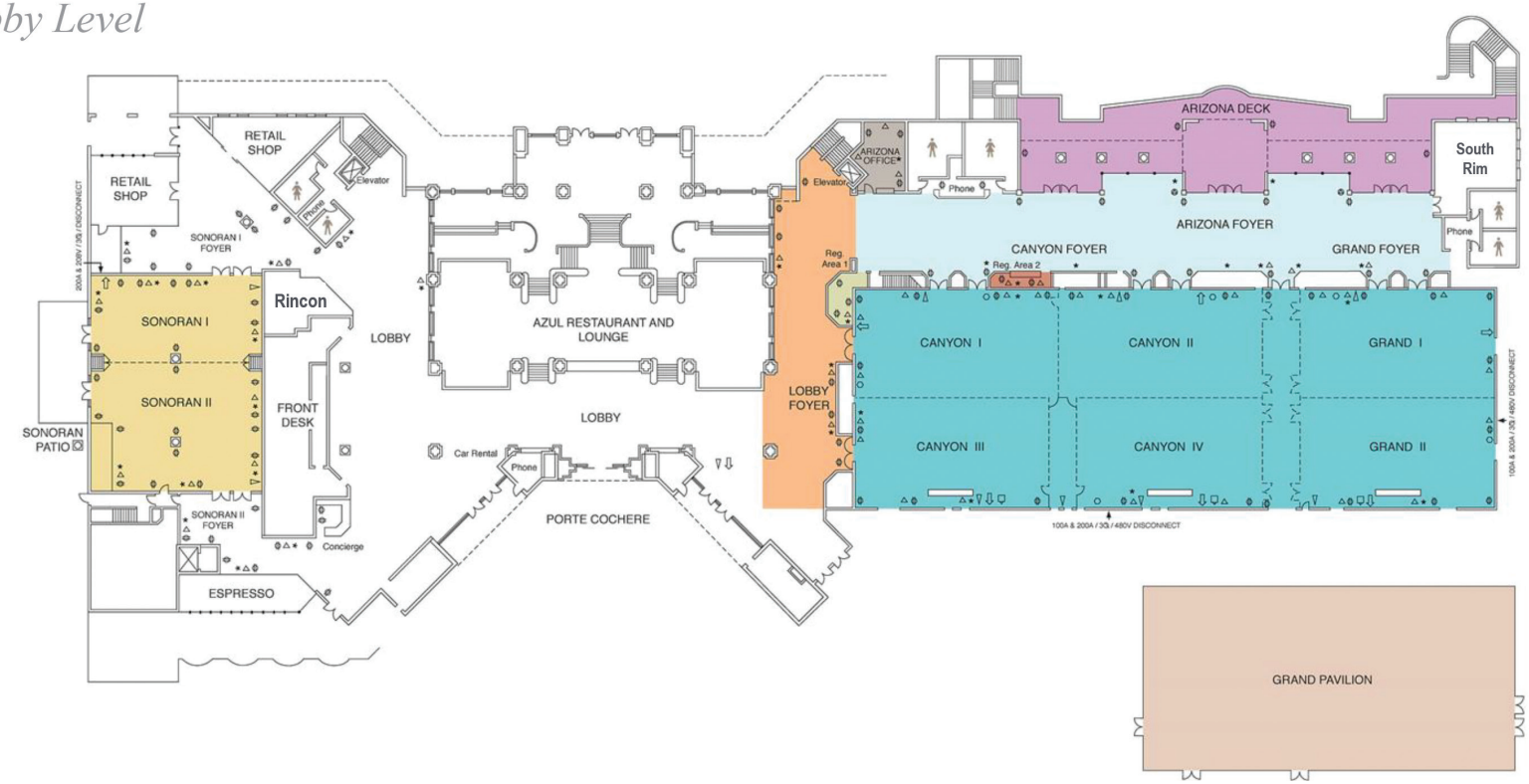
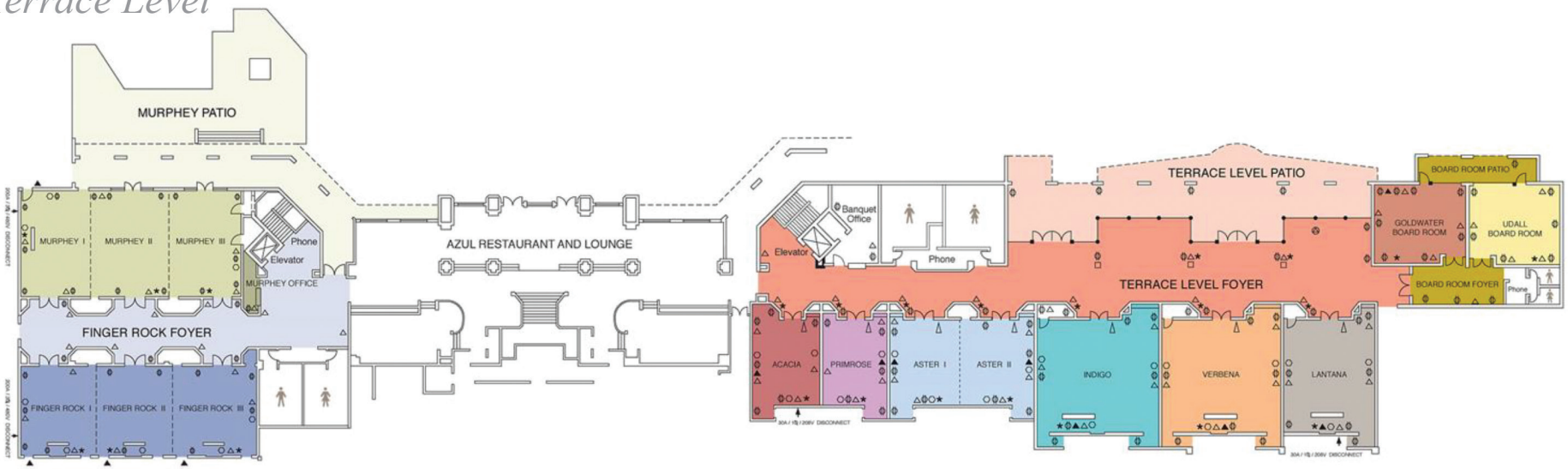
Registration Desk Hours of Operation in the LOBBY FOYER

Monday, May 7th	8:00AM – 6:00PM
Tuesday, May 8th	8:00AM – 5:00PM
Wednesday, May 9th	8:00AM – 5:00PM
Thursday, May 10th	8:00AM – 4:00PM

Lobby Level



Terrace Level



Dear friends of STM, fellow researchers, clinicians, sponsors, and colleagues,

It is my great pleasure to welcome each of you to the 35th Annual Meeting of the Society for Thermal Medicine, held at the beautiful Westin La Paloma Resort in Tucson, Arizona.

"Thermal medicine" is becoming at term that reflects many different aspects of biology and chemistry, physics and engineering, and the utilization of these scientific disciplines in medicine in areas that may involve the far-reaching effects of temperature changes. Thermal therapies cover the gamut of temperature ranges from cryotherapies to various high-temperature ablative techniques. The biologic effects of these various and sundry interventions are now becoming clearer, leading to more precise therapies, yet with systemic influences.

MICHAEL GRANER, PHD

For many years, STM was mostly focused on oncological implications; in more recent years, and again reflected in this year's Program, we enjoy a breadth of applications spanning unique model organisms in aging, to thermal medicine in infectious disease, to cardiovascular stresses, and of course, to oncology, with remarkable connections throughout these areas. The scientific categories are broad, yet frequently overlapping, including biologic and constructed nanoparticles, photonics, radiation/laser/chemical applications, and the biologies involved in these techniques and therapies. Another tightly-intertwined thread is that of the immune system in thermal approaches. In addition, extraordinary imaging technologies are being developed and employed as means of imaging thermal impacts, guiding those impacts, and in some cases, delivering those impacts. Computer modeling, phantom modeling, and tissue modeling play heavily into all of this. These research areas combine in the ultimate goal, clinical utility of our knowledge, which will be very evident in the clinical sessions during the 35th Meeting. The movement of these concepts from bench to bedside into protocols and techniques to treat patients is one of the most rewarding aspects this Meeting.

The 35th Meeting will unofficially start with an Education Day Workshop on May 7 entitled "Lights, Cameras, and Thermal Biology in Action". These talks will provide an educational overview of some of the topics covered later in the Meeting.

The Meeting officially opens that evening with the Keynote Presentation by Dr Chris Adami entitled "Discovering the Signal within the Noise: Where are the Disease Biomarkers?"

Plenary Sessions starting each of the next meeting days include

- "Personalized Treatment Planning for Photodynamic and Photothermal Therapies? Implementations of Rapid Monte Carlo Simulations and Linearized Optimization Algorithms" by Dr Lothar Lilge

- "Endoplasmic Reticulum Chaperones in Health and Disease: Molecular Mechanisms and Therapeutic Potential" by Dr Amy Lee

- "The Unusual Biology of the Longest Lived Rodent, the Naked Mole-Rat" by Dr Rochelle Buffenstein

There will be a special Workshop co-sponsored by the STM and the American Society of Mechanical Engineers (ASME) called "Closing the Gap Between Thermal Modeling/Treatment Planning and Clinical Practice, A Gap Analysis Workshop".

As noted above, we will have three sessions devoted to clinical trials and clinical applications of thermal therapies; other clinical talks will be placed in other relevant sessions. We are fortunate to have multiple sessions on biologic and engineered nanoparticles, a session devoted to photonics, a session on thermal therapy in infectious disease, a session on hyperthermic intraperitoneal chemotherapy, sessions on the biology and immunology of thermal conditions, and numerous sessions with proffered talks from an outstanding array of abstracts submitted.

This will be a truly international meeting with presenters from all over the world, and propelled with sponsorships from major players in the field of thermal medicine. We look forward to exciting presentations, collegial gatherings and exchanges, and the camaraderie typical of this group of people. The 35th Meeting looks to be another diverse meeting ranging from studies in basic science to presentations of large-scale clinical experiences. There is certainly something for everyone, and we are delighted to have you join us.

Sincerely yours,

Michael Graner, PhD

Program Chair, President-Elect, Society for Thermal Medicine

Associate Professor, Department of Neurosurgery

University of Colorado Denver

Anschutz Medical Campus

Aurora, CO, USA

MICHAEL GRANER, PHD

Program Chair, President-Elect, Society for Thermal Medicine

Associate Professor, Department of Neurosurgery

University of Colorado Denver

Anshutz Medical Campus

Aurora, CO, USA

SCHOOL OF MEDICINE
Department of Neurosurgery
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

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.

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Robert Griffin, PhD, University of Arkansas for Medical Sciences

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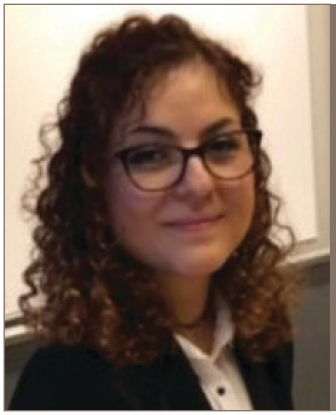
INTERNATIONAL JOURNAL OF HYPERTHERMIA BOARD MEMBERS

INTERNATIONAL JOURNAL OF HYPERTHERMIA BOARD MEMBERS

2017 TAYLOR AND FRANCIS EDITOR'S AWARD WINNERS

These chosen papers were selected by the Editorial Board of the *International Journal of Hyperthermia* as the best of Young Investigator papers (in their respective categories) that were published in 2017. Authors self-nominate themselves with the criteria being that they are less than 35 years of age. The editors have rigorous scoring criteria to help them select the winning papers.Our congratulations go to the following recipients of the 2017 awards:



PHYSICS/ENGINEERING

PEGAH TAKOOK, PHD

Compact self-grounded Bow-Tie antenna design for an UWB phased-array hyperthermia applicator

CLINICAL

GRACE TAN, MD

201 Consecutive Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Procedures in a Single Asian Tertiary Centre

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2017 TAYLOR AND FRANCIS EDITOR'S AWARD WINNERS

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BIOLOGY

CASPAR VAN LEEUWEN, PHD

3D radiobiological evaluation of combined radiotherapy and hyperthermia treatments

BIOLOGY

ARLENE LEONIE OEI, PHD

Targeting therapy-resistant cancer stem cells by hyperthermia

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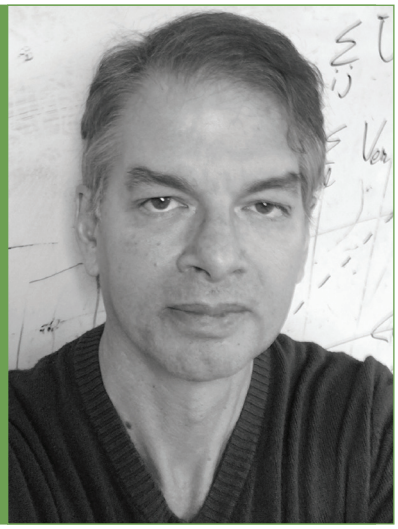
KEYNOTE SPEAKER

DR. CHRISTOPH ADAMI, PHD

Michigan State University

DISCOVERING THE SIGNAL WITHIN THE NOISE: WHERE ARE THE DISEASE BIOMARKERS?

Monday, May 7, 5:00PM – 7:00PM / CANYON I, III



CHRISTOPH ADAMI is Professor of Microbiology and Molecular Genetics, as well as Professor of Physics and Astronomy, at Michigan State University. He obtained his PhD and M.A. in theoretical physics from the State University of New York at Stony Brook, as well as a Diploma in Physics from Bonn University (Germany). His main research focus is Darwinian evolution, which he studies at different levels of organization (from simple molecules to brains). He has pioneered the application of methods from information theory to the study of evolution, and designed the "Avida" system that launched the use of digital life as a tool for investigating basic questions in evolutionary biology. When not overly distracted by living things, he studies the fate of classical and quantum information in black holes. He wrote the textbook "Introduction to Artificial Life" (Springer, 1998), and is the recipient of NASA's Exceptional Achievement Medal. He was elected a Fellow of the American Association for the Advancement of Science (AAAS) and a Fellow of the American Physical Society (APS).

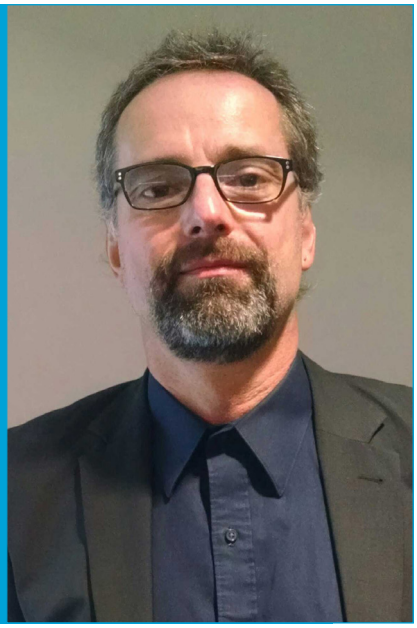
PLENARY SPEAKER

DR. LOTHAR LILGE, PHD

Princess Margaret Cancer Centre and University of Toronto, Canada

"Personalize treatment planning for Photodynamic and Photothermal therapies; Implementations of rapid Monte Carlo simulations and linearized optimization algorithms."

TUESDAY, MAY 8, 8:00AM – 9:00AM / CANYON I, III



DR. LILGE graduated with a PhD in Experimental Physics and Biophysics from the Westfaehlische Wilhelms Universitaet in Munester Germany in 1992 after having trained at the Goethe University In Frankfurt and Massachusetts General Hospital's Wellman Laboratory of Photomedicine, Boston. His thesis focused on actinometer based methods for measuring the photon density in turbid media.

Dr. Lilge completed 2 Post Doctoral Fellowships at McMaster University in Hamilton Ontario and at the Ontario Cancer Institute working on Photodynamic therapy and fluorescence guided diagnostics in the GI tract. In 1995 he started to built a BioPhotonics Industrial User Facility for Photonics Research Ontario which he lead until 2002 when he became Staff Scientist at the Princess Margaret Cancer Centre in Toronto. He joint the department of Medical Biophysics at the University of Toronto as faculty in 1997 and is full Professor (status only) since 2009.

His current research interest are in Photodynamic Therapy and Photobiomodulation in particular related to treatment planning and increased efficacy through co-therapies, personalized treatment planning and light dosimetry aspects. Research spans in vitro, pre-clinical and clinical studies.
A second research direction pertains to the identification of women with increase breast cancer risk by quantification of bulk tissue optical properties. Population based studies are currently ongoing in Australia, Canada, USA and Usbekistan.

PLENARY SPEAKER

DR. AMY LEE, PHD

University of Southern California Keck School of Medicine, Los Angeles, CA

"Endoplasmic Reticulum Chaperones in Health and Disease: Molecular Mechanisms and Therapeutic Potential"

WEDNESDAY, MAY 9, 8:00AM – 9:00AM / CANYON I, III

DR. AMY LEE is the Associate Director for Basic Research and Professor of Biochemistry and Molecular Medicine at the University of Southern California (USC) Norris Comprehensive Cancer Center, Los Angeles, California. Dr. Lee obtained her B.A. from the University of California, Berkeley, and her Ph.D. from the California Institute of Technology, Pasadena, California. Dr. Lee is currently holder of the Judy and Larry Freeman Cosmetics Chair in Basic Science in Cancer Research at USC. Dr. Lee's research focuses on the mammalian stress response and molecular chaperones. Her laboratory is the first to clone the genes coding for a set of endoplasmic reticulum (ER) stress-inducible glucose regulated proteins (GRPs) and has made numerous discoveries in understanding how these genes are regulated and their role in development and human diseases. Dr. Lee's laboratory established that the GRPs are major contributors for tumorigenesis through creation of conditional deletion mouse models of GRPs. In studying the atypical forms of GRP78 in the cytosol and at the cell surface, her laboratory has expanded the role of GRP78 as a potent regulator of cell signaling beyond the ER compartment, impacting cell proliferation, survival and invasion.

Dr. Lee is widely recognized as a leader in ER stress and her basic groundbreaking research has yielded exciting novel diagnostic and therapeutic approaches to diseases. She was the recipient of the MERIT Award from the National Cancer Institute in 1988. In recognition of her pioneering work on ER stress and its impact on cell and cancer biology, she was elected Fellow of the American Association for the Advancement of Sciences (AAAS) in 2006. Dr. Lee was the recipient of the Chinese American Faculty Association of Southern California Achievement Award in 2008. She was the recipient of the USC Mellon Award for Faculty Mentoring in 2012, the Phi Kappa Phi Faculty Recognition Award in 2015 and the National Academy of Inventors Award in 2017. Most recently, Dr. Lee was selected to receive the 2018 USC Associates Award for Creativity in Research and Scholarship, the highest honor the university bestows on its members for distinguished intellectual achievements.

PLENARY SPEAKER

ROCHELLE (SHELLEY) BUFFENSTEIN, PHD

"The Unusual Biology of the Longest Lived Rodent, the Naked Mole-rat."

THURSDAY, MAY 10, 8:00AM – 9:00AM / CANYON I, III

ROCHELLE (SHELLEY) BUFFENSTEIN, PH.D.
Senior Principal Investigator, Calico Labs

A key goal of my research is to determine the molecular mechanisms used in nature to modulate both species lifespan and healthspan. Using a multidisciplinary mechanistic approach, we specifically examine why some mammals age extremely rapidly, exhibiting pronounced declines in all aspects of their biology, and how other species can maintain physiological function and disease-free good health for a larger proportion of their long-lifespans. Elucidating these mechanisms may lead to therapeutic targets to retard the aging process and delay the onset of age-associated disability and diseases such as cancer, diabetes, and Alzheimer's disease.

I came to Calico from the Barshop Institute for Aging and Longevity Studies. There I was a professor in the Department of Physiology and track leader for the Biology of Aging graduate program. Prior to that, I was a professor in the Department of Biology at The City College of New York, and before that I spent 10 years at the Medical School of the University of Witwatersrand, in South Africa, where I pioneered the use of the naked mole-rat, as a model of exceptional bio-gerontological interest.

THE 2018 WILLIAM C. DEWEY AWARD & LECTURE

AWARD WINNER

ELIZABETH REPASKY, PHD
Department of Immunology
Roswell Park Comprehensive Cancer Center
Buffalo, NY

WEDNESDAY, MAY 9, 3:30PM – 6:00PM / CANYON I, III

The William C. Dewey award is presented every other year to an investigator who has contributed in a significant way to the mentorship and training of new investigators in the field of thermal medicine. This lecture is named in honor of Dr. Bill Dewey who trained many leaders in our field in all three disciplines (physics, biology and clinical/medical). His emphasis on making hyperthermia treatment a quantifiable therapy with a defined method for performing thermal dosimetry has stood the test of time and has influenced how hyperthermia and thermal ablation are practiced today.

Dr. Elizabeth Repasky is Professor of Oncology, the William Huebsch Professor of Immunology, and a Program Leader for the Cell Stress and Biophysical Therapies Program at Roswell Park Comprehensive Cancer Center in Buffalo NY. Training and mentorship have clearly been very important to Dr. Repasky as she has served as major advisor to 21 PhD students and 12 Postdoctoral Fellows, nearly all of whom have gone on to become successful members of the research, clinical, academic or bio-tech communities. She has also mentored numerous junior faculty members, medical/surgical oncology fellows, and more than 35 master's students. Several of her trainees are current members of the Society for Thermal Medicine. Dr. Repasky and her trainees have worked together for over two decades in a highly translational research program that has focused on exploration of the physiological and immunological responses to thermal stress which can be manipulated to alter the tumor microenvironment and improve the efficacy of cancer therapies including immunotherapy and radiation. Her most recent work has focused on the unexpected role of housing temperature-induced adrenergic stress in causing immunosuppression in mouse tumor models, work which has now led to new clinical trials combining immunotherapy with antagonists of beta-adrenergic receptor signaling. Her research program has resulted in 177 cited publications. Dr. Repasky has been given several previous awards in recognition of her mentorship abilities. She is currently a Section Editor for the International Journal of Hyperthermia, and she is a previous awardee of the J. Eugene Robinson Award from the Society for Thermal Medicine.

2018 William C. Dewey Award Presentation Students Have Always Led the Way!

In my career, I have always enjoyed training and mentoring young scientists as they work toward their PhD degree and then during their subsequent careers. A majority of the discoveries my lab has made regarding a role for mild thermal stress in immunity and in the physiology of the tumor microenvironment has been driven by talented and hardworking graduate students and fellows. This brief presentation will highlight some of the discoveries made by trainees who have been critical to my research program. I am grateful to the many trainees who have worked with me at Roswell Park, to my own mentors and colleagues, and to the STM Awards Selection Committee for this wonderful Award.

29TH J. EUGENE ROBINSON AWARD & LECTURE

AWARD WINNER

SHARON S. EVANS, PHD

Department of Immunology
Roswell Park Comprehensive Cancer Center
Buffalo, NY

WEDNESDAY, MAY 9, 3:30PM – 6:00PM / CANYON I, III

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.

SHARON S. EVANS, PH.D. is a Professor of Oncology in the Department of Immunology at Roswell Park Comprehensive Cancer Center. She was a research scientist at Merck and Company in Rahway NJ during her graduate training at New York University and her doctoral training was at the University of Buffalo. Her post-doctoral research at as an American Cancer Society fellow Roswell Park explored the role of cytokines (interferon-) in boosting antibody-mediated immune responses. Dr. Evans joined the faculty of the Department of Immunology at Roswell Park in 1987. Dr. Evans is internationally recognized in the multidisciplinary fields of cytokine biology, lymphocyte trafficking, and thermal regulation.

Dr. Evans' research program focuses on understanding the mechanistic underpinnings controlling adhesion and chemokine-dependent leukocyte trafficking within lymphoid organs and the complex tumor microenvironment. To this end, her laboratory employs live-imaging microscopy to track lymphocyte migration during acute inflammation related to the initiation and resolution phases of fever. Related projects investigate the microvasculature as a significant impediment to trafficking of blood-borne cytotoxic T cells within the tumor microenvironment. This research contributed to the current recognition that limited T cell homing is a hallmark of immune evasion in cancer that was described in Cancer Cell by Hanahan and Coussens. This line of investigation led to the novel discovery of a role for interleukin-6 (IL-6) in regulating lymphocyte trafficking during fever and cancer immunotherapy. Preclinical findings from Dr. Evans' laboratory have further guided the development of Phase I/II clinical trials in thermal therapy and for the study of tumor and lymph node vascular function by live-imaging microscopy in cancer patients.

Dr. Evans has maintained a long-standing commitment to graduate education, receiving multiple mentorship awards and training over 35 pre-doctoral fellows, MD/PhD students, Masters, and postdoctoral and clinical fellows. Dr. Evans has actively served the Society for Thermal Medicine as a board member and past-President, and scientific program chair for the STM annual meeting in Portland, Oregon.

2018 STM NEW INVESTIGATOR AWARDS

We are pleased to announce that The Society for Thermal Medicine, with funding from *The Journal of Clinical Medicine* and MDPI journals *diseases* and *medicines* is providing travel grants to 10 New Investigators to encourage participation at the 2018 STM annual meeting.

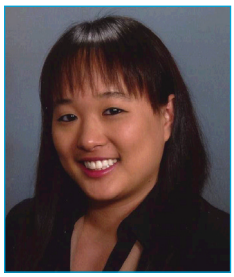
Awardees will receive a $500 travel grant and registration to the meeting.
Travel Awards recipients are based upon a competitive evaluation of their submitted abstracts and New Investigator Award applications.

CRISTINA DECESARIS
Concurrent Interstitial Thermal Therapy and Interstitial Brachytherapy for Pelvic Malignancies: A Single Institution Experience

University of Maryland Medical Center, Baltimore, MD, USA

CHUNXIAO GUO
Convergent toxicity of hyperthermic and osmotic stress sensitizes HCC cells by inhibition of HSF1

MD Anderson Cancer Center, Houston, TX, USA



LEE HWANG
Stereotactic laser ablation as a therapeutic option for recurrent glioblastoma: a large single institutional experience

The Cleveland Clinic, Cleveland, OH, USA

HILARY KOECH
Laser interstitial thermal therapy for posterior fossa lesions: An initial experience

Cleveland Clinic Foundation, Cleveland, OH, USA

DONG LIU
Endobronchial Ultrasound Thermal Therapy of Pulmonary Malignancies: a Theoretical Investigation in Patient Specific Lung Models

Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

JILL REMICK
The Impact of Hyperthermia Therapy on Patient Referrals and Patterns of Care within a Radiation Oncology Department

University of Maryland Department of Radiation Oncology, Baltimore, MD, USA

2018 STM NEW INVESTIGATOR AWARDS

STEPHANIE RICE

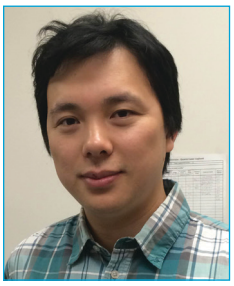
Toxicity and Efficacy outcomes of concurrent hyperthermia and radiation therapy in soft tissue sarcoma

University of Maryland Department of Radiation Oncology, Baltimore, MD, USA

MARC SANTOS

Microbubble-Assisted MRI-guided Focused Ultrasound for Hyperthermia at Reduced Power Levels

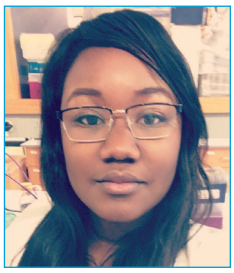
Sunnybrook Research Institute, Toronto, Ontario, Canada. University of Toronto, Toronto, Ontario, Canada



QI SHAO

Comparison of in vitro cellular response and immune priming of hyperthermia, cryosurgery and irreversible electroporation

University of Minnesota, Minneapolis, Minnesota, USA



SANDRINE SOMAN

Hyperthermia enhances radiation plus immunotherapy mediated pancreatic tumor growth inhibition in mice

University of Maryland-Baltimore, Baltimore, MD, USA

STM 2018 EDUCATION DAY WORKSHOP

LIGHTS, CAMERAS, AND THERMAL BIOLOGY IN ACTION

MONDAY, MAY 7, 10:00AM – 3:00PM / CANYON I, III

SPEAKERS		
	SHELLEY BUFFENSTEIN	LOTHAR LILGE
	ANTONIO DE MAIO	ALIREZA MOHAMMADI
	ROB GRIFFIN	BETSY REPASKY

The 2017 STM Meeting initiated a "Refresher Workshop Day", with an education session prior to the official start of the meeting, which included talks from experts in various areas of thermal medicine. The goal was to give the audience a chance to familiarize themselves with some of the Meeting's upcoming topics in a very informal setting. The 2018 Meeting will have a similar session, but now called "Education Day Workshop".

This session will feature speakers discussing:

- light propagation in biologic tissues
- the history and continuing story of heat shock proteins and cell stress
- nanoparticles across the spectrum
- the immunology of hyperthermia and what it means to medicine
- the history and evolution of intracranial hyperthermia
- what unique organisms can tell us about stress biology

This will again be an informal session (with time off for lunch), where interactions/banter with the speakers are encouraged, and the goal is to leave the session smarter than when you came in.

2018 STM ANNUAL MEETING PRESIDENT'S SYMPOSIUM

TUCSON, ARIZONA

WEDNESDAY, MAY 9, 12:00PM – 1:30PM / CANYON I, III

35 YEARS OF THERMAL MEDICINE
CONVERGENCE SCIENCE: WHAT DOES IT MEAN FOR OUR FUTURE AND HOW DO WE FUND IT?

The term convergence science was coined by a blue ribbon panel convened in 2011 by MIT and the AAAS to identify 'the creation of a new model' in which engineering and physical sciences, among other disciplines, join forces with the life sciences. Some have defined convergence as the result of a true cross-pollination of intellect and expertise; while others have observed that practitioners of convergent science must learn to become generalists in order to benefit from other disciplines. All agree, however that convergence goes beyond traditional collaborative science, thus demanding more intellectual flexibility and breadth from participating individuals.

Inherent to the convergent approach is the potential to upset paradigms and change established practices. Historically, revolutions in science were often realized when individuals approached a phenomenon from a perspective beyond the boundaries accepted by the established experts. It is recognized that transformative advances are needed in biomedical research and clinical practice to address challenging problems and to treat difficult diseases. Yet, we are faced with an inevitable conundrum – how does one approach a potentially transformative research endeavor when the established practices of the scientific enterprise and funding agencies measure the value of a proposed research direction with existing metrics?

Thermal medicine is an embodiment of convergence science. Our society, its members, and its mission for the past 35 years, have embodied this philosophy. In this symposium, perspectives of convergence science and funding philosophy intended to drive paradigm altering research and thinking will be presented.

ROBERT IVKOV, PHD
President, Society for Thermal Medicine

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

Associate Editor,
International Journal of Hyperthermia

2018 STM ANNUAL MEETING PRESIDENT'S SYMPOSIUM

TUCSON, ARIZONA

WEDNESDAY, MAY 9, 12:00PM – 1:30PM / CANYON I, III

35 YEARS OF THERMAL MEDICINE
CONVERGENCE SCIENCE: WHAT DOES IT MEAN FOR OUR FUTURE AND HOW DO WE FUND IT?

JAYNE KOSKINAS TED GIOVANIS Foundation for Health and Policy

Theodore (Ted) Giovanis, FHFMA, MBA, is President and founder of the Jayne Koskinas Ted Giovanis Foundation for Health and Policy that conducts research in the policy and clinical arenas. He is also the President of T. Giovanis & Company, LLC a health policy and reimbursement consultancy, specializing in strategic reimbursement advice and advocacy on behalf of a wide variety of clients. Ted's work has included both the Medicare and Medicaid payment areas across a wide cross section of the different payment systems over the past 40 years in the health policy, reimbursement and advocacy arenas.

Well-known in the industry, Ted is a recognized expert in Medicare and Medicaid regulation, has been an expert witness in numerous court cases and was solely responsible for the identification and prosecution of the rural floor budget neutrality issue, which resulted in a multibillion-dollar settlement for hospitals nationally and allowed for the establishment of the JKTG Foundation.

He has also served as a hospital system CFO, controller and internal auditor along with numerous other hospital management and reimbursement/ payment positions. Earlier in his career, Ted was one of the original staff at the Maryland Health Services Cost Review Commission and was a designer of the GIR (Guaranteed Inpatient Revenue) and TPR (Total Patient Revenue) payment systems.

Additionally, Ted is an accomplished professional sports car driver and team owner in the International MotorSports Association.

JOHNS HOPKINS MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER

Eleni A. Liapi, MD, ScM, is an Assistant Professor of Radiology and Oncology, at the Department of Radiology and the Sidney Kimmel Comprehensive Cancer Center, of the Johns Hopkins University School of Medicine, in Baltimore, MD. Dr. Liapi received her medical degree from the University of Ioannina, Faculty of Medicine, Ioannina in 1996, and a Master of Science (Sc.M.) in Clinical Investigation from the Johns Hopkins Bloomberg School of Public Health, in 2015. She completed a Diagnostic Radiology residency in Athens, Greece (2003) and a post-doctoral fellowship in Interventional Radiology at the Johns Hopkins University School of Medicine (2010). Dr. Liapi's research interests include translational and clinical interventional oncologic and image-guided interventions, magnetic hyperthermia, assessment of tumor response to therapy using functional MRI and CT techniques, as well as evaluation of patient reported outcomes. Dr. Liapi has been the recipient of several NIH awards, as well as a recipient of the ASCO GI symposium Merit Award in 2007, the SIR Resident/Fellow Award in 2007, the Gatewood Award in 2010 and the Johns Hopkins Clinical Research Scholarship in 2011. Dr. Liapi has co-authored and presented more than 60 peer-reviewed publications, 10 book chapters and numerous national and international scientific meeting presentations on imaging.

STM/ASME TREATMENT PLANNING WORKSHOP: CLOSING THE GAP BETWEEN THERMAL MODELING/TREATMENT PLANNING AND CLINICAL PRACTICE

A GAP ANALYSIS WORKSHOP

MODERATED BY

RYAN CRANE, *Director, Standards and Certification Initiatives, ASME*

CHRISTINE REILLEY, *Director, Bioengineering and Healthcare, ASME*

LUIS PULGARIN, *Project engineering advisor, Standards and Certification Initiatives, ASME*

CHRIS DIEDERICH, PHD, *University of California San Francisco,STM*

ROBERT IVKOV, PHD, *Johns Hopkins University School of Medicine, STM*

PUNIT PRAKASH, PHD, *Kansas State University, STM*

PAUL STAUFFER, PHD, *Thomas Jefferson University, STM*

TUESDAY, MAY 8, 2:00PM – 4:00PM / CANYON I, III

Why Attend?

• Uncover standards gaps and industry pain points in the thermal medicine area with a focus on validating and transforming imaging data into treatment planning using computational modeling. Specific modalities to explore include HIFU, HIPEC, ablation devices, hyperthermia, and cryo devices. The Workshop will also offer an opportunity to discuss other thermal medicine-related topics, applications, and standards needs.

Who Should Attend?

- Clinical practitioners
- Medical physicists
- Product developers
- Researchers

PROGRAM

SUNDAY, MAY 6TH 2018

10:00 - 13:00	**STM Governing Council Meeting**	| Acacia
14:00 - 16:00	**2019 STM Meeting Planning Session**	| Acacia
16:00 - 18:30	**International Journal of Hyperthermia Editorial Board Meeting**	| Acacia

MONDAY, MAY 7TH 2018

08:00 - 11:00	**Other STM Committee Meetings**	| Aster II
08:00 - 17:00	**Registration**	| Lobby Foyer
09:00 - 10:30	**STM Finance Committee Meeting**	| Aster I
10:00 - 15:00	**EDUCATION DAY WORKSHOP - Lights, Cameras, and Thermal Biology in Action** Chair: Michael Graner SPEAKERS: Antonio De Maio Lothar Lilge Betsy Repasky Alireza Mohammadi Rob Griffin Shelley Buffenstein	| Canyon I, III
17:00 - 19:00	**Keynote Session** Chair: Michael Graner MON 2 | Discovering the Signal Within the Noise: Where are the Disease Biomarkers? C. Adami, Michigan State University, Biomedical Physical Sciences, East Lansing, Michigan, USA	| Canyon I, III
19:00 - 21:30	**Welcome Reception**	| Fiesta Area

TUESDAY, MAY 8TH 2018

07:00 - 08:00 **Breakfast** | Lobby Foyer

08:00 - 09:00 **Plenary Session I** | Canyon I, III

Chair: Santiago Camacho López

TUES 1 | Personalize treatment planning for Photodynamic and Photothermal therapies; Implementations of rapid Monte Carlo simulations and linearized optimization algorithms.

L. Lilge, Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada

08:00 - 17:00 **Registration** | Lobby Foyer

09:00 - 09:30 **Break and Exhibit Time** | Sonoran Room

09:30 - 11:30 **Nanoparticles I- Magnetic, Metallic, and Mighty** | Canyon I, III

Chairs: Paul Stauffer, Samir Jenkins

TUES 2 | Designing Iron Oxide Nanoparticles for Image Guided Thermal Medical Applications

H. Ring, University of Minnesota, Minneapolis, MN, USA.

TUES 3 | Design and Testing of a Stable, Scaled-Up, High Heating Silica Coated Iron Oxide Nanoparticle for Biomedical Applications

Z. Gao, University of Minnesota, Minneapolis, Minnesota, USA

TUES 4 | Nanoparticle-coated surfaces provide nanoscale insight for thermal medicine

S. Jenkins, University of Arkansas for Medical Sciences, Little Rock, AR, USA

TUES 5 | A Novel Noninvasive Microwave Device to Treat Localized Tumors at Very Low Energies

A. Copty, NIMD Ltd, Jerusalem, Israel, Israel

TUES 6 | Magnetic Nanoparticle Hyperthermia Triggered Drug Release for Treating Glioblastoma Multiforme

A. Attaluri, Pennsylvania State University - Harrisburg, Middletown, PA, USA.

TUES 7 | Initial Assessment of Simultaneous Magnetic Nanoparticle Hyperthermia and Brachytherapy of At-Risk Tissue Surrounding a Brain Tumor Resection Cavity

P. Stauffer, Thomas Jefferson University, Philadelphia, PA, USA.

09:30 - 11:30 **Laser Induced/Interstitial Thermal Therapy** | Indigo

Chairs: Jennifer Yu, Hilary Koech

TUES 8 | Laser interstitial thermal therapy for posterior fossa lesions: An initial experience.

H. Koech, Cleveland Clinic Foundation, Cleveland, OH, USA

TUES 9 | Laser Interstitial Thermal Therapy for Inoperable Brain Tumors of the Thalamus and Deep Brain Structures

R. Murayi, Cleveland Clinic Neurosurgery, Cleveland, OH, USA

TUES 10 | Laser interstitial thermal therapy for treatment of brain metastasis

A. Mohammadi, Cleveland Clinic, Cleveland, Ohio, USA

TUES 11 | The Role of Interstitial Thermal Therapy in Treatment of Glioblastoma

D. Krivosheya, Cleveland Clinic, Cleveland, OH, USA

TUES 12 | Progress on the development of Carbon Nanotubes for Photothermal Therapy of Glioblastoma

R. Singh, Wake Forest School of Medicine, Winston-Salem, NC, USA

TUES 13 | A clinically-oriented computational modelling: A radiofrequency ablation of liver with internally cooled wet electrode.

E. Ewertowska, BioMIT, Department of Electronic Engineering, Universitat Politècnica de València, Valencia, Spain.

09:30 - 11:30 **Thermal Medicine and Infectious Disease** | Verbena

Chairs: Nicole Levi-Polyachenko, Rajiv Chopra

TUES 14 | Biofilm Eradication Utilizing Alternating Magnetic Fields

D. Greenberg, University of Texas Southwestern Medical Center Department of Internal Medicine, Dallas, Texas, USA

TUES 15 | Eradication of biofilm on infected metal implants using alternating magnetic fields: understanding the response of bacteria to heat

R. Saini, UT Southwestern Medical Cneter, Dallas, Tx, USA

TUES 16 | Safety evaluation of pulsed alternating magnetic field (AMF) exposures of metal implants on surrounding tissues

R. Chopra, UT Southwestern Medical Center, Dallas, TX, USA

TUES 17 | Targeted Laser Therapy Synergistically Enhances Efficacy of Antibiotics against Multi-drug Resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* Biofilms

D. Kirui, Maxillofacial Injury and Disease Department, Naval Medical Research Unit, San Antonio, JBSA-Fort Sam Houston, Texas, USA

TUES 18 | Modulating *in vivo* thermal release and therapeutic outcomes with a versatile nanotherapeutic system designed for the targeted eradication of bacterial biofilms

D. Meeker, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.

TUES 19 | Thermal therapy as a potential catheter salvage strategy for central line infection

J. VanEpps, Departments of Emergency Medicine and Biomedical Engineering, Biointerfaces Institute, Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, Michigan, USA

TUES 20 | Proposal of new concepts to treat infectious diseases in the field of hyperthermia

D. Gazel, Gaziantep University, Faculty of Medicine, Sehitkamil, Gaziantep, Turkey.

11:30 - 14:00 **Lunch and Resort Time** | Other

14:00 - 16:00 **STM/ASME Treatment Planning Workshop: Closing the Gap Between Thermal Modeling/Treatment Planning and Clinical Practice**

Moderators:
Ryan Crane, Director, Standards and Certification Initiatives, ASME
Christine Reilley, Director, Bioengineering and Healthcare, ASME | Canyon I, III
Luis Pulgarin, Project Engineering Advisor, Standards and Certification Initiatives, ASME
Chris Diederich, PHD, University of California San Francisco, STM
Rob Ivkov, PHD, John Hopkins University School of Medicine, STM
Punit Prakash, PHD, Kansas State University, STM
Paul Stauffer, PHD, Thomas Jefferson University, STM

14:00 - 15:30 **Nanoparticles II - Biology of (Bio)-Nanoparticles** | Indigo

Chairs: Antonio De Maio, Robert Griffin

TUES 21 | The HSP-Accessorized Exosome: Presence in States of Danger, Disease, and Disruption

M. Graner, University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado, USA.

TUES 22 | Heat-activated release and thermal enhancement of synergistic chemotherapies

M. Dunne, University of Toronto, Toronto, Ontario, Canada.

TUES 23 | DOES THE COMBINATION OF NANOPARTICLE HEAT THERAPY AND FOCAL RADIOTHERAPY CREATE AN ABSCOPAL EFFECT IN MOUSE PROSTATE CANCER MODEL?

M. Helenius, Johns Hopkins School of Medicine, Baltimore, MD, USA

TUES 24 | Local Mapping and Photothermal Tumor Treatment using Galectin-1 Targeting Nanomaterials

S. Jenkins, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

TUES 25 | Human urine extracellular vesicles, a potential biomarker for disease conditions

A. De Maio, UC San Diego School of Medicine, San Diego, CA, USA.

14:00 - 15:30 **Photonics South by Southwest** | Verbena

Chair: Juan Hernandez-Cordero

TUES 26 | TRIPLE FLUORESCENCE LIGHT SHEET MICROSCOPY WITH A SINGLE CHANNEL DETECTION

I. ROCHA-MENDOZA, CICESE, Ensenada, Baja California, Mexico

TUES 27 | COMPUTATIONAL STUDY OF TEMPERATURES IN A MULTILAYER MEDIUM OF AGAR AND BACTERIA IRRADIATED BY A LASER THROUGH THE NC-YSZ IMPLANT

M. Trujillo, Universitat Politècnica de València, Valencia, Spain.

TUES 28 | Fiber optic temperature sensors with polymer-based fluorescent materials

S. Sánchez, Instituto de Investigaciones en Materiales, IIM UNAM, México, D.F., Mexico

TUES 29 | Temperature changes in metallic nanoparticles estimated by Raman spectroscopy
J. Calvillo-Vázquez, CICESE, Ensenada, Baja California, Mexico.

TUES 30 | Measuring thermal gradients on micrometric areas using laser induced fluorescence
J. Hernandez-Cordero, Instituto de Investigaciones en Materiales Universidad Nacional Autonoma de Mexico, Cd. Universitaria Mexico, D.F. 04510,, Mexico

15:30 - 16:00 **Break and Exhibit Time** | Sonoran Room

16:00 - 18:00 **Ultrasound I - Clinical and Pre-Clinical** | Canyon I, III
Chairs: Cliff Burdette, Marc Santos

TUES 31 | Effect of Temperature Elevation on Short Duration Focused Ultrasound Hyperthermia Mediated Drug Delivery Using Thermosensitive Liposomes and Two-Photon Microscopy
M. Santos, Sunnybrook Research Institute, Toronto, Ontario, Canada.

TUES 32 | The Feasibility of using Focused Ultrasound to Induce Hyperthermia through the Intact Skull
A. Hughes, Sunnybrook Research Institute, Toronto, ON, Canada.

TUES 33 | Safety and feasibility of MR-HIFU mild hyperthermia with radiation and chemotherapy for recurrent rectal cancer
W. Chu, Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

TUES 34 | MRI-guided transurethral ultrasound ablation of the prostate (TULSA): state of the art
R. Staruch, Western University, London Health Sciences Centre, London, ON, Canada.

TUES 35 | Catheter-based ultrasound thermal ablation of tumors in the pancreas
C. Burdette, Acoustic MedSystems, Savoy, IL, USA.

16:00 - 18:00 **Clinical/Therapeutics I - Trials, Experiences, Retrospectives** | Indigo
Chairs: Zeljko Vujaskovic, Rudi Wessalowski

TUES 36 | Evaluation of interstitially measured and simulated temperature distributions during localregional hyperthermia treament in patients with high-risk soft-tissue sarcoma.

B. Aklan, University of Munich-Campus Grosshadern, Medical Clinic III, Munich, Bavaria, Germany.

TUES 37 | Systemic Chemotherapy plus Regional Hyperthermia for Treatment of Localized High-Risk Soft Tissue Sarcomas in Childhood

R. Wessalowski, Heinrich-Heine-University, Medical Faculty, Clinic of Pediatric Oncology, Hematology and Clinical Immunology, Düsseldorf, Germany.

TUES 38 | External Thermal Therapy combined with Radiation Therapy Results in Modest Toxicities and the Promise of Increased Efficacy: 5 years of Experience

J. Molitoris, University of Maryland Medical Center, Baltimore, MD, USA.

TUES 39 | Single Institution Experience of the Addition of Thermal therapy to Radiation Therapy for Cutaneous Malignancies

E. Kowalski, University of Maryland Medical Center, Baltimore, MD, USA.

TUES 40 | Concurrent Pencil Beam Scanning Proton Therapy and External Thermal Therapy: Initial Clinical Experience and Safety Evaluation

J. Snider, University of Maryland School of Medicine, Baltimore, MD, USA.

* TUES 41 | Concurrent Interstitial Thermal Therapy and Interstitial Brachytherapy for Pelvic Malignancies: A Single Institution Experience.

C. DeCesaris, University of Maryland Medical Center, Baltimore, MD, USA *2018 NITA WINNER

* TUES 42 | The Impact of Hyperthermia Therapy on Patient Referrals and Patterns of Care within a Radiation Oncology Department

J. Remick, University of Maryland Department of Radiation Oncology, Baltimore, MD, USA *2018 NITA WINNER

16:00 - 18:00 **Immunology I - Thermal Inputs, Immune Outputs** | Verbena

Chairs: Steve Fiering, Sandrine Soman

* TUES 43 | Hyperthermia enhances radiation plus immunotherapy mediated pancreatic tumor growth inhibition in mice.
S. Soman, University of Maryland-Baltimore, Baltimore, MD, USA.
*2018 NITA WINNER

TUES 44 | Enhancing the abscopal effect of local thermo-radiotherapy by immune checkpoint inhibitors
A. Oei, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

TUES 45 | PHOTOTHERMAL THERAPY GENERATES A THERMAL WINDOW OF IMMUNOGENIC CELL DEATH IN NEUROBLASTOMA
E. Sweeney, George Washington University, Washington, DC, USA.

TUES 46 | CpG-loaded Prussian blue nanoparticles as photothermal immunotherapy agents for cancer
J. Cano-Mejia, University of Maryland, College Park, MD, USA.

TUES 47 | *In situ* vaccination: using local antitumor immune treatments to generate systemic anti-tumor immune response
S. Fiering, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire, USA.

18:00 - 20:00 **Poster Session and Competition** | Sonoran Room

POST 1 | Clinical proofs of oncothermia
O. Szasz, Biotechnics Department, St. Istvan University, Budaors, Hungary.

POST 2 | THE EMERGING ROLE OF HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) IN CANCER IMMUNOMODULATION
I. Elhelf, University of Iowa, Iowa City, IA, USA.

POST 3 | The cryo-thermal therapy drives macrophages polarization toward M1 phenotype that remodels the tumor microenvironment triggering the durable anti-tumor memory immunity
P. Liu, School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China

POST 4 | Transmit-Only Receive-Only Half-birdcage/Surface Coil Pair for MR-guided focused ultrasound Hyperthermia on Small Rodents

A. Beserra, Lakehead University, Thunder Bay, Ontario, Canada.

POST 5 | Targetability of osteomyelitis using MR-guided focused ultrasound

A. Beserra, Lakehead University, Thunder Bay, Ontario, Canada.

POST 6 | Nanowarming of Aortic Heart Valves

Z. Gao, University of Minnesota, Minneapolis, Minnesota, USA.

POST 7 | Extending a Rapid Ultrasound Beam Modeling Method to Include Nonlinear Effects in HIFU

D. Christensen, University of Utah, Salt Lake City, Utah, USA

POST 8 | Impact of pulsed alternating magnetic field (AMF) parameters on the eradication of biofilm on metal surfaces: Implications for treatment of prosthetic joint infection.

S. Shaikh, UT Southwestern Medical Center, Dallas, Texas, USA

POST 9 | Hyaluronic Acid Targeted Nanoparticles For Detection and Targeting of Peritoneally Disseminated Colorectal Cancer

E. McCabe-Lankford, Wake Forest University Health Sciences, Winston Salem, North Carolina, USA

POST 10 | The use of fluorescent and heat generating polymer nanoparticles as a novel treatment for Staphylococcus aureus skin lesions

N. Levi-Polyachenko, Department of Plastic and Reconstructive Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

POST 11 | Sectored-tubular transurethral ultrasound for thermal treatment of Stress Urinary Incontinence: patient specific simulations and validation

D. Liu, Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA.

WEDNESDAY, MAY 9TH 2018

07:00 - 08:00 **Breakfast** | Lobby Foyer

08:00 - 09:00 **Plenary Session 2** | Canyon I, III

Chair: Michael Graner

WED 1 | Endoplasmic Reticulum Chaperones in Health and Disease: Molecular Mechanisms and Therapeutic Potential
A. Lee, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

08:00 - 17:00 **Registration** | Lobby Foyer

09:00 - 09:30 **Break and Exhibit Time** | Sonoran Room

09:30 - 11:30 **Clinical/Therapeutic II - Trials, Plans, History, and Future** | Canyon I, III
Chairs: Mark Hurwitz, Lee Hwang

*WED 2 | Stereotactic laser ablation as a therapeutic option for recurrent glioblastoma: a large single institutional experience
L. Hwang, The Cleveland Clinic, Cleveland, OH, USA
*2018 NITA WINNER

WED 3 | MR-guided thermal therapy: Implementation of a new MRI-hyperthermia-hybridsystem into clinical routine.
B. Aklan, University of Munich-Campus Grosshadern, Medical Clinic III, Munich, Bavaria, Germany.

WED 4 | Real-time monitoring of thermal therapies with volumetric multispectral optoacoustic tomography
D. Razansky, Technical University of Munich and Helmholtz Center Munich, Neuherberg, Germany

WED 5 | ANALYSIS OF CLINICAL DATA TO DETERMINE THE MINIMUM NUMBER OF SENSORS REQUIRED FOR ADEQUATE SKIN TEMPERATURE MONITORING OF SUPERFICIAL HYPERTHERMIA
H. Crezee, Academic Medical Center, Amsterdam, Netherlands.

WED 6 | Hot at Dawn - A Historical look into the thermal roots of Hippocratic Medicine
W. Remigio, Misericordia University, Dallas, Pennsylvania, USA

WED 7 | The Cancer Therapy Immune Revolution: Can Thermal Therapy be Relevant?
J. Bull, The University of Texas McGovern Medical School, Houston, TX, USA

* WED 8 | Toxicity and Efficacy outcomes of concurrent hyperthermia and radiation therapy in soft tissue sarcoma
S. Rice, University of Maryland Department of Radiation Oncology, Baltimore, MD, USA *2018 NITA WINNER

09:30 - 11:30 **Biology I - Thermal Effects on Tissues** | Indigo

Chair: Alexzander Asea

WED 9 | In vivo Hyperthermic Electrophilic Hydrolysis: Thermoembolization in Swine Liver

E. Cressman, MD Anderson Cancer Center, Houston, TX, USA

WED 10 | Microwave ablation of the adrenal gland for treatment of Conn's syndrome: preliminary results from an *in vivo* study in pigs

P. Prakash, Kansas State University, Manhattan, KS, USA.

WED 11 | Tissue Freeze Propagation Speed is Modulated by Supercooling Degree and Cryoprotectants

L. Zeng, Allergan, Pleasanton, CA, USA

WED 12 | Response of arterial vessels to two cardiovascular stressors: heat and dobutamine

A. Crouch, University of Michigan, Ann Arbor, MI, USA

WED 13 | Real Time Quantitative CT Monitoring of Thermochemistry by Novel Application of CsOH

E. Cressman, MD Anderson Cancer Center, Houston, TX, USA

WED 14 | A molecular dynamics approach for evaluating osmotic and thermal stress on extracellular proteins

D. Fuentes, MD Anderson, Houston, TX, USA.

09:30 - 11:30 **Nanoparticles III - Delivery by Design** | Aster

Chairs: Dieter Haemmerich, Timo L.M. ten Hagen

WED 15 | Drug delivery across the blood-brain barrier with hyperthermia and temperature sensitive liposomes

D. Haemmerich, Med. Univ. of South Carolina, Charleston, SC, USA

WED 16 | Novel Method for Systemic Removal of Thermosensitive Liposomal Doxorubicin to Reduce Toxicities

A. Motamarry, Medical University of South Carolina, Charleston, SC, USA

WED 17 | The need to change chemotherapy with hyperthermia-steered nano-devices

T. ten Hagen, Erasmus MC, Rotterdam, Netherlands

WED 18 | In vivo derived computational model predicts release kinetics of thermosensitive liposomes

D. Haemmerich, Med. Univ. of South Carolina, Charleston, SC, USA.

WED 19 | Nanoparticle Design for Commercial Photothermal Therapies

A. Saunders, nanoComposix, Inc., San Diego, California, USA

11:30 - 12:00 **NIH Update-Keyvan Farahani** | Canyon I, III

Chair: Michael Graner

12:00 - 13:30 **Presidential Symposium: 35 years of thermal medicine Convergence science: What does it mean for our future and how do we fund it?** | Canyon I, III

Chair: Robert Ivkov

Theodore (Ted) Giovanis, FHFMA, MBA, President and founder of the Jayne Koskinas Ted Giovanis Foundation for Health and Policy

and

Eleni A. Liapi, MD, ScM, Assistant Professor of Radiology and Oncology, Department of Radiology and the Sidney Kimmel Comprehensive
Cancer Center, of the Johns Hopkins University School of Medicine, Baltimore, MD.

13:30 - 15:00 **Resort Time** | Other

15:00 - 15:30 **Break and Exhibit Time** | Sonoran Room

15:30 - 18:00 **NITA and Poster Awards; Dewey Award and Robinson Award Presentations** | Canyon I, III

Chairs: Dieter Haemmerich, Jason Stafford, Mike Graner, Robert Ivkov

WED 22 | Students Have Always Led the Way! 2018 William C. Dewey Award

E. Repasky, Roswell Park Comprehensive Cancer Center, Dept. of Immunology, Buffalo, NY, US

WED 21 | 2018 J. Eugene Robinson Lecture: Thermo-Immunology: at the Crossroads of Immunity and Immunotherapy

S. Evans, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

19:30 - 21:30 **Robinson Award Dinner** | Murphey Patio

THURSDAY, MAY 10TH 2018

07:00 - 08:00 **Breakfast** | Lobby Foyer

08:00 - 09:00 **Plenary Session 3** | Canyon I, III
Chair: Elizabeth Repasky

THUR 1 | The Unusual Biology of the Longest Lived Rodent, the Naked Mole-rat.
R. Buffenstein, Calico Life Sciences, South San Francisco, California, USA.

08:00 - 15:30 **Registration** | Lobby Foyer

09:00 - 09:30 **Break and Exhibit Time** | Sonoran Room

09:30 - 11:30 **Ultrasound II - Advances in Therapeutic Ultrasound** | Canyon I, III
Chairs: Chris Diederich, Dong Liu

THUR 2 | Preclinical MRI guided focused ultrasound robotic system.
C. Damianou, Cyprus University of Technology, Limassol, Limassol, Cyprus

* THUR 3 | Microbubble-Assisted MRI-guided Focused Ultrasound for Hyperthermia at Reduced Power Levels
M. Santos, Sunnybrook Research Institute, Toronto, Ontario, Canada. *2018 NITA WINNER

THUR 4 | A method for quality assurance in magnetic resonance imaging-guided high intensity focused ultrasound (MRgHIFU) mild hyperthermia (MHT)
L. Zhu, Washington University in St. Louis, Saint Louis, Missouri, USA

* THUR 5 | Endobronchial Ultrasound Thermal Therapy of Pulmonary Malignancies: a Theoretical Investigation in Patient Specific Lung Models
D. Liu, Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA *2018 NITA WINNER

THUR 6 | Magnetic resonance–guided interstitial high-intensity interventional ultrasound for brain tumor ablation
E. Burdette, Acoustic MedSystems Inc., Savoy, IL, USA.

09:30 - 11:30 **Immunology II - the Hot and the Cold of It** | Indigo

Chairs: Elizabeth Repasky, Qi Shao

* THUR 7 | Comparison of in vitro cellular response and immune priming of hyperthermia, cryosurgery and irreversible electroporation

Q. Shao, University of Minnesota, Minneapolis, Minnesota, USA
*2018 NITA WINNER

THUR 8 | Dynamic imaging of immune effector function during whole-body fever-range hyperthermia

B. Weigelin, MD Anderson Cancer Center, Houston, TX, USA.

THUR 9 | The importance of understanding the impact of housing temperature on interpretation of experiments evaluating the role of hyperthermia on immunity and physiological responses in laboratory mice

E. Repasky, Roswell Park Comprehensive Cancer Center, Dept. of Immunology, Buffalo, NY, USA

THUR 10 | Clinical Study on Immunological Effect of Cryo-thermal Therapy of Liver Cancer

P. Liu, School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China.

THUR 11 | Effects of Hypofractionation and low dose mNP hyperthermia on Tumor Immunogenetics

K. Duval, Thayer School of Engineering at Dartmouth College, Hanover, NH, USA.

09:30 - 11:30 **HIPEC I - Trials, Reviews, Perspectives** | Aster

Chairs: John Stewart, Magi Senthil

THUR 12 | Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Global Perspective on Rationale and Results to Date

P. Sugarbaker, Washington Cancer Institute, Washington, DC, USA

THUR 13 | Cytoreductive Surgery (CRS) and Hyperthermic IntraperitonealChemotherapy (HIPEC): Single-Center Experience

D. Kecmanovic, School of Medicine, University of Belgrade, Dr Subotica 6, Belgrade, Serbia.

THUR 14 | HIPEC, Tumor Organoids, and Personalized Medicine

K. Votanopoulos, Department of Surgery- Oncology, Wake Forest Baptist Medical Center, Winston-Salem, NC, USA.

THUR 15 | Enhanced Recovery Protocol (ERP) Improves Outcomes in Patients Undergoing Cytoreductive Surgery (CRS) and Intraoperative Heated Intraperitoneal Chemotherapy (HIPEC) for Pseudomyxoma Peritoneii (PMP)

P. Collister, MD, Creighton, Omaha, Nebraska, USA.

THUR 16 | Response to Laparoscopic Hyperthermic Intraperitoneal Chemotherapy as an Induction Chemotherapy in Patients with Unresectable Peritoneal Surface Malignancies

E. Canbay, BIRUNI UNIVERSITY FACULTY OF MEDICINE DEPT. OF GENERAL SURGERY, Istanbul, Turkey
NPO HIPEC ISTANBUL CENTER FOR TREATMENT OF PERITONEAL SURFACE MALIGNANCIES, Istanbul, Turkey

THUR 17 | Infectious complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

N. Arslan, Department of Colorectal Surgery, Liv Hospital Ulus, Istanbul, Turkey.

THUR 18 | 300 Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy procedures : The National Cancer Centre Singapore Experience

G. Tan, National Cancer Centre Singapore, Singapore, Singapore

11:30 - 13:00 **STM Business Meeting and Working Lunch (STM members only)** | Canyon I, III

13:00 - 15:00 **HIPEC II - Trials, Tribulations, and the Future** | Canyon I, III

Chairs: Paul Sugarbaker, Brian Loggie

THUR 19 | Does the Chemotherapy for Heated Intraperitoneal Chemotherapy Matter?

J. Stewart, Duke University School of Medicine, Durham, North Carolina, USA

THUR 20 | A surgeon's perspective on choosing a chemotherapy agent for HIPEC. Evolution from Mitomycin C to Carboplatin

B. Loggie, Creighton University, Division of Surgical Oncology, Omaha, NE, USA

THUR 21 | EARLY AND LONG-TERM OUTCOMES OF CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAOPERATIVE INTRAPERITONEAL CHEMOTHERAPY IN PATIENTS WITH PERITONEAL SURFACE MALIGNANT DISEASES

E. Canbay, BIRUNI UNIVERSITY FACULTY OF MEDICINE DEPT. OF GENERAL SURGERY, Istanbul, Turkey
NPO HIPEC ISTANBUL CENTER FOR TREATMENT OF PERITONEAL SURFACE MALIGNANCIES, Istanbul, Turkey

THUR 22 | Liquid Biopsy in Peritoneal Carcinomatosis: Role of Exosomes

M. Senthil, Loma Linda University Medical Center, Loma Linda, CA, USA

THUR 23 | A potential role for Carcinoembryonic Antigen in mediating Inflammation and Angiogenesis in Pseudomyxoma Peritonei.

P. Thomas, Departments of Surgery and Biomedical Sciences, Creighton University, Omaha, NE, USA

THUR 24 | Is CRS & HIPEC a safe and effective palliative treatment strategy in patients with refractory symptomatic peritoneal metastasis?

J. Foster, University of Nebraska Medical Center, Omaha, NE, USA

13:00 - 15:00 **Modeling, Monitoring, Measuring, and Computation** | Indigo

Chair: Sam Fahrenholtz

THUR 26 | The Essentials of Magnetic Fluid Heating Evaluation

H. Ring, University of Minnesota, Minneapolis, MN, USA.

THUR 27 | Title: MRI monitoring of thermoembolization

S. Fahrenholtz, Dept of Imaging Physics UT MD Anderson Cancer Center, Houston, TX, USA.

THUR 28 | MR Thermometry: New MR Scanners – New Challenges

M. Wadepohl, Dr. Sennewald Medizintechnik GmbH, Munich, Germany.

THUR 30 | Feasibility of heating brain tumors using a 915 MHz annular phased array with 72 dipole antennas in a 3-ring configuration

D. Rodrigues, Thomas Jefferson University, Philadelphia, PA, USA.

13:00 - 15:00 **Biology II - Combined Moieties to Improve Thermal Therapies** | Aster

Chairs: Michael Graner, Chunxiao Guo

* THUR 31 | Convergent toxicity of hyperthermic and osmotic stress sensitizes HCC cells by inhibition of HSF1

C. Guo, MD Anderson Cancer Center, Houston, TX, USA.
*2018 NITA WINNER

THUR 32 | Galectin-1 inhibition overcomes acquired radiation and associated hyperthermia resistance in lung cancer

R. Dings, UAMS, Little Rock, Arkansas, USA.

THUR 33 | Comparing tumor response to photon irradiation and hyperthermia with that seen following irradiation with carbon ions alone

M. Horsman, Dept. Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

THUR 34 | Hyperthermia-mediated drug delivery induces biological effects at the tumor and molecular levels that improve cisplatin efficacy in triple negative breast cancer

M. Dunne, University of Toronto, Toronto, Ontario, Canada.

THUR 35 | Breast cancer treatment in BALB/C mice with magnetic fluid hyperthermia and its molecular mechanisms

M. Salimi, Tehran university of medical sciences, Tehran, Iran, Islamic Republic of

THUR 36 | Combined mild hyperosmotic and hyperthermal stresses overcome the cell survival mechanisms of multiple human hepatocellular cancer cell lines

E. Cressman, MD Anderson Cancer Center, Houston, TX, USA.

15:00 - 15:30 **Closing Program** | Canyon I, III

MON 1

EDUCATION DAY WORKSHOP - LIGHTS, CAMERAS, AND THERMAL BIOLOGY IN ACTION

Michael Graner

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

EDUCATION DAY WORKSHOP - LIGHTS, CAMERAS, AND THERMAL BIOLOGY IN ACTION

Lothar Lilge[1], Antonio de Maio[2], Rob Griffin[3], Betsy Repasky[4], Shelley Buffenstein[5], Alireza Mohammadi[6]
[1] *Department of Medical Biophysics, University of Toronto and the Ontario Cancer Institute, Princess Margaret Cancer Centre, UHN.* [2] *Departments of Surgery and Neuroscience, University of California San Diego School of Medicine* [3] *Department of Radiation Oncology, College of Medicine, University of Arkansas for Medical Sciences* [4] *Department of Immunology, Roswell Park Comprehensive Cancer Center*
[5] *Brain Tumor and Neuro-Oncology Center, Cleveland Clinic* [6] *Calico*

The 2017 STM Meeting initiated a "Refresher Workshop Day", with an education session prior to the official start of the meeting, which included talks from experts in various areas of thermal medicine. The goal was to give the audience a chance to familiarize themselves with some of the Meeting's upcoming topics in a very informal setting. The 2018 Meeting will have a similar session, but now called "Education Day Workshop". This session will feature speakers discussing

- light propagation in biologic tissues

- the history and continuing story of heat shock proteins and cell stress

- nanoparticles across the spectrum

- the immunology of hyperthermia and what it means to medicine

- the history and evolution of intracranial hyperthermia

- what unique organisms can tell us about stress biology

This will again be an informal session (with time off for lunch), where interactions/banter with the speakers are encouraged, and the goal is to leave the session smarter than when you came in. No pre-registration is required, but it would be nice to let us know if you plan to attend so that we can make appropriate space requests.

MON 2

DISCOVERING THE SIGNAL WITHIN THE NOISE: WHERE ARE THE DISEASE BIOMARKERS?

Christoph Adami

Michigan State University, Biomedical Physical Sciences, East Lansing, Michigan, USA

The following situation is encountered over and over again when dealing with biological data: A researchers is looking for a causative element for a particular effect. A set of plausible candidates are identified, and their effects are studied one by one. Disappointingly, each candidate only shows zero effect or at best a weak one, even if the investigator has other evidence that the agent must be involved. This scenario plays itself out when looking for genes that influence a trait, for neurons that contribute to a particular behavior, or for biomarkers that indicate a disease state. What all these situations have in common is that the investigator assumes that information is additive. In this talk I will introduce the concept of information mathematically, and show that because information is not additive, it is possible that a set of elements together can carry perfect information when each of the elements by themselves carry none of it (the hallmark of cryptography). Realizing that in biology information tends to be encoded cryptographically suggests the use of new tools that search for biomarkers via code-breaking techniques.

TUES 1

PERSONALIZE TREATMENT PLANNING FOR PHOTODYNAMIC AND PHOTOTHERMAL THERAPIES; IMPLEMENTATIONS OF RAPID MONTE CARLO SIMULATIONS AND LINEARIZED OPTIMIZATION ALGORITHMS.

Lothar Lilge

Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada

Photons, just like phonons, are an attractive thermal source for raising the temperature in biological tissues. The advantages of photons include; first, by selecting a particular wavelength, the absorption can be preferentially suggested towards a particular chromophore, in particular, melanin, haemoglobin, lipids or water come to mind; second,readily available light sources enable heat deposition over minutes as required for hyperthermia or photocoagulation, or within short pulses to target particular absorbers as implemented in selective photothermolysis. For controlled thermal therapies, the spatial and temporal distribution of the absorbed photon density is essential but difficult to predict or optimize, particularly for interstitial applications in proximity to sensitive structures. We present a Monte Carlo based approach to optimize the photon source distribution as applied to photodynamic therapy which is readily applicable to thermal therapies. For thermal therapies, the bioheat transfer equation (BHTE) needs to be applied for source optimization, while in photodynamic therapy (PDT) the reactive oxygen species (ROS) based cytotoxic dose is used.

The approach is based on our publicly available tetrahedral mesh generation and Monte Carlo codes and a novel linear optimization approach for light source placement. The result quality exceeds that of the commonly used Cimmino algorithm.

The workflow follows that applied in radiation oncology, with the oncologist defining the target volume and the desired minimum target dose and maximum permissible organ at risk (OAR) dose. Organs are delineated, and a tetrahedral mesh is generated. A large number of photon sources are placed throughout the target tissue, and the resulting primary absorbed photon distribution based on population averaged tissue optical properties is calculated. The optical power of each source is adjusted to optimize the ROS or BHTE dose volume histogram for the target and proximal OAR for PDT or thermal therapies respectively. Photon sources contribute little to the dose distribution are iteratively removed.

Simulations for 9 virtual brain tumours showed that while the attainable target dose is equal to that of the Cimmino algorithm, the volume of the OARs receiving excessive dose can be reduced by up to 50%, even for very complicated tumour shapes.

The work plan currently developed allows the generation of treatment plans for photon-based therapies in as little as 2-3 hours depending on the complexity of target and organ delineations required.

TUES 2

DESIGNING IRON OXIDE NANOPARTICLES FOR IMAGE GUIDED THERMAL MEDICAL APPLICATIONS

Hattie Ring[1], Sheng Tong[2], Zhe Gao[1], Navid Manuchehrabadi[1], Sylvie Pailloux[1], Valerie Pierre[1], Christy Haynes[1], Michael Garwood[1], Gang Bao[2], John Bischof[1]

[1]University of Minnesota, Minneapolis, MN, USA. [2]Rice University, Houston, TX, USA

Background: The impact of IONP core design (size and shape) on magnetic resonance and heating characteristics is being explored by many research groups. For instance, there has been a tremendous effort for the last decade to create a nanoparticle with high heating as a function of weight (SAR_{Fe}). Within the clinical and pre-clinical setting, there is interest in image guided heating by combining MRI contrast as a diagnostic tool and thermal therapy as an interventional therapy or a regenerative medicine approach (i.e. Nanowarming). Often quantitative MRI is only performed on the transverse relaxation rate (R_2), because the rapid R_2 signal relaxation overwhelms detection of longitudinal relaxation rate (R_1) methods. However, with the use of newly emerging ultrashort T_2 ($T_2 = 1/R_2$) sensitive pulse sequences, such as swept imaging with Fourier transform (SWIFT), it is possible to acquire quantitative R_1 maps of IONPs at concentrations relevant for magnetic fluid hyperthermia. Herein, we take a comparative look at the heating and magnetic resonance properties of IONPs as a function of IONP core size.

Methods: Magnetite nanocrystals were synthesized with diameters from 6 – 32nm. Heating and MR relaxation characterization was performed on each IONP at concentrations ranging from 0.1 – 5 mg Fe/mL suspended in 1% agarose. Heating characterization, SAR_{Fe}, was performed using a 1 kW inductive heating system with a field strength at 20 kA/m and applied frequency at 190 ± 10% kHz. Relaxivity characterization (relaxation rate vs. IONP concentration) was performed at both 1.4 and 9.4T. At 9.4T, r_2*, r_2, and r_1 were acquired with gradient echo, spin echo, and SWIFT sequences, respectively. At 1.4T, r_2 and r_1 were acquired with a Carr-Purcell-Meiboom-Gill sequence and inversion recovery, respectively.

Results: With this specific synthesis, it has already been demonstrated that SAR_{Fe} increases with IONP diameter, plateauing at 32 nm (965.1 W/g Fe) within a Ferromagnetic regime. At 9.4T, we demonstrated that r_2 and r_2* increase with IONP diameter, while r_1 decreases with IONP diameter. At 1.4T, magnetic relaxation is dependent on both Curie and Neelian magnetic relaxation, and a local maxima is observed in the r_1. At both field strengths, the IONP optimized for heating was not well suited for R_1 quantitative MRI. Thus, each of the heating and imaging parameters may be optimized with a different IONP diameter.

Conclusion: The design of an optimal IONP for image guided heating will require a compromise between heating and imaging properties.

TUES 3

DESIGN AND TESTING OF A STABLE, SCALED-UP, HIGH HEATING SILICA COATED IRON OXIDE NANOPARTICLE FOR BIOMEDICAL APPLICATIONS

Zhe Gao, Hattie Ring, Michael Garwood, Christy Haynes, John Bischof

University of Minnesota, Minneapolis, Minnesota, USA

Background: Iron oxide nanoparticles (IONP) have been extensively studied for use in hyperthermia, imaging (MRI contrast), drug delivery and most recently cryopreservation (nanowarming). For all medical applications the IONP needs to be bio-compatible and capable of being scaled to commercial quantities; for hyperthermia and nanowarming it must also be high heating. Nanowarming necessitates stability in highly viscous (6 – 9 M) and ionic cryoprotectant (CPA) and avoid or minimize cellular uptake. Finally, the impact of the thickness of the silica coating will must be understood. Herein, we reported the design and testing of a silica coated iron oxide nanoparticle (sIONP) that satisfies these criteria.

Methods: Silica was coated on a commercially available IONP core, EMG308 (Ferrotec) using poly vinylpyrrolidone (PVP) as an intermedia layer by Stober method. The surface was functionalized with PEG and a trimethyl group to enhance colloidal stability. The silica shell thickness could be tuned from single to tens of nm's by varying the silica precursor added to the reaction. The sIONP were characterized by transmission electron microscopy, dynamic light scattering, N_2 physiosorption, and inductively coupled plasma optical emission spectroscopy. The heating performance of sIONP, with different shell thickness, were assessed in water and VS55, a type of CPA (8 M). Biocompatibility and cellular uptake of the sIONP were also tested by culturing them overnight with Human Dermal Fibroblast (HDFs). Heating performance (SAR_{Fe}) of the sIONPs was measured using a 1 kW inductive heating system at 360 kHz and 20 kA/m.

Results: The sIONPs demonstrated stability in VS55 for months and a lack of toxicity with HDFs. Furthermore, very little uptake and surface attachment was observed with the HDFs. The heating performance was maintained with increasing shell thickness (SAR_{Fe} = 250 – 300 W/g Fe). The one-pot synthesis was easily scaled up to a 3 L reaction volume yielding ~ 0.9 g Fe. Finally, the addition of PVP created a micro-porosity in the silica matrix, allowing penetration of H_2O and functionality as an MRI contrast agent.

Conclusion: A new type of sIONP was designed and shown to be biocompatible for biomedical applications. Heating was maintained when the shell thickness was varied from 5 – 63 nm. Additionally, the microporosity is anticipated to allow sIONP to be used as an MRI contrast agent in the future. Finally, the facile scale of this synthesis is specifically applicable for the high IONP concentrations required for hyperthermia and nanowarming.

TUES 4

NANOPARTICLE-COATED SURFACES PROVIDE NANOSCALE INSIGHT FOR THERMAL MEDICINE

Samir Jenkins, Ruud Dings, Michael Borrelli, Robert Griffin

University of Arkansas for Medical Sciences, Little Rock, AR, USA

Nanomaterials are an increasingly studied agent in thermal medicine, due to their multimodal activities and due to their capacity to produce highly localized therapeutic effects. Two clinically used local treatments – laser thermal ablation and magnetic-based heating – can be augmented through the use of a variety of metal-based nanomaterials, although the true mechanisms of action remain somewhat elusive. The localized surface plasmon resonance of Au nanomaterials generates heat proportional to the absorption cross section under laser irradiation. Yet, many studies with these materials are extremely phenomenological due to the complexity of biological systems and the challenges associated with accurate quantification of particle uptake and thermal dose. Even accurate particle quantification still results in bulk average biases, i.e. the effect on individual cells is not measured, but rather the effect on the population. This uncertainty is confounded by variations among cell types and experimental parameters. Toward the goal of performing quantitative nanobiology, we developed a stable method for uniform coating of Au nanocages at different coverage densities (up to 680 nanocage/ um^2) on glass coverslips. This allows the effect of a known average number of particles per unit area of the cell membrane to be calculated and studied. Photothermal-inducing laser treatment (10 min) was performed on adherent 4T1 murine breast cancer cells growing on these surfaces, which eradicated the viable cells, while bulk heating (43 C, 10 m) resulted in less than a 25% reduction in viability. Conversely, roughly 80% viability was observed following laser treatment or water bath treatment when investigating a suspension cell culture (murine EL4 cells). These results indicate the close association of the particle and the cell is crucial for effective thermal treatment. Theoretical modeling was used to determine the thermal gradient at the single particle level to more accurately understand these results and estimate the temperature at the particle surface. This platform was developed using only one type of nanoparticle, but will be expanded to use Au structures with different absorption cross-sections, magnetic materials, and carbon materials. Development of this platform can enable precise understanding of the thermal dose and mechanisms of biological effect at the nano scale, which will further rational design of new nanomedicines.

TUES 5

A NOVEL NONINVASIVE MICROWAVE DEVICE TO TREAT LOCALIZED TUMORS AT VERY LOW ENERGIES

Anan Copty

NIMD Ltd, Jerusalem, Israel, Israel

Localized thermal ablation is an effective procedure to treat cancer tumors at their early stage of development. However, conventional thermal ablation devices, including radio frequency and microwave based technologies are invasive and are not selective in treating the tumor without damaging the surrounding tissue. NIMD, a medical device startup company, has developed a medical device to treat localized cancer tumors using a noninvasive microwave applicator and iron oxide (Fe_3O_4) FDA approved nanoparticles that are injected directly into the tumor. The nanoparticles are injected directly into the tumor at a concentration of 1.9mg of Fe/g of tissue. When microwave radiation is applied, through a specially designed applicator, these particles absorb the radiation more effectively than the surrounding healthy tissue, heating and destroying the tumor while the healthy tissue remains intact. The device has been tested on biological phantoms with human-like dielectric properties, and on mice. The results showed excellent selectivity where temperature differences exceeding 20°C were achieved between the tumor and the healthy tissue at only a few watts of microwave energy and with 1-2 minutes of exposure. The tumor volumes of the treated mice injected with 4T1 mice breast cancer cell-line, were significantly diminished. The main areas of application for the device include: skin, breast, and head & neck cancers to be used as a replacement for surgery.

TUES 6

MAGNETIC NANOPARTICLE HYPERTHERMIA TRIGGERED DRUG RELEASE FOR TREATING GLIOBLASTOMA MULTIFORME

Anilchandra Attaluri[1], Christopher Addonizio[2], Ryan Biggs[2], Alexis Hoerter[2], Bryan Mateus[2], Derek McMahon[2], Andrea Vernengo[2]

1Pennsylvania State University - Harrisburg, Middletown, PA, USA. 2Rowan University, Glassboro, NJ, USA

Magnetic nanoparticle hyperthermia (MNPH) can non-invasively heat the magnetic iron oxide nanopartilces in the surgical cavity of the Glioblastoma Multiforme patients. MNPH has shown to sensitize cancer cells to radiation and chemo therapires, and transiently disrupt blood-brain-barrier. Combining MNPH with thermally triggered drug release could allow high intratumor drug concentrations for longer periods, and improve drug penetration for both intratumorally and systemically delivered therapeutics.

This work studies a hydrogel-based drug delivery system composed of thermosensitive poly(N-isopropylacrylamide) grafted with chondroitin sulfate (PNIPAAm-g-CS) and combined with drug-loaded liposomes composed of 1,2-diheptadecanoyl-*sn*-glycero-3-phosphocholine (PC). The liposomes transition from a gel to liquid crystalline phase at 50°C. The work is based on the hypothesis that this composite hydrogel will provide *i)* an *in situ* gelling system that can be implanted interstitially within a tumor *ii)* a stable matrix to localize drug within the tumor and provide a barrier for prolonged release, iii) the ability to accelerate release of the model drug in response to multiple consecutive heating spikes at or near the transition temperature of PC.

PNIPAAM-g-CS copolymers were prepared as described previously. PC liposomes loaded with model drug calcein were prepared according to previously reported procedures. The composites were prepared by adding PNIPAAm-g-CS powder to a suspension of liposomes to yield a final fixed concentration of PNIPAAm-g-CS at 5% (w/v). Continuous release of calcein from the composite system over 14 days in phosphate buffered saline at 37°C was studied. The composite retains calcein, as demonstrated by the gradual release over the study period, with fractional release still increasing at day 14. In contrast, freely encapsulated calcein co-dissolved with PNIPAAm-g-CS released completely by day 3. Hydrogel composites were maintained *in vitro* for four days at 37°C. Every 24 hours, the hydrogel incubation temperature was spiked for 30 minutes to 41°C (spikes 1 and 2) and 50°C (spikes 3 and 4). Release was achieved for all four spikes. We maintain that incremental increases in the temperature of the spikes aid in enhancing release.

The preliminary work indicates that we designed a composite capable of retaining molecules at physiological temperature and accelerating release in response to elevated temperatures in the clinically relevant range for hyperthermia treatment. This system can be easily combined with magnetic nanoparticles to provide local hyperthermia to a tumor combined with the heat-triggered release of chemotherapy.

TUES 7

INITIAL ASSESSMENT OF SIMULTANEOUS MAGNETIC NANOPARTICLE HYPERTHERMIA AND BRACHYTHERAPY OF AT-RISK TISSUE SURROUNDING A BRAIN TUMOR RESECTION CAVITY

Paul Stauffer[1], Dario Rodrigues[1], Robert Goldstein[2], Thinh Nyguyen[1], Andrew Dorion[1], Laura Doyle[1], Voicha Bar-Ad[1], Wenyin Shi[1], Kevin Judy[1], Mark Hurwitz[1]

[1]Thomas Jefferson University, Philadelphia, PA, USA. [2]AMF Life Systems, Auburn Hills, Michigan, USA

Background

Hyperthermia (HT) at temperatures from 40-45°C improves the radiation (RT) response of tumor cells. Laboratory studies have demonstrated that synergism may be significantly enhanced if HT and RT are administered simultaneously, but few technologies are available to investigate this approach in the clinic. This study assessed the feasibility of applying HT and RT simultaneously using a dual-modality thermobrachytherapy (TBT) balloon implant to treat a 5-mm annular rim of at-risk tissue surrounding a tumor resection cavity.

Methods

A multi-lumen balloon catheter was designed to deliver High Dose Rate (HDR) brachytherapy simultaneously with HT. HT is delivered by filling a balloon with magnetic nanoparticles (MNP) and immersing the region in a radio frequency magnetic field. Temperature distributions in brain around 2-5 cm diameter TBT balloon implants were simulated for a range of brain blood perfusion levels using numerical modeling. A magnetic induction system was constructed and used to couple energy into MNP filled balloon implants. Dosimetry studies were performed in simple phantom models to validate the computer modeling results.

Results

Thermal dosimetry plans demonstrate our ability to heat a 5-mm annular rim of at-risk tissue around a brain tumor resection cavity between 40-48°C for 2-5 cm diameter balloon implants for the expected range of brain blood perfusion. In agreement with theory, the magnetic induction heating system produced rapid heating (>0.2°C/s) of MNP-filled balloons by depositing 0.6 W/ml into the nanoparticles with a magnetic field strength of 5.7 kA/m at 168 kHz, a level that has been proven safe in previous clinical studies.

Conclusion

Feasibility of using a dual-modality thermobrachytherapy balloon implant for simultaneous heat and radiation treatment of tumor bed is demonstrated with numerical simulations and dosimetry. This dual-modality balloon implant has the potential to simultaneously deliver radiation and heat more uniformly to tumor bed tissue surrounding a resection cavity than alternative interstitial implant technologies.

TUES 8

LASER INTERSTITIAL THERMAL THERAPY FOR POSTERIOR FOSSA LESIONS: AN INITIAL EXPERIENCE.

Hilary Koech, Hamid Borghei-Razavi, Mayur Sharma, Daria Krivosheya, Brian Lee, Gene Barnett, Alireza Mohammadi

Cleveland Clinic Foundation, Cleveland, OH, USA

Introduction

Laser interstitial thermal therapy (LITT) is an effective minimally invasive technique to treat difficult to access intracranial tumors. Application of LITT in posterior fossa tumors is challenging. To that end, we aimed to review our experience of posterior fossa tumors treated with LITT.

Methods

We retrospectively reviewed our series of eight patients with posterior fossa tumors treated using LITT (NeuroBlate system) from an IRB approved brain tumor database (2012 to 2017). We used mini-Bolt mounted to the bone in seven cases and a custom made mounting device (Star fix) for one patient. Data and outcomes of surgery (overall, progression free survival, and complications) were collected from electronic medical records.

Results

Eight patients with a median age of 59 years underwent LITT targeting three metastases (two colon and one NSCLC), two low-grade pilocytic astrocytoma, two radiation necrosis and one Glioblastoma multiforme (GBM). The mean tumor coverage was 98%, mean maximum preoperative tumor volume and post-operative ablation volume was 4.35 cm^3 and 9.64 cm^3, respectively. Six-months postoperative mean tumor volume decreased to 5.72 cm^3. Two of the tumors (GBM and metastatic adenocarcinoma) progressed after 7.5 and 8.5 months respectively with mortality after 1.1 and 1.6 years respectively. Surgical resection was performed in patient with metastatic adenocarcinoma tumor at 7.7 months after LITT. All other lesion remained stable at median follow-up of 14.8 months (0.4 – 37.5). Tumor related edema on first postoperative day increased from a mean of 15.9 mm to 16.6, which decreased to 7.6 mm at one-month follow up. Transient partial unilateral sixth cranial nerve palsy, superficial wound infection and a late obstructive hydrocephalus were noted in three patients as post op complications.

Conclusions

LITT is a safe and feasible treatment modality in patients with posterior fossa tumors. Larger studies are necessary to fully characterize the long-term therapeutic benefit in each specific pathology.

TUES 9

LASER INTERSTITIAL THERMAL THERAPY FOR INOPERABLE BRAIN TUMORS OF THE THALAMUS AND DEEP BRAIN STRUCTURES

Roger Murayi, Hamid Borghei-Razavi, Bryan Lee, Gene Barnett, Alireza Mohammadi

Cleveland Clinic Neurosurgery, Cleveland, OH, USA

Introduction: Brain tumors of the thalamus and other deep brain structures are considered inoperable by traditional surgical means due to increased risk of morbidity and mortality with open surgery. Laser Interstitial Thermal Therapy (LITT) offers a novel, minimally-invasive, surgical option for ablation of these tumors. LITT allows for focused, laser-induced tissue hyperthermia to these deep brain tumors via a small probe inserted stereotactically. A side-firing, CO2 cooled, fiberoptic catheter heats the surrounding tissue above 43 Celsius which is monitored via MRI thermometry in real time. Surgical "ablation" is thus achieved. We report on our experience with LITT on 18 patients with tumors of deep brain structures at our institution.

Methods: A retrospective analysis was conducted of 18 patients who received LITT for deep brain neoplasms at our institution. Preoperative and postoperative (1-3 months) tumor size, post-operative hospital length of stay, and complications were assessed across all patients via chart review.

Results: 18 patients treated at our institution from 2012 were analyzed including 13 thalamic tumors, 3 basal ganglia tumors, and 2 tumors in other deep brain areas (i.e. splenium, cingulate gyrus). Most were high grade gliomas (12), followed by 4 metastases, and 2 WHO grade II tumors: astrocytoma, oligodendroglioma. Mean hospital stay was 4.9 days post-operatively (range 1-19 days). Median pre-operative tumor size was 13.77 cubic centimeters and decreased on average by 46.6% at the 1-3 month MRI. Post-op complications occurred in 4 patients including 3 patients with intracerebral hemorrhage (ICH). 2 of these died in the immediate post-operative period. The last patient developed hydrocephalus requiring an external ventricular drain and eventual shunt placement.

Conclusion: We present our experience with brain tumor ablation using Laser Interstitial Thermal Therapy (LITT) for thalamic and other deep brain structures. LITT is a feasible option for these otherwise inoperable tumors. In our 18 patients, tumor size decreased significantly by 1-3 month follow-up. There were however 2 deaths in the immediate post-operative period secondary to ICH.

TUES 10

LASER INTERSTITIAL THERMAL THERAPY FOR TREATMENT OF BRAIN METASTASIS

Alireza Mohammadi

Cleveland Clinic, Cleveland, Ohio, USA

Background: Brain metastasis is the most common type of brain tumor. In many occasions initial treatment of brain metastasis is radiation treatment either whole brain radiation or radiosurgery. However in 10-15% of patients after radiation treatment progression happens. In addition, another 5-10% of patients develop radiation toxicity (necrosis). Tumor progression and radiation necrosis (RN) are very similar in MRI scan and since they have somehow opposite treatments, it is quite often that we need tissue confirmation for differentiate between them.

Method: Laser interstitial thermal therapy (LITT) is a MRI-guided controlled hyperthermic treatment that has been used for treatment of intracranial lesions including brain tumors in the past few years. This procedure is done under real time MR-thermometry guidance using low voltage (12W) laser in ND-Yag range. In this particular indication, the advantage of LITT other than the ability to obtain biopsy in the same setting and right before laser ablation procedure, is to treat the lesion regardless of being tumor progression or RN.

Result: Multiple studies have published regarding the use of laser ablation in treatment of brain metastasis. Most recently, a prospective multicenter trial, Laser Ablation After Stereotactic Radiosurgery (LAASR), was completed (manuscript in press) to further evaluate the safety and effectiveness of this treatment for brain metastasis who failed radiosurgery. 42 patients were enrolled (almost half from each progression and RN) with the primary endpoint was progression free survival (PFS). At 12 weeks, 15% of the LITT lesions were stable per RANO criteria, 22% had partial response, and 37% had a complete response. Local PFS was statistically different at 12 weeks - 100% for RN versus 54% for tumor progression ($p=0.01$).

Conclusion: LITT is a safe and effective treatment for cases of brain metastasis after failure of radiation and because of advantage of doing biopsy before surgery, could help in differentiation of two common condition (progression versus RN). In case of RN, LITT seems to be the only treatment needed and in cases of progression might need a boost of additional radiation (maybe fractionated radiosurgery) after hyperthermic treatment.

TUES 11

THE ROLE OF INTERSTITIAL THERMAL THERAPY IN TREATMENT OF GLIOBLASTOMA

Daria Krivosheya, Hamid Borghei-Razavi, Gene H. Barnett, Alireza M. Mohammadi

Cleveland Clinic, Cleveland, OH, USA

Laser Interstitial Thermal Therapy (LITT) is a minimally invasive ablative technique that continues to gain popularity in a variety of domains of neurosurgery. In neurooncology, one of the more challenging tumors to treat is glioblastoma, a primary brain neoplasm of malignant behaviour. With full treatment that includes surgery, radiation and chemotherapy, the median survival is still only 14-16 months. Recent evidence indicates that the extent of tumor resection affects patient survival. In many patients, complete resection is unachievable due tumor involvement of eloquent areas. In these cases, laser ablation was thought could provide a similar benefit of cytoreduction compared to surgical reduction, and thus affect survival. Recent studies of laser ablation in patient with recurrent glioblastoma showed that this is a feasible treatment modality. Furthermore, the outcomes of patients with newly diagnosed glioblastoma showed survival similar to patients undergoing standard of care therapy. Here we present the results of a multicenter retrospective study that compared outcomes of patients with newly diagnosed glioblastoma that were treated with either biopsy or laser ablation. The group of patients treated with laser ablation showed longer overall and progression free survival (14.4 and 4.3 months in LITT vs 8.9 and 5.4 months in biopsy patients). Furthermore, the extent of tumor coverage with thermal-damage-threshold lines correlated with better patient outcomes. These findings further add to the body of evidence that laser ablation is an effective treatment modality for newly identified and recurrent glioblastoma.

TUES 12

PROGRESS ON THE DEVELOPMENT OF CARBON NANOTUBES FOR PHOTOTHERMAL THERAPY OF GLIOBLASTOMA

Ravi Singh

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

Background: Glioblastoma (GBM) is the most common and most lethal primary brain tumor. Currently no treatment is curative and most result in eventual tumor recurrence. Tumor recurrence may be driven by the presence of unique cells that occupy the cancer stem cell niche that have pluripotent and self-renewal capabilities. These unique cells, deemed cancer stem cells (CSCs), are resistant to current therapies used to treat GBM, including ionizing radiation and temozolomide, and researchers and clinicians are looking into thermal ablative therapies as an alternative treatment option. Laser Interstitial Thermal Therapy (LITT), which is a minimally invasive therapy that uses a near infrared (NIR), interstitial fiber optic laser to generate ablative temperatures ($T \geq 55$ °C) at the tumor site over a span of minutes. Wavelengths of light in the NIR spectrum are not readily absorbed by water or blood and are poorly attenuated by tissue, which allows for significant penetration of NIR light in vivo. Intratumoral delivery of NIR absorptive nanomaterials like carbon nanotubes (CNTs) permits greater heat generation and control of the spatial and temporal distribution of heat within a tumor target than laser irradiation alone. Methods and Results: Through acid oxidation and surfactant coating, we developed CNTs with specific physicochemical characteristics designed to maximize intratumoral diffusion and NIR thermal transduction efficiency. We determined optimal NIR irradiation parameter (power and duration) for CNMTT both experimentally and using heat transfer modelling for current clinical LITT systems. We conducted in vitro studies using cell monolayer and 3D cell culture techniques in which we determined doses of CNTs that minimize toxicity but still enable effective, localized therapy. In addition, we conjugated CNTs to a potent, non-classical platinum chemotherapy drug and found that photothermal treatment using the nanotube-drug conjugates resulted in cell death under conditions for which the drug delivery system was non-toxic on its own. Thermal therapy has the potential to leave behind cancer cells exposed to sublethal stresses, which could trigger adaptive survival responses, and have been linked to increased cancer “stemness” and invasive capacity in cells surviving conventional heat-based therapy. We found that CNTs decrease the expression of stem cell-associated pluripotency factors including SOX2 and OCT4, resulting in decreased GBM neurosphere formation following CNT exposure. Neurosphere formation is indicative of cancer stem cells and is associated with poor clinical outcome; Conclusion: CNMTT may be safe and more effective than laser alone for treatment cancer stem cells in GBM.

TUES 13

A CLINICALLY-ORIENTED COMPUTATIONAL MODELLING: A RADIOFREQUENCY ABLATION OF LIVER WITH INTERNALLY COOLED WET ELECTRODE.

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Introduction: Various computational modeling studies analyzed the electrical and thermal performance of radiofrequency ablation (RFA) with internally cooled wet (ICW) electrodes with the aim of enhancing the hepatic tumor management in clinics. Still, the results could not yet be extrapolated to the clinical practice due to the lack of a detailed physical description needed to optimize the treatment. The objective of this study was to improve the existing computational models by building a clinically-oriented, three-compartment FEM model of RFA with an ICW electrode considering a more precise geometry of saline infusion and tumor embedded in a healthy tissue.

Materials & methods: RFA with an ICW electrode was simulated on a three-compartment computational model including liver tissue, tumor (<2 cm) and saline irrigated tumor. Saline spatial distribution was determined by means of an *in vivo* study on pigs using X-ray mapping. The results from three-compartment computational model were compared with single and two-compartment computational models and a clinical trial. Saline spatial distribution and tumor domain inclusion were correlated to impedance evolution, roll-off occurrence and coagulation zone size.

Results: Tumor domain inclusion resulted in a roll-off delay by >20 s whereas there was no roll-off in cases considering saline hydration domain. Both domains separately had an effect on an initial impedance decrease of 15-17% (tumor) and 10-12% (saline hydration). Inversely, saline hydration imposed greater coagulation zone size increase (22-36%) than tumor domain (18-31%). It was also seen that the spatial distribution of volumetrically identical saline affected coagulation zone size. A three-compartment model most matched the clinical results.

Conclusion: To obtain a clinically validated FEM model with ICW electrode, a precise saline spatial distribution and a three-compartment computational model are required.

TUES 14

BIOFILM ERADICATION UTILIZING ALTERNATING MAGNETIC FIELDS

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Biofilm, an aggregation of organisms surrounded by extra polymeric substances (EPS) provides multiple therapeutic challenges when treating various infections. This includes the inability of antibiotics to reach their target as well as difficulty in immune cells clearing the offending pathogen. Biofilms form on a number of abiotic surfaces including metal. Prosthetic joint infection (PJI) is an uncommon but severe complication of modern arthroplasty and frequently requires the removal of the prosthesis due to the presence of biofilm. Here we will present the development of alternating magnetic fields (AMF) as a non-invasive technique that can eradicate biofilm off of a metal surface through the generation of surface heating. The impact of heat on metal-associated biofilm has drug-like properties where the rate of killing is both time and temperature dependent. Importantly, AMF appears to enhance the activity of antibiotics which has important clinical implications.

TUES 15

ERADICATION OF BIOFILM ON INFECTED METAL IMPLANTS USING ALTERNATING MAGNETIC FIELDS: UNDERSTANDING THE RESPONSE OF BACTERIA TO HEAT

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Biofilm related infections are ubiquitous, difficult to eradicate, and cause a huge economic burden with regards to prosthetic joint infections (PJI). *Pseudomonas aeruginosa* is the most prevalent gram-negative pathogen to cause PJIs, whereas *Staphylococcus aureus* is the most common gram-positive pathogen. Explantation of prostheses is the gold standard for treatment for infected implants due to the presence of biofilm which is often untreatable with antibiotics. We are developing a non-invasive method for eradication of biofilm on metallic implants utilizing high frequency alternating magnetic fields (AMF). Metals exposed to high frequency AMF experience eddy currents on the extreme outer surface (1 mm) of the metallic object which can cause thermal destruction to biofilms attached to the surface. Preliminary studies suggest pulsed AMF producing brief thermal shocks to bacteria can effectively eradicate biofilm while minimizing thermal damage in surrounding tissue. This work investigates the response of planktonic and biofilm bacteria to thermal shock. Planktonic *Pseudomonas aeruginosa*, PA01 strain, was exposed to a range of temperatures (55-80C) and times (0-30 minutes) using heating blocks, and colony forming units (CFUs) were enumerated on blood agar plates. 48-hour PA01 biofilms were grown on metal rings and similarly heated to different temperatures and times in a water bath. A log-linear relationship was observed for planktonic *Pseudomonas* comparing CFUs versus time. The decrease in bacterial survival was also plotted against an Arrhenius fit to measure kill rate, which showed an exponential relationship with temperature. Planktonic data showed that a 2-log reduction in planktonic bacteria could be achieved in 10 minutes at 55C, 20 sec at 70C, or 10 msec at 80C, indicting a highly exponential relationship. Biofilms required longer time intervals to reach limit of detection compared to planktonic bacteria at similar temperatures. Results indicate that PA01 is significantly more resistant to heat than eukaryotic cells. With these results we can extrapolate appropriate AMF exposure parameters for including time and temperature, to best reduce biofilm burden without extensive tissue damage.

TUES 16

SAFETY EVALUATION OF PULSED ALTERNATING MAGNETIC FIELD (AMF) EXPOSURES OF METAL IMPLANTS ON SURROUNDING TISSUES

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Introduction

We are developing a non-invasive method to treat biofilm-associated metal implant infections, which utilizes alternating magnetic field (AMF)-induced rapid heating of the implant surface. Although proof-of-concept in vitro studies demonstrate the effectiveness of AMF at eradicating biofilm, there is a legitimate safety concern related to the risk of thermal damage in surrounding tissues. To address this, we conducted a comprehensive safety evaluation of AMF exposures across a range of different parameters. The extent of thermal damage around an implant in mice was examined under different exposure conditions, including: the peak temperature on the implant surface, the AMF pulse duration, pulse delay, and number of pulses.

Methods

A custom AMF system comprised of a solenoid coil, matching circuit, animal warming station, and anesthesia system was built. The system was capable of delivering exposures with a resonant frequency at 150 kHz. A 5 mm stainless steel ball was surgically implanted in the thigh muscle of mice (Swiss Webster, 30-40 g), allowing 7 days of recover to resolve the inflammatory response from the surgery. For initial temperature calibration, a fiber-optic sensor was epoxied to the implant in vivo to measure the peak temperature during AMF. After calibration, different AMF exposures including targeting temperatures (50, 70, 100 °C), pulse durations (minutes to seconds), pulse delays (5, 20, 60 mins) with a total treatment duration of 4 hours were delivered to the mice while they were anesthetized. The implant surface temperature was allowed to return to body temperature before a subsequent pulse. Mice were recovered and survived for 7 and 28 days to evaluate the acute and chronic response in tissue to the AMF exposures. After sacrifice, a pathologist blinded to the AMF exposure conditions evaluated and scored the tissue surrounding the implant.

Results and Conclusion

Target temperatures were achieved within three seconds with a precision of approximately 2 °C. The measured radii of the thermal damage for a single AMF pulse (100°C surface temperature) with different pulse durations were 3.05 ± 0.33 mm (200s), 1.33 ± 0.30 mm (6s), and 0.60 ± 0.21 mm (1s). Based on this finding, the pulse duration in multi-pulse exposures was limited within 2s. The extent of tissue injury of all the groups tested in the 4-hour multi-pulse treatment were less than 1 mm. Overall, short-duration pulsed AMF exposures can maintain the zone of damage around an implant to within 1 mm.

TUES 17

TARGETED LASER THERAPY SYNERGISTICALLY ENHANCES EFFICACY OF ANTIBIOTICS AGAINST MULTI-DRUG RESISTANT *STAPHYLOCOCCUS AUREUS* AND *PSEUDOMONAS AERUGINOSA* BIOFILMS

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Background: Multi-drug resistant (MDR) pathogens are becoming the most common cause of infectious disease-related deaths around the world. In addition to genetic resistance mechanisms, MDR bacteria commonly exhibit increased drug tolerance due to the formation of biofilms that serve as a protective barrier against antibiotic therapy. Thus, there is an urgent need to discover alternative strategies that are less prone to inducing drug resistance and can overcome the therapeutic challenges posed by biofilms. In this study, we evaluated the ability of gold nanoparticle (GNP)-targeted pulsed laser therapy to disperse and kill MDR bacterial biofilms and assessed the benefit of combining this therapy with antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* biofilms.

Methods: Overnight broth cultures of MRSA or *P. aeruginosa* were used to establish biofilms on 5-mm glass discs or in 96-well glass-bottom microtiter plates. Targeted gold nanoparticles (tGNPs) were prepared by conjugating *S. aureus* or *P. aeruginosa* antibodies to GNPs and then used to treat MRSA or *P. aeruginosa* biofilms, respectively. Biofilms were treated with 70 μg/mL of tGNPs or non-targeted GNPs and then exposed to 50 laser pulses at 532 nm (8-ns pulse, 1 Hz, $\sim$1.3 J/cm^2). GNP-targeted laser therapy was tested alone and in combination with gentamicin or vancomycin against MRSA biofilms or with amikacin against *P. aeruginosa* biofilms. The efficacy of the treatments against the biofilms was assessed using confocal microscopy, scanning electron microscopy, and colony forming unit (CFU) assays. The sensitivity of planktonic cultures of *S. aureus* and *P. aeruginosa* to the antibiotics was determined using CFU assays.

Results: The use of GNP-targeted pulsed laser therapy resulted in the dispersion of 96$\pm$3% ($p<0.0001$) and 99$\pm$0.2% ($p<0.0001$) of MRSA and *P. aeruginosa* biofilms relative to the untreated controls, respectively. Targeted laser therapy combined with antibiotic treatment resulted in a 4-log reduction ($p<0.005$) in bacterial viability in MRSA biofilms and a 4-log reduction ($p<0.0001$) in *P. aeruginosa* biofilm viability. Notably, these reductions in viability were similar to the reductions observed in planktonic cultures treated with the antibiotics alone, suggesting that GNP-targeted laser therapy effectively dispersed the biofilm matrix allowing antibiotics to access and act against the bacteria.

Conclusion: Results showed GNP-targeted laser therapy potentiates the efficacy of antibiotics against *in vitro* MDR biofilms, with significant biofilm dispersion and enhanced bacterial killing. These results are a first step toward developing a minimally invasive, efficacious, and cost-effective adjunct therapy for the treatment of topical chronic wound infections.

TUES 18

MODULATING *IN VIVO* THERMAL RELEASE AND THERAPEUTIC OUTCOMES WITH A VERSATILE NANOTHERAPEUTIC SYSTEM DESIGNED FOR THE TARGETED ERADICATION OF BACTERIAL BIOFILMS

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Background: Infections associated with the formation of a biofilm represent a serious global health concern. Biofilm formation confers upon bacteria a degree of intrinsic antibiotic resistance. In the case of infection of indwelling medical devices, therapeutically recalcitrant biofilms often necessitate surgical intervention. Thus, novel therapeutic approaches are desperately needed to address these types of infections. We previously designed a targeted nanotherapeutic system capable of generating synergistic photothermal effects and controllable antibiotic release to overcome the intrinsic resistance of *Staphylococcus aureus biofilms*. Here, we expand on this work to demonstrate the versatility of this system and explore the potential to modulate temperature changes which may greatly impact therapeutic and adverse effects.

Methods: Using an *in vitro* model of biofilm formation, we assessed the versatility of our gold nanocage system by the substitution of component parts. Specifically, we substituted either the targeting antibody or the loaded antibiotic to assess the potential for enhanced activity against *S. aureus* biofilms. By substituting both components, we also assessed the ability to target an alternative pathogen, *Pseudomonas aeruginosa*. Using *in vivo* models of infection, we assessed the ability to determine biodistribution and kinetics of our nanoparticle system using multispectral optoacoustic tomography (MSOT). Using an *in vivo* model of biofilm infection, we assessed the ability to modulate thermal profiles, and thus therapeutic outcomes, by manipulating laser irradiation parameters.

Results: We demonstrated the ability to substitute antibody and antibiotic components of our gold nanocage system to optimize targeting and eradication of *S. aureus* biofilms. By substituting both components to appropriate alternatives, we demonstrated the ability to eradicate *P. aeruginosa* biofilms, thus illustrating the potential versatility of our system. MSOT studies allowed for determination of biodistribution with confirmation of nanoparticle accumulation at distal sites of infection following systemic administration. Finally, we demonstrated the ability to achieve largely variable thermal profiles by manipulating laser irradiation parameters. These differences were evident even when the total dose of laser energy was held constant but were achieved by altering laser power density, duration, and fractionated irradiation regimens. Importantly, these changes in temperature profiles had varying effects from enhanced bacterial killing to host tissue damage resulting in increased infection severity.

Conclusions: Overall, our results describe a novel, versatile system for the targeted eradication of bacterial biofilms and emphasize the important consideration of laser irradiation parameters to balance therapeutic and adverse effects.

TUES 19

THERMAL THERAPY AS A POTENTIAL CATHETER SALVAGE STRATEGY FOR CENTRAL LINE INFECTION

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Healthcare associated infections are a leading cause of morbidity and mortality in the U.S., with over 60% associated with implanted medical devices. Despite engineering advances in materials and healthcare process improvements, infections rates remain unacceptably high. As new devices are developed, indications for use are expanded, and the immunocompromised population continues to climb this trend is likely to continue or worsen in the future. The fundamental pathogenic issue is the adhesion and subsequent colonization of implanted materials with bacterial biofilms. Biofilms on implanted devices confer significant protection from host immune response and antibiotics. Ultimately, life-sustaining devices such as dialysis catheters, pacemakers, or heart valves must be surgically removed, adding to morbidity, mortality, and cost. Our group has been focused on developing in situ treatment strategies for device salvage as an alternative to surgical removal and replacement. Understanding the complexity of biofilm microbiology and the recalcitrance to traditional antibiotic treatment we are developing synergist therapies including thermal augmentation of antibiotics and mechanical debridement of biofilms. Using soft matter rheology and microrheology we have shown that modest, human tolerable increases in temperature, permanently alter biofilm elasticity and yield stress. Furthermore, these temperatures reduce bacterial viability and cell wall structure. More importantly, antibiotic killing - normally minimal in biofilms - is significantly enhanced by elevated temperatures. Here we will describe how this fundamental understanding of thermal effects on biofilm structure, mechanics, and viability can be leveraged toward a specific example of medical device infection (i.e., central line associated bloodstream infection). We will describe computational modeling of a fluid heated dialysis catheter, development of an in vitro bacterial culture model to mimic catheter fluid dynamics, and finally an in vivo animal model for testing of synergistic combinations of thermal therapy, antibiotics, and mechanical debridement.

TUES 20

PROPOSAL OF NEW CONCEPTS TO TREAT INFECTIOUS DISEASES IN THE FIELD OF HYPERTHERMIA

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Introduction:

Antimicrobial chemotherapy is generally used for treating infectious diseases. However, several microorganisms are known to be sensitive to mild hyperthermia, and this sensitivity may be used to treat local infections caused by thermo-susceptible pathogens. According to previous studies, most species of the genus Campylobacter, Helicobacter, Citrobacter, Shigella, Yersinia, Vibrio, Enterobacter, Escherichia, Mycobacterium are sensitive to a temperature between 40 °C and 45 °C. In clinics, after analysis of thermal sensitivities of pathogens, infections caused by thermo-susceptible strains may be treated by performing local hyperthermia.

Proposed Methods:

In clinical microbiology laboratories, microbiologists should determine the minimum inhibitory temperature (MIT) of each isolated microorganism by performing thermobiograms (similar to antibiograms).

Thermobiogram: To find the MIT of a strain, broth media suspensions of the same strain are placed in various incubators with increasing temperature levels (from 37 °C to 45 °C). After one night of incubation, the temperature value of the lowest-temperature incubator with no visible microbial growth can be used as the MIT.

After thermobiogram and determining MIT, microbiologists can decide whether the isolate is thermo-susceptible or thermo-resistant according to a threshold temperature. The main parameter that can affect the threshold temperature is tissue/organ type. Here, the threshold value is the maximum temperature to which a tissue can be heated without thermal damage. Therefore, microbiologists should also review classical and new data on thermal dosimetry.

If MIT of the strain is lower than threshold temperature of infected tissue, the strain is considered thermo-susceptible. If not, it is considered thermo-resistant and cannot be inhibited by the direct effect of hyperthermia. Clinical isolates reported as thermo-susceptible can be treated by hyperthermia. Additionally, determining the MIT of isolate will help avoid administration of an excessive thermal dose to the patient.

Conclusion

Here, we highlight the potential of clinical hyperthermia in the treatment infections caused by constitutively thermo-susceptible pathogens and propose new concepts and methods to plan treatment of infections by using hyperthermia.

**Some concepts of this abstract have been published as an article in the International Journal of Hyperthermia by 25 Feb 2018 as below;*

Deniz Gazel & Mehmet Yılmaz (2018): Are infectious diseases and microbiology new fields for thermal therapy research?, International Journal of Hyperthermia, DOI:10.1080/02656736.2018.1440015

TUES 21

THE HSP-ACCESSORIZED EXOSOME: PRESENCE IN STATES OF DANGER, DISEASE, AND DISRUPTION

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Heat shock proteins (HSPs) function as chaperones under both normal and pathologic conditions. As chaperones they assist in protein folding, in holding protein complexes for current or future activation, and in the degradation of senescent proteins for recycling of components and display for immune surveillance. During stressful situations, HSP quantities and/or activities are increased as cells and tissues seek protection from insults. On occasion, these insults can result in the cell surface display of HSPs, which can then lead to the surface display of HSPs on exosomes, membrane-enclosed vesicles released extracellularly after passage thru the endosomal system. HSPs present on the cell surface or in the extracellular space are regarded as "danger signals" in an ancient biologic paradigm. HSP-accessorized exosomes may act as "danger boli", carrying not only the HSPs, but hundreds of components of the stressed parental cell, capable of prompting immune responses, or possibly immune suppression, depending on the status of the recipient cell. Here we show that exosomes from the blood of patients suffering from neurologic maladies (cancer, brain injury, multiple sclerosis) are precipitated by peptides designed to bind HSPs. Such HSP-accessorized exosomes possess inflammatory properties and may serve as biomarkers in a "liquid biopsy" setting.

TUES 22

HEAT-ACTIVATED RELEASE AND THERMAL ENHANCEMENT OF SYNERGISTIC CHEMOTHERAPIES

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Introduction: Breast cancer treatment options have improved significantly in the past 20 years with the average 10-year survival rate increasing to 83%, leading many to consider breast cancer a well-managed disease. However, due to high incidence rates breast cancer is still the second leading cause of cancer death in North American women, thus more innovative treatment options are required. This work seeks to combine chemotherapies that are enhanced by hyperthermia at the molecular level with the drug delivery advantages provided by heat-activated drug release. Specifically, this research aims to build on the clinical success achieved with ThermoDox in breast cancer through the addition of a thermosensitive liposome formulation of a heat shock protein inhibitor (HSPi).

Methods: Thermosensitive HSPi liposomes were prepared using traditional high-pressure extrusion & pH gradient active loading of the drug. Liposomes were characterized in terms of size & size distribution, zeta potential, & HSPi loading. Temperature-dependant drug release was measured by heating liposomes to clinically relevant temperatures for 2 min. Drug release was determined by size exclusion chromatographic separation of liposomes & drug & quantification by reversed-phase HPLC & UV detection. The effect of doxorubicin & HSPi alone & in combination plus the sensitizing effect of hyperthermia was measured *in vitro* using a panel of breast cancer cell lines. Cell viability was assessed using the acid phosphatase assay & combinatorial effect was evaluated using the Chou & Talalay method. Parallel studies including 1 h heating at 42°C allowed measurement of the thermal enhancement effect of the drugs alone & in combination.

Results: Thermosensitive HSPi liposomes were successfully prepared with a diameter of ~200nm. HSPi was effectively loaded with an encapsulation efficiency of >90% & a final drug concentration of 2mg/mL. Drug encapsulation was stable at 37°C & with drug being efficiently released upon heating to 42°C. *In vitro*, doxorubicin & HSPi were found to act synergistically in several breast cancer cell lines across a wide range of drug ratios with combination indices often <0.7. On average, hyperthermia reduced the IC50 of doxorubicin 1.8-fold & HSPi 4.6-fold.

Conclusion: Doxorubicin & HSPi exhibit synergistic activity for a broad range of drug ratios, allowing therapeutic efficacy at varying intratumoral concentrations. Furthermore, hyperthermia enhances the cytotoxic effect of this drug combination. In order to exploit this promising therapy, thermosensitive HSPi liposomes have been prepared & will be evaluated in preclinical models in combination with ThermoDox & hyperthermia.

TUES 23

DOES THE COMBINATION OF NANOPARTICLE HEAT THERAPY AND FOCAL RADIOTHERAPY CREATE AN ABSCOPAL EFFECT IN MOUSE PROSTATE CANCER MODEL?

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Background: Recent developments indicate that combination of focal radiation and nanoparticle mediated heat enhances local tumor control and activates a systemic anti-cancer immunological response. However, whether or not the immunological activation alone is enough to inhibit the growth of established solid secondary tumors is less studied. In this study we sought to ask if the combination of heat and irradiation induced immunological activation would be enough to inhibit the growth of solid prostate cancer tumors, which are considered to be hard targets for immunological interventions.

Methods: To explore effects of combined heat and radiation stress to mouse prostate cancer cell line (Myc-Cap) apoptosis and senescence we used clonogenic cell survival assay. Subsequently, we used the Myc-Cap cells to generate bi-lateral allografts mimicking primary and distal tumors in male FVB/N mice. We monitored tumor growth with caliper measurements, and injected primary tumors with starch coated Bionized NanoFerrite nanoparticles (BNF-NP) after the tumor reached a pre-determined volume. We heated the nanoparticles inside tumors with an alternating magnetic field and irradiated primary tumors with small animal radiation research platform. We divided the animals into therapy cohorts including: control, radiated, heated, and the combination.

Results: *In vitro* experiments demonstrated markedly increased susceptibility to the combination treatment, which is consistent with previously published results. The initial *in vivo* mouse experiments demonstrated that combinatorial therapy with heat and irradiation significantly inhibited primary tumor growth, while the single modalities provided only partial inhibition. Additional studies are ongoing to establish statistically significant dose response correlations in the untreated distal tumors. The distal tumor growth inhibition and healthy tissue toxicity seem to be reversely affected by the thermal dose, irradiation dose and scheme (single dose vs fractionated), time between the heating and irradiation. In addition, tumor size during treatment has a central role on the outcome.

Conclusions: Based upon the early studies, our preliminary conclusions are that the synergy in combinatorial therapy approach gives superior control over primary tumor growth. However, the overall survival is not enhanced because of increased healthy tissue damage. Whether or not we can measure a growth inhibition in the distal, untreated tumor seems to depend on therapy conditions and tumor size at treatment. Pending further studies will be used to refine these preliminary conclusions and additional immunotherapy could be beneficial. After establishing appropriate therapy conditions we will commence mechanistic studies.

TUES 24

LOCAL MAPPING AND PHOTOTHERMAL TUMOR TREATMENT USING GALECTIN-1 TARGETING NANOMATERIALS

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Due to their biocompatibility, functionalizability, and large optical cross-section, polydopamine-coated Au nanocages were used for photothermal treatment of tumors. Anginex, a synthetic 33mer that binds to galectin-1, was conjugated to the surface to act as a targeting moiety. Approximately $6x10^4$ peptides were conjugated to each particle, which caused the zeta potential to change from highly negative to moderately positive. The peptide retained its biological activity after conjugation, as demonstrated by migration and tube-formation assays, which indicated similar effects caused by free peptide or nanocage-bound peptide. In vitro cellular targeting was confirmed by using murine breast cancer (4T1) and endothelial (2H11) cells incubated for several hours and the particles were not rapidly internalized by these cells. Photothermal cell killing was only observed when the targeting moiety was used, even though the temperature of the well remained below 40 °C. Anginex's target, galectin-1, is overexpressed by the tumor endothelium and tumor cells themselves, and endothelial expression significantly improves nanomedicine delivery. Murine 4T1 breast tumors were grown in immunocompetent mice, and the construct was introduced intravenously at a dose of 100 ul of 100 pM AuNC solution. The particle concentration in circulation was monitored photoacoustically, and the clearance was found to be biphasic with a residual amount of particles still circulating after 24 h. No outward signs of nanoparticle-induced toxicity were observed in mice. Anginex enabled these nanocages to specifically target and remain in tumor tissue resulting in a 3 fold increase in tumor accumulation compared to non-targeted nanocages after 24 h. Subsequently, a ten minute irradiation with a continuous wave laser was used to heat the tumor to a mean temperature of ~42 °C, resulting in significant retardation of tumor growth. The tumors from another group of animals were visualized photoacoustically 24 h after nanoparticle injection and then excised. The distribution of the particles within the tumor tissue itself was determined, which allowed interpretation of the mechanism for the effectiveness of the treatment. Particles accumulated primarily in the peripheral layers of the tumor. These studies demonstrate the potency of nanocages as photothermal therapeutics and that the close association between the cells and the nanocages is critical to provide potent biological effects.

TUES 25

HUMAN URINE EXTRACELLULAR VESICLES, A POTENTIAL BIOMARKER FOR DISEASE CONDITIONS

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Cells export extracellular vesicles (ECV) as signaling agents directed at indicating their physiological conditions. During stress or pathological situations, the composition of ECV changes displaying specific markers of their new stage. These altered ECV serve as signals for the immune system indicating that homeostasis has been compromised. The sensor mechanism for the detection of ECV after an insult has been coined the "Stress Observation System (SOS)." Therefore, ECV have emerged as potential biomarkers for disease conditions. ECV can be obtained from a variety of bodily fluids (e.g., blood, urine, saliva). However, urine is a particularly ideal source of ECV because it can be obtained in great quantities, recurrently and with minimal intervention. However, the characterization of urine ECV is challenging because the preparation is usually contaminated with soluble proteins. Indeed, urine ECV co-sediment after high-speed centrifugation with uromodulin (UMOD) or Tamm-Horsfall glycoprotein that forms large extracellular filaments. Therefore, approaches to obtain cleaner preparations of urine ECV are important for any proteomic analysis. We have developed a method to obtain human urine ECV free of UMOD by the addition of $ZnSO_4$ prior to vesicle isolation by differential centrifugation. Treatment with $ZnSO_4$ did not affect the size and concentration of the vesicles and preserved the storage of the samples at low temperatures. In addition, we did not observe a variation in the number of vesicles isolated during different times of the day, during different days or between different donors. We have characterized the glycoprotein pattern of urine ECV from healthy individuals seeking markers that allow us for the comparison within a broad range of individuals of different sexes and ages as a basis for their use in pathological conditions. We found that the levels of vacuolar protein sorting factor 4A (VSPA4), dipeptidase 1 (DPEP1), and CD9 were similar in ECV preparations obtained from several healthy donors. In addition, the carbohydrate composition of ECV was very similar among various donors. In summary, we have developed a very effective method for the isolation of highly pure human ECV derived from urine samples, which may be of help in the further development of these vesicles as potential biomarkers.

TUES 26

TRIPLE FLUORESCENCE LIGHT SHEET MICROSCOPY WITH A SINGLE CHANNEL DETECTION

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Developmental biology studies require a fast visualization of different dynamic microstructures in order to elucidate their functionality in a determined biological process. For that purposes, confocal laser scanning microscopy (CLSM) has been successfully used to excite and visualize different microstructures from optically sectioned images using specific fluorescent markers. However, under CLSM each image plane is constructed sequentially, point by point while the laser is raster scanned to map the full visualization plane limiting the acquisition speed. Otherwise, light sheet fluorescence microscopy (LSFM), based on a planar illumination of the sample, has revolutionized in the last decade how optical 3D imaging of biological specimens can be performed. LSFM techniques are made possible by decoupling the light excitation and detection optical paths allowing wide field imaging by using a planar light excitation (optical sectioning). Additionally, using a light sheet excitation permits to minimize the fluorescence from out-of-focus features, and to acquire faster images with more efficient signal detection using high efficient two dimensional sensor arrays. Two main configurations are commonly used to perform LSFM differing mainly in the way the plane of light is formed. One is the so-called selective plane illumination microscopy (SPIM) and the other one is called digital scanned laser microscopy (DSLM). In SPIM, the sheet of light formed at the focus of a cylindrical lens is employed to illuminate a plane of the sample and the fluorescence signal generated is collected by an objective lens, whose optical axis is orthogonal to the illumination plane and projected onto a camera. The capabilities of SPIM to image large biological samples in 3D, at high spatio-temporal resolution and minimizing the specimen photo-damage, have been proven to visualize large living biological systems such as zebrafish, *Drosophila melanogaster* embryos, *Caenorhabditis elegans* and tumor cell spheroid, among others. In this work, I will present a cost-effective multi-fluorescent light sheet imaging system based on a SPIM configuration, three synchronized continuous wave (cw)-lasers and a single camera detection. The feasibility of tracking fast biological processes is demonstrated imaging living cells of the filamentous fungus *N. crassa* expressing proteins tagged with three different fluorescent markers.

TUES 27

COMPUTATIONAL STUDY OF TEMPERATURES IN A MULTILAYER MEDIUM OF AGAR AND BACTERIA IRRADIATED BY A LASER THROUGH THE NC-YSZ IMPLANT

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Introduction

This study is framed in the broad project called Window to the brain (WttB). One of the objectives of the WttB project is to assess the temperature profiles and thermal damage produced in the brain tissue when it is irradiated by a specific laser through the nc-YSZ implant. As a first approximation, in the present study we build a computational model based on the experimental work carried out by Damestani et al (Damestani Y, De Howitt N, Halaney DL, Garay JE, Aguilar G, Evaluation of laser bacterial anti-fouling of transparent nanocrystalline Yttria-Stabilized-Zirconia cranial implant, Laser Surg Med, 48:782-9, 2016). Damestani et al made an in vitro experiment in which a multilayer medium, formed by bacteria and agar, was irradiated by a laser device through the nc-YSZ implant. Our aim was to compare the experimental temperatures profiles obtained from this specific model of nc-YSZ irradiation with computer modeling results. The results allowed us validate the computational model, obtain more information about the thermal behavior of the nc-YSZ implant and laid the groundwork for next more complex studies involving the nc-YSZ irradiation.

Methods

The physical situation is translated into a coupled optical-thermal problem, which was solved numerically using COMSOL Multiphysics software. The outcomes of the computer model were mainly: 1) DT(°C) of upper and lower surfaces of the nc-YSZ implant at three levels of power (1, 2 and 3 W), and 2) the temporal evolution of specific points of the material involved.

Results

We found a great agreement (differences <5%) between computational and experimental results at the upper surface of nc-YSZ implant. However, there exist differences in temperatures at the lower surface of nc-YSZ implant. The thickness, the absorption coefficient and the thermal conductivity of the layer under the nc-YSZ implant were the main responsible of those differences. The temperature evolution in some points of the geometry showed that the steady state regime was not been reached at the final time of the experimental set-up (20 s).

Conclusions

The computer model provides a suitable approximation of the study of laser heating through the nc-YSZ implant. The thickness, the absorption coefficient and the thermal conductivity of the layer under the nc-YSZ were the main factors to take into account in this heating.

TUES 28

FIBER OPTIC TEMPERATURE SENSORS WITH POLYMER-BASED FLUORESCENT MATERIALS

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Biomedical applications demand temperature sensors with spatial resolution ranging from a few mm to the micron scale, where biological processes are of great relevance. Among other attractive applications, there is interest in monitoring temperature during thermal procedures for tumor treatments. Most of these techniques rely on the availability of temperature sensors that must perform adequately while exposed to electro-magnetic (EM) radiation. As an example, thermal therapy using radio-frequency (RF) signals requires a temperature sensor that must be immune to RF interference. In addition, for most of these applications, sensors with reduced dimensions are highly desirable in order to minimize the invasiveness of the procedure. Both of these requirements impose restrictions on the sensor technology that can be used for these applications.

Over the last few of decades, fiber optic sensor technology has been maturing and reaching a wide range of fields. Temperature sensing with optical fibers in particular has been demonstrated for a wide range of temperatures and spatial scales. For biomedical purposes, the most attractive features of fiber optic temperature sensors are their immunity to EM interference and their reduced size. Some thermal therapies in fact make use of fiber-based technologies for temperature monitoring. In this work, we demonstrate an optical fiber sensor based on the fluorescence emission of rare-earth active ions. The temperature sensitive composite material used in the sensors includes ions incorporated in a polymer matrix (polydimethylsiloxane, PDMS) by simple mixing. This fluorescent material can be easily incorporated on the tips of glass optical fibers to obtain a point temperature sensor. Temperature measurements are obtained through the fluorescent intensity ratio technique, which relies on comparing the fluorescence emitted by the polymer compound at two different wavelength bands. This ratiometric technique allows for obtaining a linear response from the sensor and minimizes the effects of noise sources affecting the fluorescence signal. The fiber sensors fabricated with this material have shown to provide good performance within a temperature range of 20–50 °C (suitable for hyperthermia therapy) and excellent linearity ($r2 = 0.99$). The sensors are further easy to fabricate thus making them attractive candidates for thermal therapy applications.

TUES 29

TEMPERATURE CHANGES IN METALLIC NANOPARTICLES ESTIMATED BY RAMAN SPECTROSCOPY

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When illuminated near their plasmonic resonances, metallic nanoparticles can become effective heat-sources that increase the temperature in their immediate vicinity. This is an effect that can be controlled remotely using light, that has become increasingly important in several fields of modern science. The measurement of temperature with high spatial resolution, on the other hand, has also become a subject of interest, not only in the context of the miniaturization of devices, but also in the biological and medical fields. The measurement and control of temperature at the subcellular scale, for instance, are crucial for the application of techniques like photothermal therapy and thermally-induced drug delivery. Not surprisingly, the development of non-invasive and high spatial resolution thermometers is now a very active field of research. Among the optical techniques that have been proposed to measure temperature with high spatial resolution we can mention those based on fluorescence, luminescence, up-conversion, and Raman spectroscopy. With Raman spectroscopy, the idea is to measure the strengths of a Stokes and its corresponding anti-Stokes line, and use this information to calculate the temperature considering a Boltzmann distribution for the ground and first excited state populations.

In this work, we use the enhanced Raman signal of adenine to monitor the temperature increase of metallic nanoparticles under laser irradiation. The particles were produced by chemical methods and characterized by optical and transmission electron microscopy methods. Particles with various shapes, including nanospheres and nanostars have been produced. Results for the estimated increase in the temperature of metallic particles under laser illumination will be presented. These results show that the temperature increases fairly linearly as a function of the incident irradiance. We also present calculations for the absorption cross sections of the nanoparticles, from which the temperature increase of the sample can be estimated. Employing a thermal model and fairly realistic assumptions, we are able to reproduce the experimentally observed behavior.

TUES 30

MEASURING THERMAL GRADIENTS ON MICROMETRIC AREAS USING LASER INDUCED FLUORESCENCE

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Thermal-based treatments like hyperthermia and laser ablation rely on the use of special devices and techniques to generate a local increase in temperature. When targeting small areas, temperature measurements can be challenging because of the limited spatial resolution offered by conventional measuring devices. In addition to temperature measurements, it is often desirable to visualize thermal phenomena through a spatial temperature map, particularly in microanalysis platforms such as those developed with lab on a chip technologies and microfluidic platforms. High spatial resolution temperature measurements are therefore of interest for several biomedical related applications.

Temperature measurements can be performed either through contact or non-contact techniques. While the latter are commonly inexpensive but with limited spatial resolution, the former are typical based on optical phenomena. Infrared cameras, for example, are useful for acquiring thermal images; nonetheless, achieving high spatial resolution with these systems requires expensive bulk optical devices. Fluorescent thermometry, based on the use of organic dyes with temperature dependent fluorescence intensity, can yield temperature maps at the micron-scale. In contrast to other techniques, fluorescent thermometry can be used with conventional optical instruments such as microscopes, and the spatial resolution of temperature measurements is mostly limited by the imaging optics.

Using laser-induced fluorescence (LIF), we have developed a system to acquire temperature gradients within micrometric areas. The system uses a fluorescent dye (Rhodamine B, RhB) incorporated in polymer membranes. These composite membranes offer new possibilities for using LIF in environments in which a liquid solution of RhB may be detrimental. We demonstrate the system as a test bed for photothermal devices, particularly for the characterization of optical fiber microheaters (OFMH) with 125 microns cross sectional diameter. The temperature sensitive composite membranes are excited with a 532 nm laser and the fluorescence is captured through a microscope objective and a CMOS camera to obtain a 2-D fluorescence map. Upon placing the OFMH in contact with the membrane, the fluorescence intensity varies as the temperature increases owing to the heat generated by the device. Through image processing, we are able to obtain the temperature distribution in the vicinity of the OFMH, rendering temperature maps with 2.7 μm/pixel spatial resolution within a temperature range from 20 - 90°C. The system thus offers an attractive alternative for obtaining temperature distributions with improved spatial resolution and with an adequate response time for the analysis of thermal phenomena.

TUES 31

EFFECT OF TEMPERATURE ELEVATION ON SHORT DURATION FOCUSED ULTRASOUND HYPERTHERMIA MEDIATED DRUG DELIVERY USING THERMOSENSITIVE LIPOSOMES AND TWO-PHOTON MICROSCOPY

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Background: Preclinical studies have shown that MRI-guided focused ultrasound (MRgFUS) can achieve spatially localized thermal exposures in the range of 41-43°C. It has been found that MRgFUS is capable of inducing the targeted uptake and release of doxorubicin (DOX) from thermosensitive liposomes (ThermoDox, Celsion Corporation) in tumor models, and that this gives rise to potent antitumor effects. To enable the treatment of a broad spectrum of tumor types, improved heating methods must be developed to overcome issues relating to respiratory motion, bone shielding and large blood vessel cooling during MRgFUS. We have shown previously that 10 short 30s exposures of hyperthermia to 42°C can release substantial amounts of DOX from ThermoDox. Here we investigate the effect of different temperature elevations on the spatiotemporal drug release and distribution of DOX from ThermoDox during 30s of hyperthermia using *in vivo* two-photon microscopy (2PM) with the goal of optimizing the thermal exposure.

Methods: FaDu tumors expressing GFP were implanted in the window chambers of nude mice. Temperature-based PID control of the output power was used to maintain the tissue temperature at the desired level (41°C, 42°C, 43°C or 45°C) for 10 short 30s heating bursts. The short duration was chosen to be long enough to release DOX from ThermoDox®, but also short enough to be applied during a breath hold and overcome perfusion-related limitations on sustained temperature elevations *in vivo*. The temperature elevations were chosen to be close to the phase transition temperature of ThermoDox (~41.3°C) but not no high as to cause thermal damage to the microvasculature. Serial 3D vascular and DOX images were acquired in tumor regions before, during and after each hyperthermia exposure all in the presence of ThermoDox.

Results: The PID controller was able to achieve the desired temperature response with a variable temperature elevation within the hyperthermia regime. ThermoDox drug release was successfully visualized at each temperature elevation with modest release at 41°C and more substantial release at the higher temperatures. At 45°C some potentially deleterious vascular effects were observed and may be in competition with the amount of drug released for maximum accumulation in tumors.

Conclusions: We have developed the use of 2PM to image the release of DOX from ThermoDox in real-time during FUS hyperthermia in mouse tumors. By optimizing the amount of drug released during short duration hyperthermia exposures, improvements in treatment outcome are expected and limitations on clinical MRgFUS can be overcome.

TUES 32

THE FEASIBILITY OF USING FOCUSED ULTRASOUND TO INDUCE HYPERTHERMIA THROUGH THE INTACT SKULL

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Introduction The recent clinical successes of Magnetic Resonance-guided Focused Ultrasound in the treatment of neurological conditions indicate the future promise of focused ultrasound to provide non-invasive therapy to the brain. Hyperthermia has been applied to the brain in numerous studies using a variety of modalities, including laser, microwave, radiofrequency, and ultrasound. This study seeks to determine the feasibility of applying focused ultrasound-induced hyperthermia through the intact skull and determine the safe treatment limits.

Materials and Methods A simulated treatment domain consisting of a Computed Tomography model of an *ex vivo* human skull and a hemispherical 1024-element phased array was constructed. Full-wave numerical models were used to simulate the acoustic and thermal maps resulting from treatment to a grid of points inside the skull. The resulting focal and skull heating were obtained to determine whether each point was treatable. Probit regressions on the grid locations for various scan diameters (0, 5, and 10 mm) and water temperatures (5, 10, and 15°C) were performed to determine the safe treatment limits.

Results By using a 30-second sonication scheme, it was shown that the treatment of targets less than 40 mm from the geometric center of the skull were possible with single point scans and treatment of cerebral targets less than 34.6 mm from the geometric center were possible with a 5mm-diameter scan. Scan diameters larger than 10 mm were infeasible at most steered locations and the application of these scanning patterns requires further study. The treatment range as functions of water cooling temperature and circulation did not vary significantly between 5 and 15°C. Five minutes of water cooling following each sonication was sufficient to reduce temperatures well below 38°C.

Conclusion The application of hyperthermia to the brain using 0 and 5 mm-diameter scans is likely feasible at central cerebral targets.

TUES 33

SAFETY AND FEASIBILITY OF MR-HIFU MILD HYPERTHERMIA WITH RADIATION AND CHEMOTHERAPY FOR RECURRENT RECTAL CANCER

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Introduction: Inoperable rectal cancer recurrence has marginal outcomes when treated with radiation (RT) and chemotherapy (CT). Mild hyperthermia (HT) may sensitize tumors to RT and CT, improving control and quality of life. MR-HIFU may provide safe and well-controlled HT. We report early follow-up from an ongoing Phase I trial of MR-HIFU HT as an adjuvant to RT and CT for locally recurrent rectal cancer.

Methods: This ethics-approved study plans to enroll 10 patients with inoperable recurrent rectal adenocarcinoma fit for re-irradiation and chemotherapy, and a HIFU-accessible MRI-visible lesion. Enrolled patients receive 30.6 Gy (17 fractions) and daily oral capecitabine, plus MR-HIFU HT immediately before RT on days 1, 8, and 15. Primary objectives are safety (acute toxicity) and treatment feasibility. Secondary objectives include late toxicity, pain palliation, quality of life, HT accuracy, and radiologic response. HT was delivered with the Sonalleve MR-HIFU system on an Achieva 3T MRI, under Investigational Testing Authorization from Health Canada. Feedback control parameters were prescribed to achieve a mean temperature of 42.5°C in a 18 mm diameter target region for 30 minutes, without exceeding 45°C.

Results: Of 10 screened patients, 4 have been enrolled, and 6 excluded due to patient and tumor factors. One enrolled patient did not complete 2/3 HT sessions due to scheduling and sedation difficulties, and ultimately withdrew from the study. All patients completed RT and CT. There were no intraoperative complications, and no adverse events attributable to HT, RT, or CT. Best single continuous HT session for each patient had mean (T90, T10) temperatures of 41.2 (39.3, 42.5)°C, 42.3 (40.9, 43.4)°C and 41.8 (40.3, 43.1)°C. Cumulative time in range (40-45°C) for three patients who completed 3/3 HT sessions were 37, 52.7, and 48.9 minutes, with cumulative thermal dose of 3.3, 41.3 and 17.7 CEM43. Post-treatment imaging indicated no unintended tissue damage. Sonication times were 37±13 min, cooling times between sonications restarted due to patient motion were 24±15 min, and total MRI suite times were 261±73 min. At last follow-up, patient #1 has stable disease. Patient #2 had stable disease locally, but progressed at 7 months, and died later (unknown cause). Patient #3 has ongoing local and systemic therapy for disease progression. Patient #4 withdrew without follow-up.

Conclusion: MR-HIFU HT has been safely delivered in three patients with recurrent rectal cancer.

TUES 34

MRI-GUIDED TRANSURETHRAL ULTRASOUND ABLATION OF THE PROSTATE (TULSA): STATE OF THE ART

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Introduction: MRI-guided transurethral ultrasound ablation (TULSA) uses real-time MR-thermometry to control conformal ultrasound ablation of prostate tissue using automated feedback. We report 3-year Phase I outcomes, and enrolment data from a Pivotal trial for whole-gland ablation of localized prostate cancer.

Methods: In TULSA, a transurethral ultrasound applicator (UA) with a linear array of ten 5-mm transducer elements is inserted into the prostate and held by a robotic positioning system. MR images are acquired to define patient-specific target boundaries for each UA element. MR-thermometry, acquired every 6s while delivering high-intensity directional ultrasound, is used to adjust the frequency and power of independent UA elements, and UA rotation rate, sweeping out a conformal heating pattern. Post-treatment contrast-enhanced T1 depicts acute non-perfused volume (NPV), which is compared to 55°C and 240CEM43 isocontours.

The 30-pt Phase I trial of conservative whole gland ablation had primary outcomes of safety (adverse events, AE) and feasibility (ablation accuracy and precision). To assess extent of delayed necrosis, a 3-mm 55°C margin spared 1-3 mm of peripheral prostate tissue (10% volume).

The 110-pt TULSA-PRO Ablation Clinical Trial (TACT) Pivotal study is further evaluating safety and efficacy of whole gland ablation. Primary efficacy outcome is %patients achieving PSA reduction ≥75%; secondary is 12-month biopsy and prostate volume. Safety is 12-month AE and QoL. A reduced margin (2-mm, 57°C) intends to ablate to the capsule.

Results: Phase I AEs were favorable, with urinary and erectile function returning to baseline at 3 and 12 months. Ablation accuracy and precision were 0.1±1.3 mm, with conformal NPV. Median (IQR) PSA decreased from 5.8 (3.8-8.0) ng/ml to nadir 0.5 (0.2-0.8) and 0.8 (0.4-1.6) at 3-years. 12-month MRI and biopsy showed 88% reduced prostate volume and 75% reduced cancer length, reflecting peri-capsular margin sparing. At 3-years, 7/30 patients had uncomplicated salvage therapy.

TACT enrolled 115 patients ending Feb 2018. Of the first 63 evaluable patients, median PSA reduction to-date is 93%, with 92% of patients (58/63) ≥75% reduction. 12-month safety is not yet available. Treatment time was 55 (41-70) min for targeted prostate volumes ranging 15-88cc, accuracy and precision 0.1±1.4 mm. Conformal ablation was confirmed by acute NPV.

Conclusion: TULSA provides safe and precise ablation of localized prostate cancer, while keeping salvage therapy options open. A 110-pt Pivotal trial has completed enrolment.

TUES 35

CATHETER-BASED ULTRASOUND THERMAL ABLATION OF TUMORS IN THE PANCREAS

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Background

The 5-yr survival rate of pancreatic cancer is merely 6%, making it one of the most lethal cancers. Due to absence of symptoms often pancreatic cancers are diagnosed at a late stage of the disease. The majority of patients are not diagnosed until they fall within the category of poor surgical candidates. Thermal therapy can be a complement to drug therapy, enabling enhanced delivery of chemotherapy to tumors. We propose to assess the treatment efficacy of 3D spatially-registered real-time image-guided needle/catheter based ultrasound (CBUS) thermal therapy in the pancreas in a pig.

Methods

Sectored tubular transducers with 1.5mm OD x 10-15 mm long tubular transducers, operating at 6.5 MHz, were designed for ablating the targeted tissue in the pancreas. Directional applicator was used to the appropriate active sector angle for the pancreas application. The length of the catheter was designed that can be applicable for insertion endoscopically through the duodenum into the pancreatic duct in a pig. Applicators were fabricated for insertion under fluoroscopic or MR image guidance. The ablation patterns will be characterized including beam profiles such that appropriate experimental parameters can be used to ablate the target volume in the pancreas. Performance was evaluated using phantoms and ex-vivo and in vivo pig pancreas tissue, with multi-sensor fine needle thermocouples.

Results

The intraluminal applicator was inserted through a small incision into the duodenum, through the duct and held in position adjacent to the pancreas tissue. The active sector directed toward the pancreas parenchyma. Acoustic power of 6 W (30W/cm2) for 1.5 min was applied to a single 90° sector. TTC stained sections demonstrate ablation of the pancreas from within the duodenum, with no apparent damage to the duodenum.

Conclusion

These preliminary results suggest catheter-based therapeutic ultrasound may be delivered through the duodenum to the targeted region in the pancreas. These sectored applicators may provide a novel and fast minimally-invasive treatment alternative to the traditional surgical treatment for pancreatic tumors. Such minimally invasive focused ultrasound (FUS) technology can benefit numerous patients including the patients not suitable for surgical resection.

TUES 36

EVALUATION OF INTERSTITIALLY MEASURED AND SIMULATED TEMPERATURE DISTRIBUTIONS DURING LOCALREGIONAL HYPERTHERMIA TREAMENT IN PATIENTS WITH HIGH-RISK SOFT-TISSUE SARCOMA.

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The aim of this work was to evaluate the accuracy and reliability of a hyperthermia treatment planning (HTP) in comparison to interstitial tumor thermometry during regional heating in patients with high-risk soft-tissue sarcoma (STS) located in the extremity region.
Five patients underwent CT fluoroscopy-guided catheter intratumoral implementation for the interstitial thermometry. Depending on the tumor size, between one and three tumor-catheters was implemented in each patient. All patients were treated with Sigma-Eye hyperthermia applicator. The measured temperatures along the tumor-catheters were acquired using a pulled-back thermometry system. The acquired data were then analyzed within the steady-state therapy time by calculating the index temperature T90. Additionally, the thermal dose CEM43T90 was determined from the invasive measured temperature. For the HTP procedure, CT/MR images of the five patients were segmented manually/ (semi-)automatically into fatlike, musclelike tissues, blood vessels, bone tissue and tumor. A 3D patient model was then generated from the segmented structures and used for the electromagnetic (EM) and thermal simulations using the finite element (FE) method. Similar applicator setups were employed in both measurement and simulation. The simulated data were then evaluated in a similar manner to the measured data. In order to determine the deviation between measurement and simulation, the relative error in the index temperatures as well as in the temperature increase was calculated.
The invasive thermometry data indicated that different temperature profiles with varied thermal doses were observed across the five patients depending on: 1) Anatomical heterogeneity (liquid, solid and necrotic part) within the tumor resulting into different dielectric tissue properties; 2) Intratissue perfusion of the tumor; 3) Location of large blood vessels close to the tumor; 4) Anatomical location of the tumor in the lower extremities (upper legs). Higher temperatures were measured, when the tumor was not seated close to large blood vessels and featured a high amount of liquid and/or necrotic fraction. The deviation between measured and simulated tumor temperatures was found to be ±22%, which may be caused by serval Effects, such those mentioned above (1-4). Further, intratissue variation of delectrical properties, real patient position and applied optimization method may have an impact on the simulation results. On the measurement site, real catheter and patient position as well as the accuracy of the thermometry measuring device may affect the measured data. Considering all these effects would help to significantly reduce the error between the real patient treatment and the HTP.

TUES 37

SYSTEMIC CHEMOTHERAPY PLUS REGIONAL HYPERTHERMIA FOR TREATMENT OF LOCALIZED HIGH-RISK SOFT TISSUE SARCOMAS IN CHILDHOOD

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Background: Survival has dramatically increased over the last 30 years in childhood soft tissue sarcomas; however, improvements in disease control are still needed, especially for the majority of patients with gross residua after resection or metastatic disease at the time of diagnosis. Our rationale for the use of microwave-induced regional hyperthermia (RHT) in the range of 41–43°C with chemotherapy alone or in combination with additional radiotherapy in those cases was based on the observation that hyperthermia is a potent chemo- and radiosensitizer.

Methods: We aimed to determine whether objective tumor response could be achieved in children with localized refractory or recurrent rhabdomyosarcomas (RMS) and RMS-like tumors with chemotherapy (cisplatin 40 mg/m2 or adriamycin 30 mg/m2, days 1+4; etoposide (100 mg/m2, days 1–4); and ifosfamide (1800 mg/m2, days 1–4) with microwave-induced RHT (41–43°C, days 1+4) alone or in combination with radiotherapy (19·2–50·4 Gy) as salvage treatment.

Patients: From 8 May 1998 to 12 February 2016 a total of 43 children/adolescents (16 female, 27 male) at 0;7-19;2 years of age (median: 6;5 years) with refractory or recurrent RMS and RMS-like tumors were treated according to the Hyper-PEI-protocol. Histopathological examination revealed 29 embryonal RMS, 8 alveolar RMS, 3 undifferentiated sarcomas, 2 extraosseous Ewing sarcomas, 1 synovial sarcoma.

Results: In 34/43 patients with a measurable tumor in diagnostic imaging before systemic chemotherapy in combination with RHT clinical tumor response was assessed: CR (n=4); PR (n=15); SD (n=12); PD (n=3). After thermo-chemotherapy a 2nd-look operation was performed in 28/43 patients: R0 (n=10); R1 (n=11); R2 (n=2), biopsy (n=5). Event-free survival (EFS) and overall survival (OS) in this poor prognostic patient population was significantly better for refractory and residual tumors than for recurrences.

Conclusion: The resulting data concerning local tumor control - which is essential for long-term cure - suggest that the use of microwave-induced RHT at temperatures of 41–43°C in combination with standard chemotherapy ± additional radiotherapy should be considered at an early stage after initial treatment failure.

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TUES 38

EXTERNAL THERMAL THERAPY COMBINED WITH RADIATION THERAPY RESULTS IN MODEST TOXICITIES AND THE PROMISE OF INCREASED EFFICACY: 5 YEARS OF EXPERIENCE

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Background: Hyperthermia is well-known to act as radiosenstitizer when delivered during radiation (RT). Advances in technology are allowing for increased availability of External Thermal Therapy (ETT) for superficial tumors, particularly those known to be hypoxic and/or recurrent. While ETT increases tumor response to RT, concern is prudent for increasing side effects to surrounding normal tissues. Our goal is the report on the acute and chronic toxicities along with overall survival (OS) and local control (LC) from our 5 year institutional experience.

Methods: We retrospectively reviewed all patients treated at our institution who received ETT concurrently with RT spanning 03/2013 to 02/2018. Patient characteristics including age, gender, race, primary disease site, histology, RT dose, RT technique, ETT temperature, and ETT duration. Outcomes evaluated were acute and late toxicities as well as LC and OS.

Results: One hundred patients received ETT/RT to 107 treatment sites. The most common malignancies were breast cancer (33%), soft tissue sarcomas (28%), and skin (13%). Seventy-three percent were treated at the time of tumor recurrence and 57% of treatments were re-irradaition. The median RT dose 50.4Gy (range, 24 – 70Gy); the median ETT treatment number and prescribed treatment time were 9 (range, 2-23) and 60mins (range, 45 – 60mins), respectively. Target tumor temperature was 40-42C with applicator bolus temperature of 39-40C. Median follow up was 23.5 months. Of the 107 treatments acute toxicities included dermatitis (grade 2 – 30%; grade 3 – 14%) and pain (grade 2 – 21.5%; grade 3 – 1.8%). Three patients required a treatment break and one patient discontinued early. In total, there were 7 (6.5%) grade 3 chronic toxicities including skin/soft tissue (n=2), lower extremity edema (n=2), joint stiffness (n=2), and pneumonitis (n=1). Median and 2-year OS were 23.7 months (95% CI 13.4 – 34.0) and 48.9% (95% CI 43.0 – 54.8), respectively. Median duration of local control was 22.2 months (95% CI 7.3 – 37.0) and 49.8% (95% CI 42.9 – 56.7). Median LC in reirradiation scenarios was 15.1 months (95% CI 12.5 – 17.6).

TUES 39

SINGLE INSTITUTION EXPERIENCE OF THE ADDITION OF THERMAL THERAPY TO RADIATION THERAPY FOR CUTANEOUS MALIGNANCIES

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Background

Hyperthermia therapy (HT) is utilized with external radiation therapy (RT) to enhance treatment response.

Methods

We conducted a retrospective review of the 17 patients treated at our institution with HT and RT for skin malignancies, from the years 2013-2018. Histopathologies included squamous cell (n=8), basal cell (n=2), basosquamous (n=1), Merkel cell (n=1) and melanoma (n=5).

Results

Patients were older (median 71 years), mostly Caucasian (82%) and evenly split between genders. Three patients were organ transplant recipients and prescribed immunosuppression. Our patient population was advanced, 35% presented with Stage IV disease, many treated lesions were large, (T3-T4, n=8, 47%) and most patients presented with recurrences (n=10, 59%). Head and neck (n=8, 47%) and lower extremity (n=6, 35%) lesions and most patients were treated with external beam techniques including intensity modulated radiotherapy (n=7, 41%) and electrons (n=6, 35%) to a median dose of 60 Gy (range 25-74 Gy) in a median fraction size of 2.4 Gy (range 1.2 Gy to 5 Gy). Patients received a median of eight (range 4-18) HT treatments, target temperature was 40-44 degrees for a duration of 40-60 minutes. Eleven patients underwent adjuvant treatment, three patients received prior systemic therapy and four were reirradiaiton. Three patients received concurrent systemic therapy and three patients continued on to systemic therapy after treatment.

Treatments were well tolerated over the course of the median of 16 months of follow up. No grade 4 or 5 toxicities were reported by physicians. The most common acute toxicities were grade 3 dermatitis (n=5), grade 1-2 dermatitis (n=11), grade 1-2 pain (n=10) and grade 1-2 fatigue (n=9). No chronic toxicity was recorded.

Median local control was 25 months (95% CI 21.1 – 28.9 months). Patients experiencing local failure after combined treatment (n=6, 35%) commonly had squamous cell skin lesions (n=4, 67%) and the majority were being treated for recurrent disease (n=4, 67%) and had undergone prior therapy. One transplant recipient taking chronic immunosuppression failed locally. Median overall survival was 23 months (95% CI 19.5 – 26.5 months).

Conclusion

Our experience demonstrates that in this population of advanced, often recurrent skin malignancies HT in combination with RT is feasible and associated with minimal grade 1-3 toxicity.

TUES 40

CONCURRENT PENCIL BEAM SCANNING PROTON THERAPY AND EXTERNAL THERMAL THERAPY: INITIAL CLINICAL EXPERIENCE AND SAFETY EVALUATION

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Background

Hyperthermia (HT) offers an excellent adjuvant to conventional, photon radiotherapy that increases treatment efficacy through multiple mechanisms including inhibition of DNA repair and increasing radiosensitivity of hypoxic tumoral cell populations. HT in combination with proton radiotherapy has been suggested to mimic high linear energy transfer particle therapy (e.g. carbon ion therapy) by improving perfusion/tumoral oxygenation – thus reducing the oxygen enhancement ratio and increasing relative biological effectiveness – in the setting of a particle beam with finite range [Datta et al. 2014]. However, to date, very few institutions have the capacity to deliver both therapies. We, herein, report, to our knowledge, the largest experience to date with combined pencil beam scanning proton therapy (PBSPT) and HT from treatments at a single institution.

Methods

At the Maryland Proton Treatment Center, PBSPT has been utilized in over 800 patients since initiation of therapy in 2016. Of these, 15 patients have undergone concurrent administration of HT by external thermal therapy (ETT) at the University of Maryland Medical Center. These courses were administered for tumors of varying histology: sarcoma (n=5), breast cancer (n=4), ureteral cancer (n=1), cutaneous squamous cell carcinoma (n=1), ovarian cancer (n=1), vulvar cancer (n=1), head and neck cancer (n=1), and mesothelioma (n=1). Radiotherapy doses ranged from 40.8 Gy(RBE) to 69 Gy(RBE) (median, 60 Gy(RBE)). ETT was delivered on the BSD-500 microwave hyperthermia platform. Target temperatures for all patients ranged from 40-44°C with a water bolus temperature of 39-40°C. Patients were treated for 45-60 minutes per session for a total of 4-11 treatments (median, 7 ETT treatments per patient).

Results

Concurrent PBSPT and ETT was well tolerated. There were no acute grade 4+ complications. Only 3 patients experienced acute grade 3 complications which was limited to moist skin desquamation in the treatment field. Other common toxicities included grade 2 or less pain, fatigue, gastrointestinal disturbance, and hyperpigmentation. Two patients reported late grade 3 complications of lymphedema and range of motion limitations (breast cancer and inguinal nodal disease, vulvar cancer). While follow-up is early (median 4, range 0-14 months), patient tolerance has been promising. Of these patients, 4 have experienced local recurrence/progression of disease, while 6 have died.

Conclusion

Concurrent PBSPT and ETT appears effective and safe in this single institution experience. Further investigation is warranted pending long-term follow-up and broadened experience.

TUES 41

CONCURRENT INTERSTITIAL THERMAL THERAPY AND INTERSTITIAL BRACHYTHERAPY FOR PELVIC MALIGNANCIES: A SINGLE INSTITUTION EXPERIENCE.

Cristina DeCesaris, Stephanie Rice, Jason Molitoris, James Snider III, Kimberly Marter, Valerie Smith, Mariana Guerrero, Byong Yong Yi, Pradip Amin, Zeljko Vujaskovic, Pranshu Mohindra

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Background:

Interstitial brachytherapy (IBT) is sometimes needed in the setting of bulky or recurrent pelvic malignancies when alternative radiotherapy (RT) approaches would exceed the dose tolerances of nearby critical structures. External hyperthermia has been combined with radiation therapy as a potent radiosensitizer, though data regarding interstitial thermal therapy/ hyperthermia (ITT) with IBT is limited. We present our institutional experience combining these therapies.

Methods:

All patients treated with concurrent IBT and ITT for pelvic malignancies were retrospectively reviewed. Local control (LC) was the primary end-point. Toxicity was scored using CTCAE v4.0. Each patient received 1 or 2 ITT administrations immediately following IBT fractions with target temperature of 43 C (range 39-43 C) utilizing the BSD-500 unit.

Results:

IBT/ITT was delivered to 14 patients (female: 12, male: 2) with a median age of 65 years. Diagnoses were cervical (n=4), endometrial (n=3), vaginal (n=2), vulvar (n=2); testicular angiosarcoma (n=1), urothelial bladder cancer (n=1), and rectal adenocarcinoma (n=1). Tumor types were recurrent (n=8) and primary bulky disease (n=6). Prior RT was delivered in 6/8 patients with recurrent disease.

EBRT (median 45 Gy, range 30.6 – 55Gy) in combination with IBT/ITT was used in 11/14 patients. Median IBT dose for these patients was 22.5Gy (10-26.25Gy); median fraction size 5 Gy (4.5-7Gy). Median number of ITT treatments was 2 (1-2). None of the 11 patients who received EBRT + IBT/ITT have experienced local failure to date (range 35 days-4.0 years).

The remaining three patients received palliative IBT/ITT alone after declining pelvic exenteration; median IBT dose 11Gy (10-12 Gy), median fraction size 6 Gy, median number of ITT treatments was 2. All three eventually had local failure prompting exenteration 6-12 months post-treatment.

IBT/ITT was well tolerated with expected grade 1-2 peri-procedural pain and bleeding. Chronic toxicity was most commonly grade 1-2 vaginal atrophy/stenosis. One grade 2 rectovaginal and one grade 2 vesicovaginal fistula was reported; the latter was noted in association with percutaneous nephrostomy tube.

Conclusions:

The delivery of ITT/IBT is feasible with use of modern IBT setup. In a patient population with recurrent or advanced bulky disease, we note durable local control in patients receiving combined EBRT + ITT/IBT. When combined with ITT, IBT alone effectively delayed time to exenteration in patients not suitable for other treatments including EBRT. Future efforts will continue to further evaluate the efficacy of concurrent ITT/IBT in comparison to IBT alone.

TUES 42

THE IMPACT OF HYPERTHERMIA THERAPY ON PATIENT REFERRALS AND PATTERNS OF CARE WITHIN A RADIATION ONCOLOGY DEPARTMENT

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Background:

Hyperthermia therapy (HT) is an excellent tool in radiation therapy (RT) to enhance tumor responsiveness. The utility of RT with hyperthermia for various cancer sites is expanding. Despite this, only few cancer centers nationwide offer this treatment. We hypothesize access to HT within a radiation oncology (RO) department leads to new patient referrals resulting in increased RO department revenue generating activity.

Methods:

We conducted a retrospective review of all patients treated with HT at our institution (n=117). To isolate new patient referrals, patients were excluded if their date of entry into our medical center electronic medical record (EMR) pre-dated their consultation for HT. For the remaining patients (n=42), data pertaining to referring provider, patient and tumor characteristics and RT details was gathered.

Results:

A total of 42 patients met inclusion criteria for new external patient referrals. Of these, 19 (44%) were specifically referred to our department for HT, whereas 23 (55%) were initially referred for RT (17) or interstitial brachytherapy (6) and subsequently received HT in our department.

Focusing on patients specifically referred for HT, 13 (68%) were referred by a radiation oncologist, 4 (21%) by a medical oncologist and 2 (11%) by another specialist. 9 (47%) patients were referred from our community based RO centers and/or university-affiliated hospitals, 6 (32%) were referred in-state outside our hospital system and 4 (21%) were from out of state. The most common histology was invasive ductal carcinoma (11) and sarcoma (3). The most common location of disease was chest wall (13) and head and neck (3) locations. The majority of patients, 15 (79%), were referred for re-irradiation as defined by overlap with prior RT and 6 (31%) patients had metastatic disease.

All patients received external thermal therapy with concurrent RT. Electrons was the most common concurrent RT used (7), followed by photons (9) and protons (3). 14 (74%) patients received RT within our department, whereas 4 received RT at one of our community sites and 1 received RT elsewhere. Concurrent chemotherapy was given in 7 patients, all of which were administered at an outside facility.

Conclusions:

Access to HT within a radiation oncology department attracts new patient referrals resulting in increased RO revenue generating activity. We anticipate this number will continue to grow as our understanding of HT broadens across our radiation and medical oncology community and may serve to incentivize the development of more hyperthermia programs centers.

TUES 43

HYPERTHERMIA ENHANCES RADIATION PLUS IMMUNOTHERAPY MEDIATED PANCREATIC TUMOR GROWTH INHIBITION IN MICE.

Sandrine Soman[1], Javed Mahmood[1], Allen Alexander[2], Santanu Samanta[1], Hem Shukla[1], Eduardo Davila[1], France Carrier[1], Isabel Jackson[1], Zeljko Vujaskovic[1]

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Introduction: With a dismal 5-year survival rate of 8%, Pancreatic Cancer (PC) is the 4th most lethal cancer nationally. Radiotherapy (RT) and chemotherapy are largely infective in increasing patient`s survival. Monotherapy including check-point inhibitors are essentially ineffectual, suggesting critical need for a combined therapeutic modality approach. Targeted Hyperthermia (HT), an adjuvant anti-cancer treatment modality, shows promise when combined with other therapeutic modalities. HT (40°∼43°C) is cytotoxic and acts as a RT sensitizer with immune triggering potential. Heat shock proteins (HSPs) are released in response to cell stress and can act as tumor specific antigens, causing enhanced immune response. Anti-OX-40 (CD134) is an immune-modulator which works by preventing OX-40 binding thereby downregulating immunosuppressive regulatory T-cells. Hence, we hypothesize that combinatorial treatment approach can unleash anti-tumor immune response, altering the suppressive PC tumor microenvironment (TME). Method: Using a syngeneic flank PC mouse model, a combinatorial treatment using tumor-targeted hyperthermia (41.50C) followed by fractionated RT (8Gy in 4Gy/fraction) using small animal radiation research platform (SARRP), and anti-OX40 (CD134) immunotherapy (IT) were delivered 3 doses on 0, 5, and 10 days. In house 3D-printed HT apparatus with water bath was used to administer HT. One-day gap was given between to avoid thermal tolerance. Cohorts of animals were euthanized at 10 days and 45 days post-treatment for flow cytometry and immunohistochemistry using tumor and blood samples. Results: The combination of treatments demonstrated a significant tumor growth inhibition ($p<0.0001$) up to 45 days post-treatment compared to RT plus HT or RT plus IT treated mice. Compared to the control, 39.1 ± 3.5 times fold reduction in the final tumor volume was observed in the combinatorial treated animals with increased survival. Tumor and blood samples revealed a significant immunomodulatory effect compared to the untreated animals. Specifically, a significantly increased ($p<0.01$) population of CD4+, and CD8a+ cells were observed in the TME compared to all individual treatment groups at 10 days post-treatment. Combinatorial treated mice showed a 2.5-fold ($p<0.05$) higher cell population of LAG3 (CD223+) cells in the TME indicated increase in dendritic cells compared to no treatment. No toxicity was seen in animals with any single or any combination of treatments. Conclusion: This proof of concept study provides strong preclinical evidence about the effects of a combinatorial treatment to improve the PC tumor response and increase survival as a novel therapeutic option.

TUES 44

ENHANCING THE ABSCOPAL EFFECT OF LOCAL THERMO-RADIOTHERAPY BY IMMUNE CHECKPOINT INHIBITORS

Arlene L. Oei[1,2,3], Preethi Korangath[1], Mikko Helenius[1], Jacqueline Stewart[1], Brian Simons[4], Coen R.N. Rasch[3], Johannes Crezee[3], Lukas J.A. Stalpers[2,3], H. Petra Kok[3], Nicolaas A.P. Franken[2,3], Robert Ivkov[1]

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Abstract

Despite many developments in optimizing anti-cancer treatments, recurrences and metastases are correlated with (very) poor prognosis. About 10-15% of all breast cancer patients suffer from an aggressive version and they will develop metastases within 3 years after diagnoses of the primary tumour. Whereas radiotherapy and hyperthermia have been found successful in treating breast cancer recurrences, a new strategy to target metastases is needed.

Radiotherapy, chemotherapy and hyperthermia are good treatment strategies in treating the primary tumours. Moreover, all therapies have the ability to trigger parts of the immune system, which may prevent occurrence of metastases and/or secondary tumours for several years. In order to enhance the immune responses, to target metastases and improve the disease-free survival, in our set up we added immunological checkpoint inhibitors to thermo-radiation, the combinational treatment of radiotherapy and hyperthermia.

In a highly metastatic breast cancer mouse model, we determined the addition of immune checkpoint inhibitors (PD1-i and CTLA4-i) to local radiotherapy and magnetic nanoparticle hyperthermia. Our data demonstrates that the tumour growth of the primary tumour is suppressed when immune checkpoint inhibitors are added. Furthermore, the number of liver metastases was significantly lower after any treatment, and mostly after the triple combination. In the number of lung metastases a similar trend was observed. We show that all effects could be correlated to immune cell population in the tumour microenvironment.

In conclusion: The enhanced abscopal effect induced by immune checkpoint inhibitors in addition to local thermo-radiation can manipulate the tumour microenvironment in both the primary tumour and their metastases, subsequently resulting in a significantly smaller primary tumours and lower number of metastases in different organs. This potent anti-tumour effect may be further enhanced when thermo-radiation is combined with further synergistic agents to achieve stronger synthetic lethality in the tumour.

TUES 45

PHOTOTHERMAL THERAPY GENERATES A THERMAL WINDOW OF IMMUNOGENIC CELL DEATH IN NEUROBLASTOMA

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Background: Nanoparticle-based photothermal therapy (PTT) has been widely investigated in cancer therapy as a rapid and minimally invasive tumor ablation technique. An emerging area of interest is the effect of PTT on the immune system, since PTT not only causes tumor cell death, but can also release tumor antigens and endogenous adjuvants (e.g. heat shock proteins, damage-associated molecular patterns (DAMPs)) under certain conditions. Immunogenic cell death (ICD) is a highly favorable cell death phenotype that initiates an adaptive immune response and is associated with improved therapeutic outcomes in cancer. Engaging the immune system during PTT is important as it offers the potential for persistent treatment responses and immunological memory.

Methods: Here, we use Prussian blue nanoparticle-based PTT (PBNP-PTT) on Neuro2a neuroblastoma cells to describe the effects of PBNP-PTT on ICD, and subsequent tumor growth or regression. Three consensus guidelines were measured after *in vitro* PBNP-PTT treatment (ATP and HMGB1 release, calreticulin exposure) by flow cytometry. Neuro2a cells treated *in vitro* with PBNP-PTT were then prophylactically injected into mice, which were then inoculated with untreated neuro2a cells, to examine the *in vivo* effect of immune memory and subsequent tumor rejection.

Results: We describe a thermal "window" of ICD elicited by PBNP-PTT in neuroblastoma. In studies using PBNP-PTT to established localized Neuro2a tumors, we observed that PBNP-PTT conformed to the "more is better" paradigm, wherein higher doses of PBNP-PTT generated higher cell/local heating and thereby more cell death, and consequently improved animal survival. However, *in vitro* analysis of the biochemical correlates of ICD elicited by PBNP-PTT demonstrated that PBNP-PTT triggered a thermal window of ICD. Specifically, the aforementioned markers of ICD were more highly expressed within an optimal temperature (thermal dose) window of PBNP-PTT (63.3-66.4°C; ~5.6log(CEM43)) as compared with higher (83.0-83.5°C; ~12.8log(CEM43)) and lower PBNP-PTT (50.7-52.7°C; ~3.3log(CEM43)) doses. Subsequent vaccination studies in the neuroblastoma model confirmed our *in vitro* findings wherein PBNP-PTT administered within the optimal temperature window (63.3-66.4°C; ~5.6log(CEM43)) resulted in long-term survival (33.3% at 100 days) compared with PBNP-PTT administered within the higher (0%) and lower (20%) temperature ranges, and controls (0%).

Conclusions: Our findings demonstrate a tunable immune response to heat generated by PBNP-PTT, which should be critically engaged in the administration of PTT, both alone and when PTT is administered with immune adjuvants (e.g. TLR agonists) and/or immunotherapies (e.g. immune checkpoint inhibitors) for maximizing its therapeutic benefits.

TUES 46

CPG-LOADED PRUSSIAN BLUE NANOPARTICLES AS PHOTOTHERMAL IMMUNOTHERAPY AGENTS FOR CANCER

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Nanoparticle-based photothermal therapy (PTT) has been widely investigated in cancer therapy as a rapid and minimally invasive tumor ablation technique. An emerging area of interest is the effect of PTT on the immune system during tumor therapy, since PTT not only causes tumor cell death, but can also release tumor antigens and endogenous adjuvants under certain conditions. We describe biofunctionalized PBNPs as an enhanced "photothermal immunotherapy" wherein PBNP-based PTT is used for tumor ablation and in situ vaccine effects, complemented by adjuvant CpG-ODN biofunctionalization that increases antigen-processing and presentation. We believe PTT-elicited cell death combined with released antigens and added adjuvants will result in stronger/better engagement of an antitumor immune response. Building on our previously published studies, we assembled CpG on PBNPs using a layer-by-layer methodology. Nanoparticle characterization, therapeutic efficiency, and immune effects elicited by the therapy were tested *in vitro* using cell lines for both neuroblastoma and melanoma. Specifically, we looked at dendritic cell (DC) activation and T cell expansion after treatment with CpG-PBNPs and CpG-PBNP-based PTT. *In vivo* responses will be tested using syngeneic mouse models, wherein the mice will be intratumorally injected with CpG-PBNPs for PTT, and their tumor growth, survival, and immune responses will be studied. Our data suggests that CpG-PBNPs exhibit size, charge, and NIR spectrum stability over 7 days compared to naked PBNPs. Our CpG-PBNPs encapsulate CpG at a concentration of 40ug/mL, a concentration that is comparable to those used for current therapies. When CpG-PBNP was co-cultured with splenic DCs, there is an increased activation of DCs (measured by %CD40, CD80, CD86 expression levels) compared to DCs co-cultured with unmodified PBNPs and untreated controls. Further, the CpG-PBNP activated DCs increased proliferation of CD8+ T cells compared to controls. These findings demonstrate the potential of the modified PBNPs to overcome immune tolerance by increasing dendritic cell activation and T cell proliferation. In conclusion, we describe a "nano-immunotherapy" for treating cancers using CpG-PBNPs that leverages the ablative properties of PBNPs and the immunostimulatory properties of CpG. This combination treatment allows for a response that will lead to long-term survival and immune memory. Photothermal immunotherapy using CpG-PBNPs therefore have the potential of greatly improving the treatments and responses to cancer.

TUES 47

IN SITU VACCINATION: USING LOCAL ANTITUMOR IMMUNE TREATMENTS TO GENERATE SYSTEMIC ANTI-TUMOR IMMUNE RESPONSE

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Background: Immunotherapy for cancer is having impressive clinical impacts and is receiving large amounts of investment and attention because it has the potential to treat metastatic disease which currently is only treatable with chemotherapy. One strategy very relevant to thermal medicine is *in situ* vaccination. This approach puts immunostimulatory reagents into a tumor or treats a tumor with an immunostimulatory physical treatment like heat, cold, phototherapy, radiation or ultrasound. *In situ* vaccination is designed to break the local immunosuppression, stimulate a local anti-tumor immune response and most importantly stimulate systemic antitumor immune responses to eliminate metastatic disease. This is essentially an antitumor therapeutic vaccination, because the treated tumors provide the antigens and the adjuvants are the immunostimulatory reagents or physical treatment, thus "*in situ* vaccination". There are many immunostimulatory reagents that can be used and each has different capabilities.

Methods: Here we report on plant-derived viral-like nanoparticles from Cowpea Mosaic Virus (CPMV) studied in mouse cancer models and to combine with radiation to treat canine oral melanoma in community dogs. These particles are only composed of viral capsid proteins, have no nucleic acids and have no recognized immunostimulatory reagents.

Resuts: The particles are recognized by an unidentified toll-like receptor, since a mouse without the MYD88 signaling molecule does not respond. CPMV is initially recognized by innate immune cells and rapidly changes the numbers and characteristics of these innate cells, in particular reducing the numbers of myeloid derived suppressor cells (MDSC) in the tumor, draining lymph node and spleen. Initial responses to treating tumors with CPMV does not require lymphocytes, IFN-g or IL-1R. Splenocytes from CPMV treated tumor bearing mice are less inhibitory in nonspecific stimulation of T cells. Exposing splenocytes to CPMV stimulates a variety of cytokine and chemokine expression.

Conclusion: In situ vaccination in general and CPMV nanoparticles in particular have considerable clinical potential for cancer immunotherapy and the concept fits very well with the concepts of thermal medicine.

POST I

CLINICAL PROOFS OF ONCOTHERMIA

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Background - Objective: Modulated electro-hyperthermia (mEHT), is an improved application of conventional hyperthermia in oncology. It heats the heterogeneous structure of the tumor selectively targeting the malignant cells, it does not approach isothermal condition. It has multiple clinical advantages like abscopal effect induced by the immunogenic cell-death combined with a stable, safe, low toxicity procedure. Our presentation intends to show clinical proofs of mEHT in the therapy of various advanced malignancies.

Methods: Practices of various university research centers provide the proofs of clinical feasibility of mEHT, based on intensive previous laboratory research. Clinical proofs are collected on different levels of evidence from case reports to a Phase III trial. Most of the applications are complementary with classical gold-standard therapies.

Results: After a set of special cases which are usually not treatable with conventional hyperthermia therapies we show new complementary combinations (like check-point inhibitors) of mEHT with other methods followed by information about the trials. Such sensitive organs like the brain were successfully treated even with high dose mEHT without extra side effects. The clinical advantages of glioma treatment show important addition to the survival time like it is shown recently. The small and non-small lung cancer were also successfully treated with mEHT, even in advanced cases.

A set of results for gastrointestinal malignancies show the success of the mEHT method: the liver metastases in colorectal tumors, the primary hepatocellular carcinoma, pancreas carcinoma and unresectable biliary cancer were successfully treated in various institutions. Bone metastases, sarcomas and even the mEHT treatment of malignant ascites prove the theoretical and experimental results in clinical practice. In gynecology, for ovary, for breast and in cervix studies showed the advantages of the method. The interim analysis of the presently ongoing (follow-up stage) Phase III radio-thermo-chemo trial for advanced cervix carcinoma shows the positive results in both the local control and overall survival.

Conclusion: The clinical achievements of mEHT proven by clinical studies form a stable basis of the clinical applications in many advanced primary and metastatic malignancies even in terminal cases.

POST 2

THE EMERGING ROLE OF HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) IN CANCER IMMUNOMODULATION

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Immunomodulation is an exciting approach for treatment of cancer. Boosting the immune system through the use of immune modulating drugs and/or loco-regional ablation techniques can significantly improve systemic anti-cancer immune response. Enhanced anti-tumor immune response following radiation therapy and thermal ablation has been documented. High intensity focused ultrasound (HIFU) is an attractive non-ionizing, noninvasive tool that is being used for treatment of cancer. Research studies showed favorable systemic antitumor response after HIFU therapy. In this educational poster, the mechanisms of HIFU ablation as well as the main concepts of immunomodulation following HIFU therapy will be discussed. The unique immune response to HIFU versus other loco-regional treatments, like radiation therapy, will be highlighted as well. Important preclinical studies investigating HIFU induced anti-tumor response for treatment of different cancers will be reviewed. This poster aims at introducing the readers to the basics of immunomodulation following HIFU ablation.

POST 3

THE CRYO-THERMAL THERAPY DRIVES MACROPHAGES POLARIZATION TOWARD M1 PHENOTYPE THAT REMODELS THE TUMOR MICROENVIRONMENT TRIGGERING THE DURABLE ANTI-TUMOR MEMORY IMMUNITY

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Recently, overcoming immunosuppressive microenvironment and induction of durable anti-tumor immunity are regarded as effective therapeutic approaches for metastatic cancer. Antigen-presenting cells (APCs), including macrophages and dendritic cells, are capable of bridging to adaptive immune responses against tumor. However, APCs can be induced into immunosuppressive phenotype in the tumor microenvironment. It is critical to re-orienting APCs from tumor supportive to suppressive profiles, and the plasticity of these APCs would be provided an opportunity for exploring novel cancer treatment strategy. Previously we developed a novel cryo-thermal therapy to repress implanted malignant melanoma and achieve long-term survival. The cryo-thermal therapy enhanced the cytotoxic function of $CD8^+$ T cells, and $CD4^+$ T cells differentiation into dominant CD4-CTL and Th1 providing a durable anti-tumor memory immunity. However, the mechanism involved in inducing durable systemic anti-tumor memory immunity was not studied. In this study, we revealed that the cryo-thermal therapy remodeled the tumor microenvironment triggering the durable anti-tumor memory immunity to inhibit metastasis in B16F10 melanoma model. The cryo-thermal therapy persistently modulated the phenotypic and functional maturation of DCs and re-educated macrophages polarization to M1 phenotype along with high expression levels of co-stimulatory molecules, increasing production of pro-inflammatory cytokines and down-regulating the expression of immuno-inhibitory molecules. Furtherly, we found that the cryo-thermal–induced macrophages polarization to M1 phenotype reshaped tumor immunosuppressive microenvironment as proved by the fact that the subsequent DCs activation and maturation, $CD4^+$ T cells differentiation into Th1 and CTL sub-lineages, and generation of cytotoxic $CD8^+$ T cells. Moreover, the cryo-thermal therapy-induced macrophages polarization to M1 phenotype could not only triggered maturation and activation of DCs to enhance $CD4^+$ T cells differentiation, and generation of cytotoxic $CD8^+$ T cells, but also directly promote $CD4^+$ and $CD8^+$ T cells proliferation and differentiation. Our finding was further emphasized that the cryo-thermal-reeducated macrophages polarization to M1 phenotype was essential to mediate anti-tumor memory immunity leading to long-term survival. Thus, the cryo-thermal therapy could develop a promising strategy that remodeled the tumor microenvironment triggering persistent memory immunity for tumor eradication and inhibition of metastasis.

POST 4

TRANSMIT-ONLY RECEIVE-ONLY HALF-BIRDCAGE/SURFACE COIL PAIR FOR MR-GUIDED FOCUSED ULTRASOUND HYPERTHERMIA ON SMALL RODENTS

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Background: Administering hyperthermia in small animals can be challenging due to small target volumes and the need to maintain temperature control for long exposure times. This is especially true when using a clinical Magnetic Resonance Imaging (MRI) scanner to perform experiments with small animals. The use of MRI coils specifically designed for small targets has the potential to increase the accuracy and reproducibility of thermometry. Such coils when integrated to ergonomic animal beds with software that allows for parameter and imaging control can provide a tool to perform reliable ultrasound-induced hyperthermia in small animals.

Methods: A transmit-only-receive-only (TORO) coil pair was designed and tested for the application of Magnetic Resonance-guided Focused Ultrasound (MRgFUS) hyperthermia in mice. The coil was integrated to a treatment bed designed for targeting structures on the flank of mice. The design combined a half birdcage placed above the animal for transmission and a receive coil bellow the animal, between the transducer and the target. This geometry allows for transmission and reception of the MR signal close to the animal while the transducer can be localized for targeting. It also allows for an acoustic window for ultrasound exposure. A software platform was developed using a previously developed suite by our team (Proteus MRI-HIFU Software Development Suite) to provide real-time targeting, motorized movement to the target and real-time thermal maps, as well as to analyze temperature stability and precision and to deliver closed-loop controlled ultrasound exposures. MR thermometry measurements were conducted on different targets and the performance of the coil pair was evaluated under heating and non-heating conditions.

Results: The TORO coil showed resilience to temperature drift with a 0.29 ± 0.12°C after 15 minutes of thermometry. The stability, precision and temperature spread during this 15-minute imaging were 0.90 ± 0.08°C, 0.15 ± 0.07°C and 0.76 ± 0.11°C, respectively. It was possible to conduct a 15-minute long PID-controlled hyperthermia exposure to achieve a +3°C increase of temperature with less than 1°C temperature spread and a settling time of 142 seconds

Conclusions: The proposed TORO coil pair integrated into the small animal platform allowed repeatable positioning and targeting on mice to perform MRgFUS hyperthermia. Temperature maps obtained using MR thermometry were accurate and allowed for closed-loop controlled exposures. Overall, the TORO coil demonstrated stable and accurate thermal maps with low temperature drift.

POST 5

TARGETABILITY OF OSTEOMYELITIS USING MR-GUIDED FOCUSED ULTRASOUND

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Background: Osteomyelitis is a complex inflammatory process involving infection of the bone and adjacent structures, often not responding to antimicrobial therapy. It is a common and serious complication linked to diabetes and increases the possibility of limb amputation. There exists a clinical need to improve management of osteomyelitis, especially for diabetic patients who may present with chronic osteomyelitis associated with clinical complications. Magnetic resonance guided focused ultrasound (MRgFUS) can offer an option for the management of osteomyelitis by providing a non-surgical and potentially rapid-recovery treatment.

Methods: A retrospective study using magnetic resonance imaging or computed tomography from patients diagnosed with osteomyelitis located on a limb was conducted. An in-house adaptation of the clinical treatment software used to plan MRgFUS with the Sonalleve platform (Profound Medical, Mississauga, Ontario, Canada) was developed and used to evaluate the targetability of osteomyelitis. Targets were evaluated based on their location and surrounding structures within the ultrasound beam path. The anatomic locations of the bone infection and required positioning of the patient to reach the target with the platform was evaluated. After processing images to place a target volume at the infection site, treatment planning was conducted. A safety margin of 1 cm between any treatment cell and sensitive structures was established. The treated volume was taken from the Sonalleve planning calculation. The target volume was obtained using Osirix 3D reconstruction from 2D user-defined ROIs on the series. The percentage of the bone infection that could be targeted after accounting for safety margins was calculated.

Results: In average, 93.93±3.07% of the target was considered reachable using treatment cells available at the Sonalleve system. The main limitation to full coverage was the localization of the target site close to the skin, making the treatment volume drop. Some treatment cells were placed partially on surrounding tissues and therefore the reachable volume is slightly overestimated. To diminish this effect, we did not place any treatment cell that did not have at least 80% of its volume within the affected region.

Conclusion: This retrospective study design is a first step to demonstrate feasibility of MRgFUS for the thermal treatment of osteomyelitis. Cases where the infection is located in the extremities are promising since his approach can be particularly well indicated for patients with strong associated comorbidities. Future work will include analysis of osteomyelitis in spinal cases where more sensitive structures may limit the reachable targets.

POST 6

NANOWARMING OF AORTIC HEART VALVES

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Background: Long-term tissue storage is enabled by vitrification, a cryopreservation process where tissues are stored in an ice-free glassy state. Frozen cryopreserved human heart valves demonstrate ECM damage and post-transplantation structural deterioration. In contrast ice-free vitrification of heart valves results in ECM preservation and freedom from structural deterioration. However, rewarming of vitrified samples using cryoprotectant formulations designed to maintain both the ECM and cell viability fail at volumes >3 mL due to devitrification, ice crystallization during rewarming. Previously, we reported on the use of nanowarming using radio frequency excited magnetic Fe nanoparticles to rapidly rewarm tissues with high recovery of cell viability and tissue function in carotid arteries in both 1 mL and 50 mL systems. The current work focuses on aortic heart valves in which cryoprotective agent diffusion plays an important role in the recovery of the tissue.

Methods: Porcine aortic heart valves were used as a thicker biological sample for nanowarming. The valves have three tissue components (aortic artery, cardiac muscle and leaflets) that vary in thickness and cellularity. Valves were vitrified after step-loading of cryoprotectants with Fe nanoparticles in the last step, stored in vapour phase nitrogen and nanowarmed in a radio frequency coil to -20°C. After tissue washing, the viability of valve components was tested by alamarBlue assay and the results normalized to untreated fresh controls. Analytical and numerical modelling methods were used to simulate cryoprotectant loading versus experimental viability results.

Results: Modelling of 2mm thick aortic artery demonstrated that increasing cryoprotectant loading step intervals resulted in higher central tissue concentrations going from 0% in 15-minute loading intervals to 40% in 60 minute intervals. However, longer cryoprotectant exposure caused cytotoxicity (32% viability in aorta when loading interval is 60 min). We could only increase the loading steps from 15 to 30 min before cytotoxicity became an issue. Using 30-minute intervals the viability of the artery component increased to 37% from 19% using 15 minutes intervals. A faster rewarming rate is necessary for thick sample warming.

Conclusion: Computational modelling revealed that longer diffusion times would result in higher cryoprotectant concentrations however longer times increased risks of cytotoxicity. We would propose using higher Fe concentrations, metal forms such as foil, or finding new approaches to increase the warming rates using more powerful coils with higher field strengths and frequencies to achieve faster rewarming rates to improve the recovery of thicker tissues viability.

POST 7

Extending a Rapid Ultrasound Beam Modeling Method to Include Nonlinear Effects in HIFU

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Background: We have extended the application of a rapid ultrasound beam modeling method, called the hybrid angular spectrum (HAS) technique, to include nonlinear effects that can have a noticeable impact in high-intensity focused ultrasound (HIFU) therapeutic treatments. The HAS numerical tool has been found useful both for therapeutic system design and for planning treatment protocols. Since it models propagation in the spatial-frequency domain, it uses fast Fourier transforms to significantly speed up the calculation time. As an extension of the traditional angular spectrum approach, HAS allows modeling of inhomogeneous tissue regions.

Methods: Previously, HAS has been based on purely linear systems modeling of the beam, ignoring possible nonlinearities. But, depending upon the specific tissue type and the input power level, nonlinear tissue behavior can generate significant higher harmonics from the fundamental ultrasound beam, causing changes in focal position and enhanced local heating. A recently published study added nonlinear terms to the traditional angular spectrum method by adopting the slowly varying envelope approximation (SVEA). We have combined that approach with the HAS technique, but with two differences: 1) Inhomogeneous tissue regions (with varying acoustic properties, including the nonlinearity coefficient) can be modeled, and 2) by limiting the sonication to be a quasi-continuous source—valid for most HIFU treatments—memory and time requirements of the simulation are considerably eased compared to the earlier published implementation.

Results: We have compared our results to another ultrasound modeling method, k-Wave, and have found they match closely for the first- and second-harmonic shape and intensity. Importantly, we have shown in a realistic breast model that nonlinear effects can modify the resulting focal intensity pattern and strength, features that determine the safety and effectiveness of HIFU breast treatments. We show that such effects are strongly dependent on the intensity of the incident ultrasound beam.

Conclusions: For high-intensity therapies, it is important to account for nonlinear effects. Such additional capability has now been added to the HAS simulation software.

POST 8

IMPACT OF PULSED ALTERNATING MAGNETIC FIELD (AMF) PARAMETERS ON THE ERADICATION OF BIOFILM ON METAL SURFACES: IMPLICATIONS FOR TREATMENT OF PROSTHETIC JOINT INFECTION.

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Introduction

Prosthetic joint infection (PJI) is a major complication of joint arthroplasty. Although only 1-2% of cases become infected, over a million joint replacements per year are performed in the US alone, making this a prevalent issue. Effective treatment of PJI frequently involves prolonged antibiotics plus removal and replacement of the infected joint. While effective, this is expensive and detrimental to patient quality of life. We are developing a non-invasive thermal treatment to target biofilm on metal implants. Infected prosthetics become colonized with bacteria within a polymeric matrix that resists antibiotics and immune-mediated clearance. This concept utilizes alternating magnetic fields (AMF) to generate surface heating on metal through induction. The purpose of this in vitro study is to understand the impact different AMF parameters have on the eradication of biofilm grown on metal surfaces.

Methods

Biofilms were grown on stainless steel rings using the frequently encountered pathogens (Pseudomonas aeruginosa (PAO1) and Staphylococcus aureus (UAMS-1) bacteria. Rings were then exposed to AMF in a custom-built 32 channel solenoid coil system. Combination of power (W) and exposure duration (s) and pulse delay were utilized to achieve intermittent exposures across a range of target temperatures (50, 60, 70 & 80 °C). The exposures were conducted for up to 24-hours with and without the antibiotic ciprofloxacin. After AMF exposure, rings were either sonicated to enumerate the bacteria via drip plate assay, or imaged with scanning electron microscopy (SEM) to evaluate the spatial integrity of the biofilm.

Results

AMF exposures demonstrate a 4-log reduction with exposure duration of 1.5 minutes at 80°C. At 70°C a 2.5-log reduction is observed with same exposure duration. SEM shows removal of biofilm matrix with AMF alone. When AMF is applied in presence of antibiotics, enhanced biofilm reduction is observed, even with sub-therapeutic doses.

Conclusion

Our current studies confirm that AMF is detrimental to biofilms on metal surfaces. There are dose-dependent relationships between temperature and exposure time with respect to reduction of bacterial burden. Ongoing studies are evaluating the effect of pulse parameters on the effectiveness of AMF and antibiotics on biofilm.

POST 9

HYALURONIC ACID TARGETED NANOPARTICLES FOR DETECTION AND TARGETING OF PERITONEALLY DISSEMINATED COLORECTAL CANCER

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BACKGROUND: Colorectal cancer is the third most common cancer and second most prominent cause of cancer-related deaths in the United States. A primary course of treatment at our institution for metastatic colorectal cancer is Hyperthermic Intraperitoneal Chemoperfusion (HIPEC). HIPEC is a dual combination therapy involving cytoreduction surgery and perfusion of (40-42°C) warmed chemotherapy circulated throughout the patient's abdomen. The HIPEC regimen has greatly improved the survival of metastatic colorectal cancer patients from a five-year survival rate of 12.5% to above 50% but is still limited by the detection and treatment of remnant micro-tumors.

METHODS: Photothermal ablation therapy using specific formulations of fluorescent nanoparticles that can absorb light in the near-infrared (NIR) and emit the energy as heat allows for precise detection and destruction of metastasis. The utilization of nanoparticles can be further improved by functionalizing their surfaces with targets that bind to receptors overexpressed on cancer cell surfaces, such as hyaluronic acid. Our group has developed multi-purpose fluorescent-heating nanoparticles, called H-DAPPs (Hybrid Donor Acceptor Polymer Particles), synthesized using 95% (w%) of the fluorescent polymer Poly[(9,9-dihexylfluorene)-co-2,1,3-benzothiadiazole-co-4,7-di(thiophen-2-yl)-2,1,3-benzothiadiazole] (PFBTDBT10) to 5% (w%) of the heat producing polymer Poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b']dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) that are functionalized with hyaluronic acid.

RESULTS: Balb/c mice were induced with luminescent colorectal cancer disseminated throughout the peritoneum and an abdominal perfusion of saline and/or HA-functionalized H-DAPPs was performed to model the use of nanoparticles as an adjuvant therapy to the HIPEC procedure. Approximately 6 mL of saline or HA-functionalized H-DAPPs at 80 μg/mL were perfused at 100-200 mL/hr throughout the abdomens of the mice for 30 minutes. The abdomens of the mice were then flushed using 0.9% saline to remove excess ascites and unbound nanoparticles. The In Vivo Imaging System (IVIS) was used to confirm that the nanoparticles had selectively bound to the micro-tumors. After euthanasia of the mice, the abdominal organs were removed were analyzed using ICP-MS to quantify the amount of selenium, (a component of the nanoparticles) in μg/g of tissue.

CONCLUSION: These data will help to determine whether functionalized H-DAPPs will be a beneficial adjuvant therapy for treating metastatic abdominal cancers.

POST 10

THE USE OF FLUORESCENT AND HEAT GENERATING POLYMER NANOPARTICLES AS A NOVEL TREATMENT FOR STAPHYLOCOCCUS AUREUS SKIN LESIONS

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Introduction: Skin infections due to bacteria represent significant morbidity and mortality in healthcare. Staphylococcus aureus (SA) is of particular importance because it is the most commonly isolated pathogen in surgical site infections, diabetic foot ulcers, and chronic wounds1. The current treatment for skin infections ranges from empiric antibiotic therapy to aggressive surgical debridement. Mild hyperthermia, defined as temperatures less than 42°C, has been show to enhance antimicrobial activity and represents a new approach for the treatment of local infections2, 3. The aim of this study was to investigate whether novel polymer nanoparticles, capable of producing localized mild hyperthermia when exposed to infrared light, can be used to more effectively treat infectious skin lesions while sparing the surrounding healthy tissue.

Aim: Evaluate the efficacy of nanoparticle-mediated mild hyperthermia to augment localized antibiotic activity and reduce bacterial colonization in an infectious skin lesion mouse model.

Methods: Sixteen Balb/C mice received subcutaneous injections of live bioluminescent SA to develop the skin lesions. After three days, the mice were randomly sorted to receive standardized concentrations of intralesional gentamicin, intralesional nanoparticles, and/or localized infrared laser therapy. Twenty-four hours after treatment, the animals were imaged with the in vivo imaging system (IVIS) to detect SA bioluminescence and nanoparticle fluorescence within the lesions. Each lesion was analyzed using region-of-interest photon emission from the SA colonies.

Results: Bacterial bioluminescence was detected using IVIS and allowed for the identification of bacteria within and outside the visible lesion. Nanoparticle fluorescence was also detected and demonstrated successful co-localization with bacteria in the skin lesions. Treatment with nanoparticles, gentamicin, and infrared light resulted in a 92% reduced detection of bacterial colonies compared to treatment with gentamicin alone.

Conclusions: This project establishes an innovative animal model to investigate the use of mild heat-generating nanoparticles as a novel treatment for infectious lesions. Treatment with nanoparticles, gentamicin, and infrared light was the most successful at limiting bacterial proliferation as detected by luminescence signal. Now that a preclinical animal model utilizing bioluminescent bacteria and fluorescent nanoparticles has been established, this study can be expanded to include larger sample sizes, as well as to explore the effects of localized mild hyperthermia on antimicrobial activity, long-term wound healing, aesthetics, and pathogen eradication. In addition, the successful use of bioluminescent bacteria for in vitro colony identification and differentiation can be expanded to other non-sterile infectious models and those with a risk of sample contamination.

POST 11

SECTORED-TUBULAR TRANSURETHRAL ULTRASOUND FOR THERMAL TREATMENT OF STRESS URINARY INCONTINENCE: PATIENT SPECIFIC SIMULATIONS AND VALIDATION

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Introduction:

Stress Urinary Incontinence (SUI) is often due to weakness of endopelvic facia and tissues adjacent to the urethra. The object of this study is to perform biothermal simulations on patient specific pelvic models of thermal treatments for SUI using a dual- sectored tubular transducer transurethral device with fixed positioning, and to compare the simulations against in-vivo ewe studies.

Methods:

3D patient models were generated from MRI images of female pelvic anatomy. Acoustic simulation and FEM-based thermal simulations were performed in Matlab and COMSOL Multiphysics, incorporating heterogeneous tissue acoustic and thermal properties. Tubular transducer (3.5mm OD, 14mm length, 6.5MHz) with two opposite active angles within a 7mm OD inflated cooling balloon was positioned in the mid-urethral region. Parametric studies of powers (2.5-4W), surface intensities (7.3-11.7W/cm^2), durations (2-3 mins), sectored active angles (75-105°), and inactive angles (52-62°) were performed to determine the best configurations for extents of thermal coverage while protecting urethra mucosa, vagina and adjacent bone. Performance metrics including temperature, coverage angles, non-lethal sparing (<30EM43°C), penetration depth (>60EM43°C), moderate dose (>60EM43°C) and coagulation (>240EM43°C) volumes were calculated. With the selected configurations of the applicator and placement strategies from patient specific simulations, comparisons were made to in-vivo experiments as previously conducted in female ewes.

Results:

Tubular transducer with dual 75-105° active angles created maximum temperature 53.1-57.0°C, 1.3-1.9mm urethral sparing, 9.2-11.1mm penetration from the balloon, and 1.2-1.5cm^3 moderate treated volume on tissues lateral to the mid-urethra, varying with acoustic intensities and durations. By adjusting the applicator positioning and angular gap between the dual tubular sectors with 52-62° inactive angles, based on patient pelvic anatomy, both vagina and bone were protected with non-lethal thermal damages (<40EM43°C). Similar to simulations, in-vivo studies with selected settings (3-4W, 2mins, 90° active angles, 62° inactive angles) demonstrated clear control of ultrasound energy into target tissue lateral of urethra, with 10-12mm thermal damage penetration laterally from urethra, while preserving the urethral mucosa and vagina.

Conclusion:

Simulation, in agreement with in-vivo evaluations, demonstrated that sectored-tubular catheter based transurethral ultrasound applicators can treat targeted pelvic supportive tissues lateral to the mid-urethra as a potential minimally invasive SUI treatment. With adjustment of positioning and orientation, the tubular transducer can create two large sector shaped therapy zones while preserving urethral mucosa, vagina and pubic bone.

WED 1

ENDOPLASMIC RETICULUM CHAPERONES IN HEALTH AND DISEASE: MOLECULAR MECHANISMS AND THERAPEUTIC POTENTIAL

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The glucose regulated proteins (GRP78, GRP94, GRP170 and GRP75) are members of the heat shock protein family primarily residing in the endoplasmic reticulum (ER) or the mitochondria and they are induced at the transcriptional level upon ER stress (1). As molecular chaperones, the GRPs regulate protein quality control and degradation, with GRP78 serving additionally as a pivotal regulator of the unfolded protein response (UPR) and the apoptotic machinery associated with the ER (2, 3). The GRPs can be actively translocated to other cellular locations and secreted, and assume additional functions that control cellular signaling, proliferation, invasion, apoptosis, inflammation and immunity, which have major implications in health and disease (4). Specific roles of GRPs in development, organ homeostasis, tumorigenesis, metastasis and angiogenesis have been validated in genetically engineered mouse models. GRP overexpression is widely reported in many human cancers and associated with aggressive properties, suggesting potential prognostic value and that interfering with their production or activities in those tumors might provide new approaches for anti-cancer treatment and to combat therapeutic resistance. The recent discovery that cell surface GRP78 is preferably expressed in cancer and stressed endothelial cells leads to the development of therapeutic agents specifically targeting cell surface GRP78 capable of inducing cancer cell apoptosis and suppressing tumorigenesis with minimal toxicity. While the GRPs are attractive targets for drug development, they can also serve as mediators for cancer specific drug delivery and transcriptional targeting of cancer. They can also be exploited for vaccine development as exemplified by the large chaperone GRP170 with superior property in presentation of protein antigens, thus opening up a new platform for antigen-targeted cancer immunotherapy.

References

1. Ni M, Lee AS (2007) ER chaperones in mammalian development and human diseases. FEBS Lett 581(19):3641-3651.

2. Lee AS (2014) Glucose-regulated proteins in cancer: molecular mechanisms and therapeutic potential. Nat Rev Cancer 14(4):263-276.

3. Luo B, Lee AS (2013) The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anticancer therapies. Oncogene 32(7):805-818.

4. Ni M, Zhang Y, Lee AS (2011) Beyond the endoplasmic reticulum: atypical GRP78 in cell viability, signalling and therapeutic targeting. Biochem J 434(2):181-188.

WED 2

STEREOTACTIC LASER ABLATION AS A THERAPEUTIC OPTION FOR RECURRENT GLIOBLASTOMA: A LARGE SINGLE INSTITUTIONAL EXPERIENCE

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The prognosis of patients diagnosed with recurrent glioblastoma remains dismal, and therapeutic options are limited. The median survival is only 3-5 months. Stereotactic laser ablation is a minimally invasive technique used as an ablative treatment. Its safety, precision, and technical feasibility have already been established. We report outcomes of the largest single institutional patient database of recurrent glioblastoma treated with laser ablation.

Between 2011 and 2017, 31 patients with recurrent (per RANO criteria) glioblastoma were treated with laser ablation out of more than 250 laser ablation cases for brain tumors. This population included 17 males and 14 females. Age at the time of diagnosis ranged from 27 to 77. 84% underwent surgical resection as the initial treatment. 65% were treated with laser ablation after the first recurrence of previously treated glioblastoma. Furthermore, six patients were treated with laser ablation after the second recurrence and five patients after the third recurrence, status post various therapies, including surgery, Gamma Knife radiosurgery (GKRS), and chemotherapy. The average number of postoperative hospital days was 2.8, and most patients went home. Out of the 26 patients who maintained follow-up at The Cleveland Clinic, 22 received chemotherapy after laser ablation, most commonly Lomustine. 54% remained neurologically stable without new postoperative deficits, and 52% had no reported change in Karnofsky Performance Scale (KPS) from before to after laser ablation. The longest follow-up time was 44.5 months, and the estimated median survival was 13 months. The 12-month survival rate was 54%, and the 18-month survival rate was 38.5%. 18 patients progressed, and the estimated median progression-free survival was 5 months. Upon further analysis of the timing of laser ablation correlated to overall and progression-free survival, patients who underwent laser ablation as a second treatment after recurrence had lower risk of progression, compared to those who underwent the procedure as a first or a third treatment.

Laser ablation has been used to treat various intracranial lesions at The Cleveland Clinic, particularly recurrent glioblastomas. This treatment modality can be utilized at any point of recurrence in a selected group of patients with appropriate clinical and radiographic characteristics. In addition, the minimally invasive nature as well as the relatively short hospital stay in comparison to surgical tumor resection make laser ablation favorable. Laser ablation is becoming a valuable tool in a multidisciplinary approach to treating recurrent glioblastoma.

WED 3

MR-GUIDED THERMAL THERAPY: IMPLEMENTATION OF A NEW MRI-HYPERTHERMIA-HYBRIDSYSTEM INTO CLINICAL ROUTINE.

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Introduction

The aim of this work was performance evaluation of a new 1.5 T MRI-hyperthermia-hybridsystem to be implemented into clinical routine. The new system will be used for MR image guided real-time non-invasive thermometry during regional deep hyperthermia treatment of patients with high-risk soft-tissue sarcoma (STS).

Methods

A new design of an Universal MR-compatible multi-antenna applicator of the type SIGMA-Eye (BSD-2000/3D/MR, Pyrexar Medical Corp., Salt Lake City, UT), which can be opened from the side for easy patient access, is integrated in a digital 1.5 T MRI-system (Ingenia, Philips) with an axial coverage of 55 cm and a gantry diameter of 70 cm. The hyperthermia (HT) system has a new water control and temperature calibration system. The new water system features a closed circulation loop between water tank, which is located outside the MR room, and applicator bolus, which is filled using a fill/drain water pipe system. In order to minimize the interaction between the two systems, special filters are installed in both systems, thus eliminating interference problems.

The performance of the hyperthermia system alone was assessed by evaluating reflected power, stability of the HT-amplifier and possible hardware and software errors during the heating process. For these experiments a homogenous gel/water phantom as well as a lamp phantom was used. The hyperthermia applicator was tested with all channels set to 100%, 700 W, focus (0, 0) and 90min-heating time. After that the steering accuracy was tested by shifting the heating focus from (0, 0) cm to (0, ±3) cm in all three directions in space applying 300 W. Furthermore, the centering of the temperature distribution of the target was investigated inside and outside the MR-bore. For these experiments a homogeneous phantom was used with 400W and 20min heating duration.

Results & Conclusion

The overall results indicated that the hyperthermia system is stable und showed a global reflected power on average of less than 10% at all antenna. The heating focus could be steered from (0, 0) cm to (0, ±3) cm in vertical, horizontal and longitudinal directions. Moreover, the heating quality inside the MR-bore was not significantly affected when compared to operation outside the bore. The new system is currently under preparation toward the first clinical hyperthermia patient treatment with STS.

WED 4

REAL-TIME MONITORING OF THERMAL THERAPIES WITH VOLUMETRIC MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY

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The talk focuses on the recent advances in multi-spectral optoacoustic tomography (MSOT), in particular its recent application to real-time monitoring of thermal therapies. MSOT has already shown unmatched imaging capacity in high-resolution visualization of structural, functional, metabolic and molecular information deep from optically opaque living tissues entirely non-invasively. The modality is uniquely endowed with rich and label-free hemodynamic contrast and is suitable for deep tissue high-resolution imaging of oxygenation/hypoxia or targeted molecular probes and genetically expressed agents in living animals. State-of-the-art handheld MSOT imaging solutions are further transforming optical imaging by offering novel precision in clinical observations of patients, demonstrating high diagnostic efficacy in a number of indications, including breast cancer, inflammatory bowel disease and lymph node metastases. Optoacoustic imaging represents an advantageous approach for monitoring thermal therapies due to its high sensitivity to temperature variations (via the Grüneisen parameter) as well as changes in the tissue optical properties induced by coagulation. Indeed, accurate real-time mapping of the dynamic lesion progression and temperature field distribution during thermal therapies is an unmet clinical need that can greatly affect the outcome of these interventions. The current lack of simple and reliable non-invasive imaging feed-back represents a major barrier towards broader adaptation of thermal therapies in pre-clinical research and clinical routine. We have recently demonstrated a fast three-dimensional temperature mapping method based on real-time optoacoustic sensing of photothermally-treated region coupled with a thermal-diffusion-based model of heat distribution in tissues. The approach is seamlessly applicable in a catheter-based setting of radiofrequency ablation treatments as well as high- and medium-intensity ultrasound interventions where it was additionally shown capable of sensing multiple parameters in real time, including 3D temperature distribution, lesion boundary and blood-related contrast. Our recent results indicate that volumetric MSOT imaging may emerge as a promising tool for quantitative monitoring of thermal therapies, thus holding potential for improving safety and efficacy of those procedures.

References:

J. Rebling, F. J. Oyaga Landa, X. L. Deán-Ben, A. Douplik, D. Razansky. Integrated catheter for simultaneous radiofrequency ablation and optoacoustic monitoring of lesion progression. *Opt Lett* (2018), in press.

X. L. Deán-Ben, S. Gottschalk, B. McLarney, S. Shoham, D. Razansky. Advanced optoacoustic methods for multi-scale imaging of *in vivo* dynamics. *Chem Soc Rev* 46, 2158—2198 (2017)

F. J. Oyaga Landa, X. L. Deán-Ben, R. Sroka, D. Razansky. Volumetric optoacoustic temperature mapping in photothermal therapy. *Sci Rep* 7, 9695 (2017)

WED 5

ANALYSIS OF CLINICAL DATA TO DETERMINE THE MINIMUM NUMBER OF SENSORS REQUIRED FOR ADEQUATE SKIN TEMPERATURE MONITORING OF SUPERFICIAL HYPERTHERMIA

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Background: Tumor response and treatment toxicity are related to minimum and maximum tissue temperatures during hyperthermia, respectively. The reported number of temperature sensors in the clinic varies between 1 and 82, with a median of 8 per study for recurrent breast cancer treated with reirradiation and hyperthermia. Using a large set of clinical data, we analyzed the number of sensors required to adequately monitor skin temperature during superficial hyperthermia treatment of breast cancer patients.

Methods: Hyperthermia treatments monitored with ≥60 stationary temperature sensors were selected from a database of patients with recurrent breast cancer treated with reirradiation (23 × 2 Gy) and hyperthermia using single 434 MHz applicators (effective field size 351-396 cm^2). Two subsets of stationary sensors were analyzed to mimic temperature monitoring schemes using reduced and randomly selected subsets of stationary sensors, and another subset to simulate thermal mapping profiles. Temperature differences (T) between the subsets and complete sets of sensors were evaluated in terms of overall minimum (Tmin) and maximum (Tmax) temperature, as well as T90 and T10, which are the 90^{th} and 10^{th} percentile of the temperature measurements, respectively. We investigated the risk of a Tmax exceeding 43.0°C going undetected when using smaller subsets of sensors.

Results: 80 patients were included in the analysis yielding a total of 400 hyperthermia sessions. Median T between subsets (8-126 sensors/session) and complete sensor sets (60-147 sensors/session) was <0.01°C for T90 with a 95% confidence interval (CI) ≤0.5°C, when >50 sensors were used. Subsets of <10 sensors result in underestimation of Tmax up to -2.1°C (T 95% CI), which decreased to -0.5°C when >50 sensors were used. Thermal profiles (8-21 probes with 60-147 temperature points) yielded a median T <0.01°C for T90 and Tmax, with an T 95% CI of -0.2°C and 0.4°C, respectively. The detection rate of Tmax ≥43°C is ≥85% using >50 stationary sensors, or thermal profiles with ≥60 measurement points.

Conclusion: Adequate monitoring of the skin temperature distribution during superficial hyperthermia treatment (T10 and T90) requires the use of >50 stationary sensors per 400 cm^2 applicator. Thermal mapping with ≥8 catheters is a valid alternative.

WED 6

HOT AT DAWN - A HISTORICAL LOOK INTO THE THERMAL ROOTS OF HIPPOCRATIC MEDICINE

Wilton Remigio

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An Oslerian version of the modern synthesis of medicine would differ from the Hellenistic roots medicine in that whilst the first emerged from bedside observation the later emerges out of poolside inquiry. The Aesculapian spa temples were the great internship theater where the forefather of medicine developed his medical doctrine describing of four elemental conditions observed in the sick, i.e., cold, hot, dry and moist patient, still recognized today, and set in motion the rudiments of a consolidated profession of medicine. Temples for the 'serpent God' were purposefully built in sites calculated to exploit the available geothermal energy flowing in the various hot springs of ancient Greek states. The therapeutic advances of the Greeks populated the roman world with the construction of many sumptuous public baths, using several healing and cooling modalities and were generously assimilated by the famous Roman physicians.

The hot curative springs were disseminated throughout all the ancient world. Its traditions combined pleasure and therapy , popular and cultic health seeking societal ritual. In medieval times, the public baths gradually disappeared, to give rise to the more medicinal strategic use of thermal therapy at the hands of Father Sebastian Kneipp with the "water cure movment". Kneipp's therapy capitalized on the use of water ablations at very low temperature exploring autonomic reflexes completely unkown in his time. In Britain, the "water cure" received great attention from the public under the name of Hydropathy though reviled by the medical orthodoxy of the time. In America, Dr. J.H. Kellogg, exalted the water cure movement to the pinnacle of success with the famous Battle Creek hospital largely based on Thermal therapies (hydrotherapy), surgery, electrotherapy and lifestyle enhancement. The glory of his work and that of others such as Simon Baruch and Hinsdale was offset by the advent of modern pharmacology and antimicrobial therapy. Hyperthermia however remained a proficient investigation in a camp untouched by antibiotics. At first viewed with suspicion by the American Cancer society oncologic hyperthermia is still in its development with new frontiers integrating many lines of clinical and experimental fields into an important therapy yet to be more fully embraced in America.

WED 7

THE CANCER THERAPY IMMUNE REVOLUTION: CAN THERMAL THERAPY BE RELEVANT?

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BACKGROUND: Novel clinical immune cancer therapies have recently emerged. New checkpoint inhibitors, antigen-specific adoptive cell transfer (ACT), CAR-T therapy and viral vectors show increasing efficacy for primary and metastatic malignancies.

METHODS: We treat a burgeoning number of malignancies with checkpoint inhibitors. Combining several or adding cytotoxic therapy improve response rates. However, scarcity of CD8+ Tcells in the tumor environment eliminates response to checkpoint inhibitors. ACT of antigen-specific T cells, as well as CAR-T cells increase the number of tumor-specific T-cells in the tumor microenvironment. CAR-T therapies against CD19 are FDA approved for treatment of acute lymphocytic leukemia and high-grade lymphomas. These potent, live, MHC-independent drugs induce startlingly high responses in B-cell malignancies. While not yet effective in solid tumors, anecdotal responses in both glioblastoma and pancreas cancer suggest CAR-T therapy may soon show efficacy in epithelial malignancies. Viral vectors of immune therapy are clinically investigated and show promise in difficult-to-treat cancers such as glioblastoma.

Importantly, the gut microbiome is crucial to both incidence of cancer and to therapy-induced response. It is particularly important to immune therapy. Antibiotics lessen this intrinsic resource.

RESULTS: Not all malignancies respond to immune therapy. Checkpoint inhibitors do not induce responses in most gastrointestinal (GI) cancers, yet GI cancers with mismatch repair defects respond well. In addition, antigen-specific ACT is a highly effective immune therapy in GI malignancies. Primary brain cancers do not generally respond to checkpoint inhibitors, yet there are anecdotal response to checkpoint inhibitors, CAR-T therapy, and viral vector therapy. However, patients want more and greater responses. We know that thermal therapy (systemic, local/regional, ablative HIFU or cryotherapy) boosts host immune response escalating the anti-tumor cytotoxicity of effector T-lymphocytes. Yet we have not clinically investigated thermal therapy with checkpoint inhibitors, ACT of antigen-specific T cells, CAR-T cells or with viral vectors of immune therapy. In addition, altering the microbiome needs investigation.

CONCLUSION: The types of malignant diagnoses that respond to immune therapy have rapidly increased over the past few months, and immune therapies now improve survival of these patients. However, patients deserve even greater responses. Thermal therapy promises to increase response rates to immune therapies by increasing the ability of cytotoxic CD8+ T-cells to enter the tumors, recognize the cancer cells and thus increase tumor kill. However, thermal therapy combined with immune therapy still needs investigation.

Another over-arching problem remains. Immune therapies must become cost-effective with or without thermal therapy.

WED 8

TOXICITY AND EFFICACY OUTCOMES OF CONCURRENT HYPERTHERMIA AND RADIATION THERAPY IN SOFT TISSUE SARCOMA

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Background: Soft tissue sarcoma (STS) remains a challenging entity to treat, with high propensity for local recurrence and hematogenous spread. We present a single institution experience of hyperthermia [external thermal therapy (ETT) or interstitial thermal therapy (ITT)] concurrent with radiation therapy (RT) for the management of de novo, recurrent, and/or reirradiation STS.

Methods: A retrospective database of patients treated with ETT/ITT at our institution from 2012-2017 was evaluated for patients with primary, radiation-induced, and/or recurrent sarcoma. ETT was given over 45-60 min, and ITT over 30-35 min to a maximum temperature of 44 degrees Celsius using the BSD-500 microwave hyperthermia system, most commonly twice weekly with concurrent RT. Acute toxicity was graded according to the common terminology criteria for adverse events (CTCAE) v 4.0. Logistic regression was used to evaluate progression free survival (PFS) and overall survival (OS).

Results: Twenty-eight lesions from 26 unique patients were treated to a median RT dose of 60 Gy (range 14-74.4 Gy) and median of 10 ETT treatments (range 3-15) or 2 ITT treatments (n=1). The cohort had a median age of 66 years (range 25-88), 62% (n=16) male, and 81% (n=21) Caucasian. Half of lesions (n=14) were treated with re-RT, 60% (n=17) of lesions were recurrent, and 19% (n=5) of patients were metastatic at time of treatment. Histology included angiosarcoma (n=6), myxofibrosarcoma (n=6), spindle cell (n=5), liposarcoma (n=2), synovial cell (n=2), undifferentiated pleomorphic (n=2), and other (n=5), six of which were classified as radiation-induced. Grade ≥ 2 acute radiation dermatitis, hyperpigmentation, pain, and fatigue were noted in 46% (n=13), 4% (n=1), 25% (n=7) and 14% (n=4) of lesions treated, respectively. Chronic toxicity occurred in 18% (n=5) of patients and included grade 2 joint stiffness, grade 3 radiation pneumonitis, two non-healing wounds, and grade 2 fibrosis. At a median follow up of 16 months, 8 (29%) local failures occurred. Six patients received neoadjuvant ETT/RT, with the five immunocompetent patients showing 40% viable tumor (VT), 20% VT, 10% VT, microscopic disease and pathologic complete response in respective pathology specimens while the immunocompromised patient had no tumor regression on pathology. The median and 2 year PFS and OS were not reached and 55% and 36 months and 62.3%, respectively.

Conclusion: Concurrent hyperthermia (ETT/ITT) and RT leads to durable progression free and overall survival, acceptable acute and chronic toxicity, and excellent pathologic response in immunocompetent patients. Prospective validation is warranted.

WED 9

IN VIVO HYPERTHERMIC ELECTROPHILIC HYDROLYSIS: THERMOEMBOLIZATION IN SWINE LIVER

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Introduction:

Embolization methods to treat large or multiple tumors leave untreated tumor in many instances. It is not clear that added drugs actually contribute to improved outcomes in many instances as carefully conducted trials have shown no difference between arms with and without drug. Hyperthermia locally has also proven challenging to deliver effectively by this route as a means to augment embolization. We report here our first in vivo results using an in situ chemical reaction technique called thermoembolization in a pig model comparing controls to an experimental group.

Materials/Methods:

Outbred swine were used in two groups (n=5/group control and experimental). Ethiodized oil was the control, and the experimental group utilized dichloroacetyl chloride at a concentration of 2 mol/L in ethiodized oil as the vehicle. To avoid premature reaction, it was delivered as a sandwich with 100 μL ethiodized oil at the leading edge and 500 μL ethiodized oil at the trailing edge. It was delivered into a branch of the hepatic artery using a microcatheter with coaxial technique. Medications required, vital signs, and lab values were all recorded. At 24 h post procedure, a noncontrast CT scan was acquired and animals were euthanized. Tissue samples were obtained for histology.

Results:

In the control group, there was no discernible effect. Although the embolic agent was seen on CT, as a diffuse region of attenuation, it did not affect the tissues. In contrast, the experimental group showed a markedly different response. The CT appearance was that of vascular casts with only a small amount more diffuse in the periphery. At histology, the experimental group showed areas of necrosis that measured several hundreds of microns in a concentric pattern centered on treated blood vessels. There was no difference between groups in medications required, vital signs during the procedure, or in laboratory values.

Conclusion:

The initial results showed no evidence of systemic toxicity for the animals in either group. Damage to the tissues in the experimental group was significant, especially when viewed in light of the small dosage used. Thermoembolization may prove a powerful strategy for image-guided intervention. It appears to warrant further investigation in appropriate circumstances.

WED 10

MICROWAVE ABLATION OF THE ADRENAL GLAND FOR TREATMENT OF CONN'S SYNDROME: PRELIMINARY RESULTS FROM AN *IN VIVO* STUDY IN PIGS

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Primary aldosteronism (PA), the unregulated secretion of aldosterone from adenomas in one or both adrenal glands, is the most common secondary cause of hypertension, representing ~6-20% of all hypertensive patients. For unilateral aldosterone producing adenomas, adrenalectomy offers definitive management. For bilateral adrenal disease, pharmacologic mineralocorticoid antagonists (MRA) are indicated, but are often poorly tolerated due to off-target androgen receptor effects. Thermal ablation provides a plausible minimally-invasive technique to definitively manage PA, affording thermal destruction of the targeted adenoma, while preserving adjacent normally functioning adrenocortical tissue. Ablation techniques involving radiative applicators, such as microwave or ultrasound energy, provide a means for controlling thermal damage to the targeted adenoma, without requiring direct insertion of the ablation probe into the adrenal gland. The objective of this study was to determine the relationship between extent of microwave ablation zones in adrenal glands on adrenal function. We employed a 2.45 GHz water-cooled directional microwave ablation applicator to evaluate thermal ablation in porcine adrenal gland *in vivo* (KSU IACUC protocol no. 4019). Eight male pigs (40.2 – 47.7 kg) were divided into three sub-groups: sham treatment in both glands ($n = 2$ animals); only one gland ablated ($n = 3$ animals); and both left and right glands ablated ($n = 3$ animals). Microwave ablations were performed with the applicator positioned on the surface of the adrenal gland, with 70 W power at 2.45 GHz applied for 60 s; this energy dose was selected based on preliminary experiments in *ex vivo* tissue. Following experimental procedures, animals were recovered from anesthesia, and survived for 48 h. Heart rate and central arterial blood pressure were recorded during experimental procedures. A central venous catheter was used to take blood samples before, during, and following ablations, as well as prior to animal sacrifice, in order to assess the effect of extent of thermal ablation on adrenal function, as measured by changes in aldosterone, renin, cortisol, and metanephrines. The extent of ablation zones was assessed histopathologically with H&E staining. Analyses from this study are underway and will be presented at the meeting. Further investigation of microwave thermal ablation as a minimally-invasive modality for targeted destruction of benign aldosterone producing adenomas is warranted.

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WED 11

TISSUE FREEZE PROPAGATION SPEED IS MODULATED BY SUPERCOOLING DEGREE AND CRYOPROTECTANTS

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INTRODUCTION: In cryosurgery and cryopreservation, tissue is cooled below its thermodynamic melting point, i.e., the tissue is supercooled. Heterogeneous freezing is then randomly nucleated and the freeze subsequently propagates throughout the supercooled space. This work aimed to reveal the modulating factors of freeze propagation speed.

METHODS: In this work, porcine dermal tissue was first supercooled at different conditions before initiation of an on-command freeze, using a novel freeze inoculation technique. Experimental variables included supercooling degree, cryoprotectant type, and cryoprotectant concentration. An infrared (IR) camera was used to record the freezing of the tissue, and the freeze propagation speed was subsequently calculated from the acquired IR video.

RESULTS: Here we report that the freeze propagation speed is modulated by several factors. Specifically, freeze propagation speed was found to depend on the supercooling degree, with a larger supercooling degree associated with larger freeze propagation speed; the presence of cryoprotectant in the supercooled tissue was found to reduce the freeze propagation speed, with higher cryoprotectant concentration resulting in lower freeze propagation speed; further, it is found that different cryoprotectants vary in their ability to reduce the freeze propagation speed, with propylene glycol being the most effective in reducing the freeze propagation speed among cryoprotectants investigated in this work.

CONCLUSION: Multiple factors affect freeze propagation speed with increasing supercooling degree and decreasing cryoprotectant concentration correlating with increased freeze propagation speed. Results obtained in this study may aid in the understanding of tissue freezing dynamics and thus offer insights into cryosurgery and tissue cryopreservation.

WED 12

RESPONSE OF ARTERIAL VESSELS TO TWO CARDIOVASCULAR STRESSORS: HEAT AND DOBUTAMINE

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Introduction: The healthy mammalian cardiovascular system is highly adaptive. Two common cardiovascular stressors are exercise and heat. At rest, there is minimal muscle heat generation, and core temperature is greater than muscle temperature (Tc>Tm). Conversely, during exercise there is maximum muscle heat generation, with Tm>Tc, due to increased metabolic requirements. This reversal in the temperature differential between muscle and core elicits a response which diverts blood flow from the muscle to the skin in an effort to increase heat dissipation, potentially decreasing muscle function. External temperature, alone, typically does not stress the cardiovascular system as much as exercise; however, temperature can compound the stress of exercise. A better understanding of how the cardiovascular system responds to these two stressors, independently and combined, could provide motivation for using exercise and/or heat as a prophylactic or therapeutic method.
Methods: Male mice were anesthetized and imaged at 7T. Anatomical and functional data included the neck (carotid artery), torso (suprarenal and infrarenal aorta and iliac artery), and periphery (femoral artery). Intravenous dobutamine (tail vein catheter, 40 μg/kg/min, 0.12 mL/hr) was used as a clinically-relevant surrogate to exercise. Baseline and dobutamine data were acquired at minimally hypothermic (35°C) and minimally hyperthermic (38°C) core temperatures. Average, maximum, and minimum cross-sectional vessel areas and maximum cyclic strain were measured across the cardiac cycle.
Results: Vascular response varied by location and by core temperature as quantified by changes in average, maximum, and minimum areas and cyclic strain. For minimally hyperthermic conditions (38°C), average and minimum vessel areas decreased between baseline and dobutamine at all locations; whereas, maximum vessel areas increased at the iliac and femoral locations only. Normalizing the data, the average delta between baseline and dobutamine for average, maximum, and minimum areas were: -5.8%, -17.4%, and -12.4%, respectively. In contrast to the similar trends seen in vessel response at warmer core temperatures, for minimally hypothermic conditions (35°C), all areas increased for carotid and femoral arteries, all areas decreased for suprarenal aorta, and response varied in the infrarenal and iliac arteries. For both temperatures, maximum cyclic strain increased between baseline and dobutamine at all locations.
Conclusion: This work is a novel approach to studying the effects of thermoregulation and exercise by using non-invasive imaging techniques to quantify functional changes of the blood vessels themselves.

WED 13

REAL TIME QUANTITATIVE CT MONITORING OF THERMOCHEMISTRY BY NOVEL APPLICATION OF CSOH

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Introduction:

Local recurrence and incomplete ablation of solid tumors are frequent problems due to heat sink issues among other limitations. Chemical ablation using ethanol injection, on the other hand, is not affected by heat sink but suffers from systemic toxicity that limits the dose. In situ thermochemistry offers a potential solution because it exploits the principle of convergent toxicity to achieve cell death locally. Local hyperthermia is combined with osmotic stress with synergistic effects constrained in time and space. Monitoring this technique is necessary to ensure control during the procedure, and quantification is necessary to correlate dose with outcomes. This is challenging in the example of sodium acetate produced in situ from acetic acid and NaOH, since it is similar in appearance to surrounding tissues on CT. Cesium is located adjacent to barium on the periodic table and hence blocks x-rays well. We report on a new method using CsOH in thermochemical ablation to address this challenge since the cesium atom should provide contrast and be readily identified on CT.

Materials/Methods:

Solutions of CsOH were prepared across a range of dilutions up to 150 mmol/L and included as standards when scanning. Fresh pig liver tissue was thermochemically ablated by simultaneous injection of 1 mL each of 10 mol/L solutions of acetic acid and base. The base was 10 mol/L in hydroxide prepared by the addition of 5.7 mol/L (50%) CsOH solution to a solution of 19.4 mol/L NaOH (50%) that was brought to the desired final concentration. Tissue was scanned using multi-energy CT technique. Attenuation was measured in Hounsfield units and compared to standards.

Results:

CsOH was readily apparent at CT down to the lowest concentration prepared (25 mmol/L), and readily appreciated in tissues as well. Treated areas were clearly seen. The gradient in attenuation from the central injection point outward was relatively flat with a sharp marginal zone.

Conclusion:

The addition of a small amount of CsOH in the base solution, combined with CT monitoring, enables real time tracking of the injected material in thermochemical ablation. Since CT scanners are much more widely available, this new approach may facilitate clinical translation.

WED 14

A MOLECULAR DYNAMICS APPROACH FOR EVALUATING OSMOTIC AND THERMAL STRESS ON EXTRACELLULAR PROTEINS

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Introduction. Thermochemical ablation (TCA) provides a novel conceptual platform for minimally invasive therapy of hepatocellular carcinoma (HCC): an acid and a base are mixed immediately prior to injection into the target tissue. Heat is released due to the neutralization reaction directly prior to entering the target tissue as a hot salt solution. Here we present a molecular dynamic approach toward understanding fundamental mechanisms of protein structural changes arising from combined thermal and osmotic stress.

Methods. Target proteins for the effects of thermal and osmotic stress were extracellular matrix proteins (fibronectin, collagen, laminin) known to facilitate cell survival and proliferation. We model the extracellular environment produced by TCA at the lesion boundary through systematic permutations of increasing temperature (37degC, 43degC) and salt (NaCl) osmolarity (0 mM, 40mM, 80mM, 160mM, 320mM). Atomistic simulations of the solvated proteins were performed using the GROMOS96 force field and the TIP3P water model. The interaction between extracellular proteins and the characteristic environment of TCA was quantified using root mean square distance, root mean square fluctuation, and percentage of native bonds from an initial stable conformation under no thermal and osmotic stress. Free energy, preferential interaction coefficients, and potentials of mean force were used to quantify stability of conformational states as a function of the radius of gyration. Computational results were compared to viability studies of human HCC lines HepG2 and Hep3B subjected to a combined hyperthermal stress and hyperosmotic stress at matching experimental conditions.

Results. Correlation analysis demonstrated that the trends in the cell viability under hyperthermal stress and hyperosmotic stress agreed with our in-silico models. A Pearson correlation coefficient of .74 and -.65 was observed between cell viability and interaction coefficients and protein stability in the Hep3B cell line (p.05). Similarly, a Pearson correlation coefficient of .60 and -.58 was observed in the HepG2 cell line.

Conclusion. Results suggest that the addition of salt to the solution increases the stability of folded states. Thus, the inverse correlations between viability and stability implies that protein aggregates and non-functional states of the protein have a role in the TCA-induced cell stress.

WED 15

DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER WITH HYPERTHERMIA AND TEMPERATURE SENSITIVE LIPOSOMES

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Background:

Delivering chemotherapeutic drugs across the blood brain barrier (BBB) is a major challenge in the treatment of brain tumors. The BBB can be transiently opened by the application of hyperthermia (>40 °C). Temperature sensitive liposomal doxorubicin (TSL-Dox) is a drug delivery system that rapidly releases the contained drug in response to hyperthermia. The goal of this study was to demonstrate delivery of doxorubicin across the BBB by TSL-Dox combined with local hyperthermia.

Methods:

TSL-Dox was infused intravenously over 30 minutes at a dose of 0.94 mg/kg in anesthetized beagles (age ~17 months). Following, a hyperthermia probe was placed 5-10 mm deep through one of 4 3-mm skull trephinations. Hyperthermia was performed randomized for 15 or 30 minutes, at either 45 or 50 °C. Blood was drawn at baseline, immediately after completion of doxorubicin infusion, and then every 30 minutes for up to 180 minutes. Non-survival studies were performed in four dogs, where brain tissue at the hyperthermia location was extracted following treatment to quantify doxorubicin uptake via HPLC and to visualize cellular uptake via microscopy. Survival studies for 6 weeks were performed in 5 dogs treated by a single hyperthermia application.

Results:

Local doxorubicin delivery ranged from 0.11 to 0.74 ng/mg of brain tissue at the hyperthermia locations, with undetectable drug uptake in unheated tissue. Fluorescence microscopy demonstrated cellular doxorubicin uptake. Histopathology in H&E stained samples demonstrated localized heat-induced damage near the probe. No animals in the survival group demonstrated significant neurological deficits.

Conclusion:

Localized doxorubicin delivery to the brain can be facilitated by TSL-Dox with localized hyperthermia with no significant neurological deficits.

WED 16

NOVEL METHOD FOR SYSTEMIC REMOVAL OF THERMOSENSITIVE LIPOSOMAL DOXORUBICIN TO REDUCE TOXICITIES

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Background:

Thermosensitive liposomes (TSL) are a promising nanoparticle drug delivery system that rapidly releases the contained drug in response to hyperthermia (>40 °C). Combined with localized hyperthermia, TSL allow highly localized delivery (~10-30x local dose compared to unencapsulated drug). As the release of the drug only takes place in the heated tissues, only a small fraction of administered drug is released in the target tissue. Most of the drug is eventually taken up by non-targeted tissues due to gradual drug leakage from TSL in systemic circulation, and by other mechanisms, leading to unwanted toxicities. The goal of this study was to demonstrate the ability to rapidly remove the drug not released in the targeted tissues by filtration in an extracorporeal circuit (ECC).

Methods:

Norway brown rats were anesthetized and catheters were implanted into the jugular vein and carotid artery. After allowing 48 hours for recovery, blood was drawn for baseline analysis. Then, TSL encapsulated doxorubicin (TSL-dox) at a dose of 7mg/kg was infused via venous catheter in anesthetized animals. 15 min after the infusion was completed, an ECC was established between arterial and venous catheters. The ECC consisted of a novel device designed to remove TSL-dox from systemic circulation by first heating the blood for 5-10 seconds to 42°C to release drug from TSL, followed by filtration of the released drug. Blood from the artery was passed through a lab-made heating element to achieve almost complete release of drug from TSL, passed through an activated charcoal filter to remove released drug, and finally returned to animal through the catheterized vein. ECC filtration was performed for 1 hour at a flow rate of 0.35 ml/min in 3 animals. Blood samples were collected before and after the charcoal filter every 20 min after completed drug infusion. ECC filtration was performed in 3 animals, and TSL pharmacokinetics was measured in 2 control animals without filtration.

Results:

20% and 29% of the infused dose were removed from systemic circulation within 40 and 60 min of ECC. The activated carbon filter efficacy was between 90% (start of ECC) and 60% (end of ECC).

Conclusions:

The proposed method can rapidly remove TSL encapsulated chemotherapy from systemic circulation, potentially reducing systemic toxicities by removing drug that is not delivered to targeted tissues. This method is most effective in TSL that have good plasma stability (i.e. with limited systemic drug leakage before filtration is complete).

WED 17

THE NEED TO CHANGE CHEMOTHERAPY WITH HYPERTHERMIA-STEERED NANO-DEVICES

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Delivery of compounds to solid tumors is a crucial factor in cancer therapy. Chemotherapeutics, immunomodulating agents, or check-point inhibitors mostly end up in healthy tissues, are degraded or excreted. Little arrives at the target site. Different approaches have been used by us and others to diminish systemic exposure, improve local levels and augment accumulation in tumor. We and others showed that application of an isolated perfusion results in drastically improved clinical outcome. Unfortunately, proper isolation of a region is technically demanding and not realistic in many cancer patients. Therefore, nano-device were introduced which may impair degradation, improve circulation time, diminish side-effects and enhance local delivery. As these aspects counteract each other, e.g. long circulation time demands high stability, whereas the compound needs to separate from the carrier to be bioavailable. Lipid-based nano-carriers, i.e. liposomes, are versatile carriers which can be functionalized (targeted with surface moieties, rendered sensitive to mild stimuli and made to interact with cell membranes), which we coined smart drug delivery system (SDDS). Using drug loaded SDDS we and others showed that these can be triggered to release content in a matter of seconds when exposed to 42°C, while good stability was maintained at 37°C. As we are able to heat tumors better, we might have established an optimal combination treatment approach. However, we observed that with the ability to achieve instantly high local concentrations cellular uptake of the compound became the limiting factor. Cells cannot absorb the drug fast enough resulting in redistribution to the system, and thus side-effects are likely to occur and treatment is suboptimal. Now we focus on which drug to use to get the best combination of triggered release, tumor penetration and intratumoral distribution, as well as cellular uptake. Here these results will be presented and discussed.

WED 18

IN VIVO DERIVED COMPUTATIONAL MODEL PREDICTS RELEASE KINETICS OF THERMOSENSITIVE LIPOSOMES

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Introduction:

Development of novel drug delivery systems (DDS) such as thermosensitive liposomes (TSL) rely largely on trial-and-error in vivo studies to evaluate performance. The goal of this study was to demonstrate the ability of a computational model to predict TSL drug delivery, to 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=3), a 1x1 mm tumor segment was imaged. Images were obtained at 1/s rate following bolus administration of unencapsulated carboxyfluorescin (CF) (n=3) to determine tumor transport properties such as clearance and perfusion. In additional animals, studies were performed during 10 minute hyperthermia (42 °C), after administering thermosensitive liposomes (TSL) filled with CF. Two types of TSL were studied, including a slow- and a fast-release formulation (n=3 each). Via image processing methods, intra- and extra-vascular fluorescence time course was determined. 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 for both TSL formulations, and model results compared to measured results.

Results:

The fast TSL formulation delivered 11 times more CF to the tumor than slow TSL in vivo, and 20 times more in the computer model. Absolute drug concentrations were about 2 times higher in vivo compared to the computer model.

Conclusions:

Computer models may serve as tool to predict and optimize performance of novel DDS such as TSL.

WED 19

NANOPARTICLE DESIGN FOR COMMERCIAL PHOTOTHERMAL THERAPIES

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Plasmonic metal nanoparticles – including gold, silver, and platinum – are highly efficient at absorbing and scattering light. Despite their subwavelength size, the particles behave as tiny antennas that strongly couple to incident light and enable applications ranging from diagnostics to sophisticated hyperthermia and photothermal treatments. The ability to control nanoparticle size, shape, and composition allows the resulting optical properties to be tuned to strongly overlap with a chosen excitation wavelength. The most common method of measuring optical properties for colloidal particles, UV-visible spectroscopy, only measures the total extinction, however, which contains contributions from both scattering and absorption processes. While different particles may exhibit similar overall optical extinction, differences in the absorption cross-section can lead to different photothermal efficiency; here we discuss an approach combining experimental and modeled data to measure and understand photothermal efficiency, and present other design considerations for using such particles in commercial therapies.

Using colloidal synthesis methods, nanoparticles with different morphology and composition – including gold nanorods, gold nanoshells, bimetallic hollow nanoshells, and silver nanoplates – can be fabricated that have overlapping peak optical resonances in the near-infrared. Bulk photothermal measurements are performed on nanoparticle dispersions by measuring temperature changes as a function of time during continuous laser irradiation, and an energy balance is used to model the experimental thermal response. Despite the superficial agreement in optical properties, measurement of the light absorption-to-thermal energy conversion efficiency shows material-specific behavior that can be attributed to relative differences in the scattering and absorption contributions to the overall optical properties. Additional measurements of strongly scattering or absorbing particles provide a relative scale for classifying nanoparticle efficiency, and comparison of particle performance with calculated absorption and scattering spectra provides additional context for understanding the photothermal response of these materials.

In addition to the photothermal efficiency of the particles, their use in a particular application depends on whether they will be used *in vivo* or for topical applications, which in turn influences choice of surface functionalization, particle composition, and manufacturing methods. We describe additional design criteria for nanoparticles we currently manufacture for use in photothermal applications ranging from treatments for head, neck, or skin cancer, clinical trials for light-pigmented hair removal and acne therapy, and the rapid thawing of cryogenically-preserved embryos and tissue.

WED 21

2018 J. EUGENE ROBINSON LECTURE: THERMO-IMMUNOLOGY: AT THE CROSSROADS OF IMMUNITY AND IMMUNOTHERAPY

Sharon Evans

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Hyperthermia is recognized as a cardinal feature of fever and has been used for centuries in the clinical treatment of cancer. However, the underlying mechanisms by which hyperthermic temperatures impact health and disease are not fully understood. Research in thermal medicine has provided a platform for novel discoveries of the immunoprotective function of hyperthermic temperatures. The prevailing view had previously been that elevated temperatures contribute to host protection by directly destroying invading pathogens or cancer cells. Recent research has enlarged on this view, showing that even non-cytotoxic temperatures within the febrile range can be protective by boosting adaptive immunity. Specifically, these studies showed that fever-range thermal stress stimulates lymphocyte trafficking to lymph nodes that are the powerhouse of the immune system. Preclinical studies of murine and patient cancer further established that tumor vessels can be converted from 'cold' to 'hot' sites of T cell trafficking using thermal medicine regimens, thus allowing for localized destruction of tumor cells. Thermal sensing in both lymphocytes and blood vessels surprisingly was found to depend on the evolutionarily conserved inflammatory cytokine, interleukin-6. Recent investigation of thermal medicine has revealed a unique role for tumor-induced immunosuppressive myeloid cells in subverting adaptive immunity during immunotherapy. Thus, the field of thermo-immunology is at the crossroads of protective immunity and cancer immunotherapy and can be expected to provide critical insight into the mechanisms of resistance that continue to thwart the success of cancer immunotherapy.

WED 22

STUDENTS HAVE ALWAYS LED THE WAY! 2018 WILLIAM C. DEWEY AWARD

Elizabeth A. Repasky

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In my career, I have always enjoyed training and mentoring young scientists as they work toward their PhD degree and then during their subsequent careers. A majority of the discoveries my lab has made regarding a role for mild thermal stress in immunity and in the physiology of the tumor microenvironment has been driven by talented and hardworking graduate students and fellows. This brief presentation will highlight some of the discoveries made by trainees who have been critical to my research program. I am grateful to the many trainees who have worked with me at Roswell Park, to my own mentors and colleagues, and to the STM Awards Selection Committee for this wonderful Award.

THUR 1

THE UNUSUAL BIOLOGY OF THE LONGEST LIVED RODENT, THE NAKED MOLE-RAT.

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Naked mole-rats (Heterocephalus glaber) are unlike other mammals in several ways. These rodents are best known for their exceptional longevity, living an order of magnitude longer than similar sized mice and the absence of an age-associated increased risk of mortality and resistance to cancer. Unlike other mammals they lack an insulatory pelage, and individuals isolated from their colony, despite the presence of large brown adipose fat pads and the employment of endothermy show pronounced thermolability. Despite an increase in brown adipose tissue with acclimation to 25°C, thermogenic capacity is unchanged. Moreover, housing naked mole-rats at 25°C -5°C below the lower critical limit of thermoneutrality- resulted in a 4 -fold reduction in successful pregnancies and significantly smaller litters. Animals housed at 30°C, show negligible hallmarks of aging with well-maintained physiological and molecular functions, commonly altered with age in other species. This non-aging phenotype is attributed to a well maintained and enhanced suite of molecular adaptions to stress resistance, including elevated levels of heat shock proteins and well maintained proteostasis.

THUR 2

PRECLINICAL MRI GUIDED FOCUSED ULTRASOUND ROBOTIC SYSTEM.

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Introduction: An MRI-guided focused ultrasound (MRgFUS) system was developed that can be used for preclinical studies in small animals.

Materials and methods: A single element spherically focused transducer of 3 cm diameter, focusing at 6.5 cm and operating at 0.5 MHz was used. The positioning device incorporates only MRI compatible materials. The propagation of ultrasound is a bottom to top approach.

Results: The system was tested successfully in agar/silica/evaporated milk phantom for various tasks such as MR thermometry, and functionality. Hyperthermic temperatures (43 oC) were achieved using the proposed system

Conclusions: This system has the potential to be marketed as a cost effective solution for performing experiments in small animals. With minimum changes this robotic system can be converted into a device for performing interventions with focused ultrasound in humans in the brain, abdominal area and breast.

THUR 3

MICROBUBBLE-ASSISTED MRI-GUIDED FOCUSED ULTRASOUND FOR HYPERTHERMIA AT REDUCED POWER LEVELS

Marc Santos[1,2], Sheng-Kai Wu[1,2], Zhe Li[1], David Goertz[1,2], Kullervo Hynynen[1,2]

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Background: Focused ultrasound (FUS) has been employed for decades in thermal therapy and can non-invasively treat cancerous tumors. By combining FUS with magnetic resonance imaging (MRgFUS) thermometry, feedback control methods have been reported in hyperthermia applications. There are however cancers located at sites posing significant challenges for FUS-based heating approaches, such as the liver or the head and neck. Tumors in these locations are limited by bone shielding, respiratory motion and large blood vessels which act as heat sinks. New heating methods are required to overcome these issues in order to expand the range of tumors that can be treated. In this work we investigate the use of microbubbles in combination with MRgFUS hyperthermia. A primary objective is to determine if it can reduce the power requirements to achieve hyperthermia in healthy muscle and experimental tumors.
Methods: Experiments were performed in 39 rabbits with Vx2 tumors implanted in 22/39 rabbits. MRgFUS temperature feedback controlled hyperthermia (42°C for 20min) was achieved using continuous wave sonication and a hydrophone was used to monitor acoustic cavitation during sonication. Once the target thigh muscle, or Vx2 tumor, reached 42°C Caelyx® (2.5mg/kg of doxorubicin) was administered over 5min. A subset of rabbits received microbubbles (Definity®, 20μL/kg) following the injection of Caelyx® and a second subset received saline without microbubbles. This was the case for rabbits with and without Vx2 tumors. Doxorubicin concentrations in heated and unheated tissues were measured with fluorometry.
Results: Applied power levels required to maintain the hyperthermia temperature elevation dropped significantly in healthy muscle when microbubbles were administered compared to the administration of saline without microbubbles. Elevated levels of subharmonics and ultraharmonics were present during exposures indicating substantial microbubble oscillations. Doxorubicin concentration in heated muscle tissue was higher in the group that received microbubbles. In Vx2 tumors the power drop following the injection of microbubbles dropped significantly even when compared to the power drop observed in healthy muscle tissue with microbubbles. No significant differences were observed in the drug concentration in heated tumors.
Conclusions: These results demonstrate the ability of systemically circulating microbubbles to reduce the required power levels during controlled MRgFUS hyperthermia. This has implications for treatments in highly perfused targets, and those shielded by bone such as in the liver. Future work will entail the evaluation of this technique on its ability to improve survival in a rabbit Vx2 tumor model.

THUR 4

A METHOD FOR QUALITY ASSURANCE IN MAGNETIC RESONANCE IMAGING-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MRGHIFU) MILD HYPERTHERMIA (MHT)

Lifei Zhu, Hong Chen, Yaoheng Yang, Michael Altman

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Introduction: MRgHIFU is a promising MHT modality which can potentially achieve noninvasive, localized, uniform, and accurate MHT for a broad range of solid tumors. Clinical translation of MRgHIFU HT has been hampered by the lack of the quality assurance (QA) procedures. We present a QA method that uses the gamma index, similar to that used in radiation therapy (Low et al., Med Phys, 1998), to compare phantom-based two-dimensional temperature distributions.

Methods: A clinical MR-HIFU system (Sonalleve V2, Profound Medical) was used to deliver twelve one-hour MHT sessions to vendor-provided QA phantom (3 sessions for each four cell size ranging from 18-54 mm). Temperature maps with a pixel size of 2.5x2.5 mm2 were acquired from five coronal slices and one sagittal slice from all MHT sessions. Temperature distributions were analyzed using the gamma index to compare phantom-to-phantom and phantom-to-muscle temperature maps with variable percent temperature difference (%TDiff) and distance-to-agreement (DTA) parameters. Both dynamic-by-dynamic temperature maps (dynamics being maps acquired every 3s during heating) and average temperature maps throughout heating (Tavg) were analyzed. For each comparison, %TDiff of 1%, 2%, and 3% and DTA of 2.5 mm and 5 mm were analyzed. For each dataset, the average gamma pass-percentage (PP, the percentage of pixels where gamma$<$1) of all the dynamics and the Tavg maps throughout heating were calculated. Strong agreement was benchmarked at PP$>$95%. Temperature maps acquired from three one-hour MHT sessions in porcine muscles in vivo were also compared with ones from phantom with the same cell sizes.

Results: For all cell sizes, intercomparisons between phantom sessions with the same cell size showed a PP$>$95% for 2%/2.5mm %TDiff/DTA for the Tavg maps and 3%/2.5mm %TDiff/DTA for the average PP of all the dynamics. Increasing the DTA to 5.0mm showed negligible change in the results while changing the %TDiff (1-3%) resulted in significant differences in PP ($p<0.05$). The phantom-to-pig PP comparison failed our benchmark for any condition tested, an expected result showing the gamma criteria could distinguish dissimilar temperature maps. PP among different MHT sessions in phantom did not present significant differences ($p>0.05$), demonstrating the repeatability of MHT in phantom.

Conclusions: The gamma analysis of temperature distribution is repeatable in commercial phantom across multiple MHT sessions, showing its validity as a potential QA tool for MRgHIFU MHT. 2%/2.5mm and 3%/2.5mm %TDiff/DTA were found to be appropriate criteria for analyzing Tavg and dynamic-averaged temperature maps, respectively.

THUR 5

ENDOBRONCHIAL ULTRASOUND THERMAL THERAPY OF PULMONARY MALIGNANCIES: A THEORETICAL INVESTIGATION IN PATIENT SPECIFIC LUNG MODELS

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Objective:

To investigate the performance of endobronchial ultrasound applicators for treatment of pulmonary malignancies through biothermal simulations on 3D lung models.

Methods:

Two types of applicator configurations, each with inflatable water coupling balloons, are considered: a) a planar transducer (10mm x 10mm, 3MHz) for targeting tumors adjacent to the primary bronchus or large airways; b) a catheter-based tubular transducer with 360° active angle (1.7mm OD, 10mm length, 7MHz) for targeting tumors adjacent to or encapsulating tertiary and smaller bronchioles in deep lung. 3D models with lung, airway and tumor were generated from CT images using a segmentation algorithm. 3D acoustic and biothermal simulations incorporating heterogeneous acoustic and thermal tissue properties were performed. Three different types of lung tissue, as to be anticipated in clinical practice, were modeled in proximity to the tumor: saline flooded lung emulating a lavage procedure to providing acoustic access to lung tumors; atelectatic lung between tumor and bronchioles, surrounded by inflated lung; and inflated lung. Acoustic intensities of 1.3-12W/cm^2 for 3-5 minutes were applied. Performance measures including acoustic pressure/intensity and temperature, penetration(>50°C) and coagulation volumes (>240EM43°C) were determined.

Results:

At primary bronchus, flooded lung, as a pathway of acoustic energy, enabled the planar transducer applicator to create a larger coagulation volume (2.1-2.7cm^3 vs 0.7-1.0cm^3) than atelectatic and inflated lung with similar maximum temperature (83.1°C vs 82.9°C), showing enhanced thermal coagulation of the tumor. In certain cases with atelectatic lung a greater penetration into the tumor (22.9-23.2mm vs 19.7-21.0mm in flooded lung) was found. Fairly uniform acoustic pressure profiles within tumor, and near full reflection at tumor/inflated lung boundary, are shown to localize thermal treatments. Catheter-based tubular applicator in deep lung generated maximum temperature (66.1°C vs 75.6°C) with deeper penetration (11.0-12.5mm vs 9.0-10.1mm diameter) and greater coagulation volume (2.6-4.2cm^3 vs 2.2-3.3cm^3) with inflated lung compared to flooded lung, respectively, indicating no advantage to flooding. In deep lung inflated lung parenchyma encapsulates the thermal and acoustic energy to the tumor.

Conclusions:

Endobronchial ultrasound applicators can effectively treat lung tumors adjacent to large airways, and extending into deep lung. Flooded lung procedures may enhance acoustic energy transmission and thermal tumor coagulation near major airways. By encapsulating acoustic power/energy within the tumor, tumors surrounded by inflated lung appear to be preferentially treatable by ultrasound in deep lung.

THUR 6

MAGNETIC RESONANCE–GUIDED INTERSTITIAL HIGH-INTENSITY INTERVENTIONAL ULTRASOUND FOR BRAIN TUMOR ABLATION

Jacquelyn MacDonell[1], Tamas Heffter[2], Emery Williams[2], Niravkumar Patel[3], Sebastian Rubino[1], Roy Hwang[1], Goutam Ghoshal[2], Gregory Fischer[3], Julie G. Pilitsis[1], E. Clif Burdette[2]

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Background

Treatment of localized brain tumors is limited to one or a combination of resection, chemotherapy, radiotherapy, and ablation. The main goal of treatment of intracranial neoplasms is to eradicate tumor cells with minimal disruption of surrounding normal parenchyma. Thermal ablation has gained increased use in recent years. In this work, MRI-guided robotic assisted (MRgRA) high-intensity interventional ultrasound is being explored.

Methods

ACOUSTx applicators, which contain multiple, cylindrical/curvilinear, MRI compatible transducers at 6-7MHz that afford multi-directionality for precise shaping of the radial ablative zone and irregular shaped tumor ablation were developed and tested. This is achieved by independently activating transducers along the length of the applicator and with specific desired angular patterns. The applicator is encased in a Celcon catheter, circulating degassed water over the transducers, protecting them from thermal effects, couples the ultrasound energy, and increases thermal penetration into the target volume. In-vivo experiments were conducted in porcine brains. A stereotactic robotic assisted positioning and placement system, in combination with MRI was used to insert the applicator into the target region in pig brain through a 17mm diameter burr hole skull entry point. Post treatment, brain tissue was harvested and triphenyltetrazolium chloride–stained and coronal brain slice were analyzed.

Results

After robotic positioning and alignment of the 3 DOF position and 2 DOF orientation,

the neurosurgeon introduced a cannula held by the robotic assistant through the corticotomy. The MrgRA then inserts the interstitial HIFU needle through the cannula

and images are obtained to confirm placement prior to ablation. Therapy is then guided through MR thermal imaging. The preliminary data determined that energy is delivered at a 4-W acoustic output power over 180 seconds to obtain a 2-cm3 ablation zone.

Conclusion

Interstitial HIFU therapy for intracranial tumors utilizes ultrasound as a minimally invasive method of tumor ablation. Using a catheter delivery system, the natural barrier of the calvaria is circumvented. Interstitial HIFU also enables diagnostic capabilities through the cannula and precise conformal tumor ablation. The application of an automated system via integrated robot and FDA cleared ablation system improves workflow and efficiency of the delivery system, and has been shown to work in animal models as a proof of concept.

THUR 7

COMPARISON OF IN VITRO CELLULAR RESPONSE AND IMMUNE PRIMING OF HYPERTHERMIA, CRYOSURGERY AND IRREVERSIBLE ELECTROPORATION

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Energy-based focal therapies including hyperthermia (heat), cryosurgery (cryo) and irreversible electroporation (IRE) for cancer are increasingly used as an alternative to surgical resection or radiotherapy. However, focal therapies continue to suffer from local recurrence and systemic spread. Emerging work including the combination of checkpoint blockade has shown that some focal therapies can help engage immune system to address these shortcomings. Nevertheless, the cellular response to focal therapy and its underlying mechanism to promote immune priming of the immune system remain largely unclear.

B16-F10 (murine melanoma) cells in suspension (1.5E7/ml) were lethally treated by Heat (50°C, 30min), Cryo (-80°C, 30min) and IRE (1250V/cm, 50μs, 99 pulses and 1Hz). Cell lysates were then collected to compare the difference in viability (by CCK8 assay), protein release (by BCA assay), protein denaturation (by spectroscopy-FTIR), TRP2 antigen release (by Western Blot), and antigen-specific CD8 T cells activation. The T cell assay consisted of incubating lysates with differentiated bone marrow-derived dendritic cells followed by the addition of naive TRP2-specific T cells. T cell activation was quantified by, measuring the percentage of T cells undergoing division (dilution of CTV, a cell label).

Of the therapies IRE releases the most protein (2.7±0.8mg/ml), followed by Cryo (2.3±0.3mg/ml) and Heat (1.0±0.4mg/ml). In contrast, Cryo released the most native (not denatured) protein (2.2±0.7 mg/ml), compared to IRE (1.9±0.4mg/ml) and Heat (0.2±0.3mg/ml). When comparing the release of TRP2 antigen, IRE dramatically outperformed Cryo and Heat with 174±113% vs. 64±27% and 13±14% relative intensity (to LN_2 control) respectively. IRE treated lysates also promoted a higher T cell proliferation index than Cryo or Heat (both $p<0.01$ from 5.6E3 to 1.2E6 cell equivalent) while cryo was modestly outperformed heat ($p<0.05$ at higher cell equivalents).

This study demonstrates that while all focal therapies cause cell death, the "quantity" (amount) and "quality" (physiochemical conditions) of tumor protein antigen released from cancer and the ensuing priming of the immune system differ. Further investigation of the mechanism(s) by which focal therapies promote protein release and antigen presentation is warranted for specific cancer antigens to yield predictable and robust immune response. This information will ultimately help in designing combinatorial immunotherapies and focal therapies with adjuvant properties for in vivo use to treat cancer in the future.

THUR 8

DYNAMIC IMAGING OF IMMUNE EFFECTOR FUNCTION DURING WHOLE-BODY FEVER-RANGE HYPERTHERMIA

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For many cancer types, immunotherapy is an emerging first-line treatment, with the potential to reach complete regression in patient subsets. The main effector cells mediating tumor eradication are cytotoxic T lymphocytes (CTL), which kill cancer cells in a cell-contact and tumor-antigen-specific manner. Adoptive transfer of ex vivo activated tumor-specific CTL (ACT) is, thus, a promising strategy to increase anti-tumor immunity but its capacity to control tumor growth is often insufficient. External application of heat in the fever-range (38 – 40 °C) has been shown to activate and support immune effector functions in tumors. However, the rational design of ACT and hyperthermia combinations is currently hampered by an incomplete understanding how both therapies synergize and which remaining immunosuppressive mechanisms limit their combined efficacy.

By using live-cell microscopy and optical reporters, we monitored structural damage induced by OVA-specific CTL to the cellular and nuclear membranes and DNA double-strand breaks in B16F10/OVA melanoma cells. CTL-mediated damage was predominantly sub-lethal and followed by rapid recovery of the tumor cell. Treatment with 39.5 °C, applied either continuously or for 1 – 3 h on 2 consecutive days, significantly increased tumor apoptosis rates and correlated with stabilized CTL-tumor cell contacts and impaired recovery of melanoma cells from CTL-mediated damage.

To evaluate the efficacy of ACT and whole-body hyperthermia (WBH) in the context of the melanoma microenvironment, we used intravital multiphoton microscopy combined with an imaging window for longitudinal monitoring of CTL effector function. Following intradermal tumor injection and adoptive CTL transfer, we applied WBH of 39.5 °C for 1 or 2 h and repeated the treatment every other day for one week. Directly following the first treatment, imaging revealed an immediate block of tumor cell proliferation and increased apoptosis rates. Time-lapse microscopy showed enhanced CTL killing activity while CTL-tumor cell interaction dynamics remained unchanged, ranging from stable, long-lasting to highly dynamic contacts. The combination of ACT and WBH further induced the infiltration of phagocytic cells which was absent in tumors of mice treated with either therapy alone. Macrophage infiltration partially resolved or stabilized despite repeated WBH treatments. Subregional analysis of tumor cell viability further revealed a resistance of tissue-invading tumor cells to WBH monotherapy which was overcome by combined ACT/WBH treatment.

Thus, kinetic imaging and intravital microscopy were successfully applied to deepen the mechanistic understanding of immune cell function during fever-range WHB which forms the basis for improved, rationale design of combination therapies.

THUR 9

THE IMPORTANCE OF UNDERSTANDING THE IMPACT OF HOUSING TEMPERATURE ON INTERPRETATION OF EXPERIMENTS EVALUATING THE ROLE OF HYPERTHERMIA ON IMMUNITY AND PHYSIOLOGICAL RESPONSES IN LABORATORY MICE

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Our laboratory has worked on mouse models for many years to study the impact of hyperthermia treatments on tumor progression, tumor microenvironment and on anti-tumor immunity. Throughout most of this research, groups of mice have been housed at standard, IACUC mandated temperatures (~22 °C, or ST) which are enforced world-wide in research Institutes; we assumed that control groups of mice housed under these mandated conditions were "normothermic" and were suitable as controls for comparison to mice treated with hyperthermia. However, while these control-group mice do indeed maintain a normal core body temperature of ~37 °C, their thermoregulatory system is significantly influenced by the fact that these mice are housed, from birth, in mildly cool, sub-thermoneutral temperatures, which results in chronic and increased adrenergic stress. This fact led us to more carefully evaluate our assumptions regarding "normothermia" in laboratory mice. What we found was that our control mice, though able to maintain a normal body temperature, exhibit significant metabolic abnormalities associated with their need to make additional heat (i.e., adaptive thermogenesis) which requires a large increase in energy associated with mitochondrial heat production. This "shift" in energy utilization has surprising effects on other homeostatic systems, particularly in the ability of mice to mount a normal anti-tumor immune response, which also requires considerable energy. Specifically, compared to mice housed at a "thermoneutral" temperature (~30 °C, or TT), mice housed under standard cool temperatures are profoundly immunosuppressed. We also found significant differences in the ability of mice to undergo mild whole-body hyperthermia (WBH) after being housed for several weeks at ST vs TT in terms of a stress response. Specifically, mice housed at ST and given mild WBH (bringing core temperature to ~39.5 °C) exhibit much more behavioral stress during heating than seen in mice housed at TT given the same hyperthermia treatment, suggesting the existence of "adaptation" to housing temperature which could be influencing the physiological response to hyperthermia in mice. Together, these data suggest that caution should be given to interpreting the impact of hyperthermia protocols in mice when measuring anti-tumor immunity or other important endpoints since baseline stress is causing abnormalities in these parameters. We suggest that these types of experiments should be performed at both ST and TT to obtain the most complete picture of the pre-clinical impact of hyperthermia. Supported by R01CA205246, The Roswell Park Alliance Foundation, and P30CA016056.

THUR 10

CLINICAL STUDY ON IMMUNOLOGICAL EFFECT OF CRYO-THERMAL THERAPY OF LIVER CANCER

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Introduction: A novel cryo-thermal therapy was developed for tumor ablation by alternating cooling and radio frequency (RF) heating of tumor tissues. Thermally inducing a whole-body immune response against distal metastases has been proven in animal model. In this study, we aimed to assess the efficacy of the cryo-thermal therapy of liver cancer in clinic.

Methods: 21 patients with colorectal cancer liver metastases were included in this pilot study. Another 5 patients with colorectal cancer liver metastases were treated with RFA as control. First, Argon-helium knifes were inserted into the target area with the distance between adjacent probes less than 15 mm. When the ice ball was 5mm beyond the boundary of the tumor, the power was reduced to maintain ice ball size unchanged up to 15min. After rewarming, RF heating was performed by Umbrella Electrode. The power and heating time was set to maintain the tissue temperature at 50 degrees in 5mm outer the tumor edge for 15min. All patients underwent standard magnetic resonance imaging of liver cancer prior to the treatment procedure, and 1 month and 3 month after. The blood sample were collected and immune cell subsets were measured by multi-colour flow cytometry before and on day 3, 1, 3, 6 and 12 month after the treatment.

Results: The treatment was well tolerated in all patients without major complications or procedure-related mortality. Complete response was achieved in all treated lesions. A relatively higher number of CD11c+CD86+IL-12+ DC subsets, CD11c+HLA-DR+IL-12+ DC subsets and CD14+CD169+IL-12+ M1 macrophages were observed in patients treated by the cryo-thermal therapy, in comparison with those in patients treated by RFA. In addition, the level of CD56+CD16-IFN- + NK cell subsets was also relatively higher on day 3 after the treatment. Furthermore, the cryo-thermal therapy induced a relatively higher number of CD4+T cells while decreasing the percentage of Tregs, CD4+PD-1+ T cell subsets and CD4+ Th2 subsets on day 3 following the cryo-thermal therapy. The elevated matured DCs, M1 macrophages, CD4+T cells and decreased Tregs, CD4+PD-1+ T cells and Th2 cell subsets were correlated with good prognosis.

Conclusion: Cryo-thermal therapy is safe and highly effective to induce systemic immune response.

THUR 11

EFFECTS OF HYPOFRACTIONATION AND LOW DOSE MNP HYPERTHERMIA ON TUMOR IMMUNOGENETICS

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Background: In some cancer sites radiation therapy is moving towards fewer, but larger fraction sizes (hypofractionation). Both of these treatment modalities have been shown to result in an enhanced immune response, as compared to conventional fractionation. The addition of an immune stimulator can further improve the evoked immune response. The mechanism and optimal radiation and mNP (magnetic nanoparticle) heat doses and dose timing remain unknown, although a number of related research studies are ongoing. In this study we have used a B16 F10 murine melanoma model (B6C57 mice), hypofractionated radiation (3x8Gy, 1x15Gy) and mNP hyperthermia (CEM 30x2) to better understand the immune potential of this therapy. Assessment techniques include quantitative RNA and protein expression, quantitative pathology/ immunohistochemistry and tumor efficacy (tumor regrowth). There is a significant body of work investigating hyperthermic treatment using iron, but not much has been determined on the genetic pathways involved, or the combination with radiation.

Methods: *In vitro* methods involve using a monolayer or pellet of B16F10 mouse melanoma cells and assessment of radiation induced, mNP hyperthermia induced, or combinatorial radiation/mNP heating induced immunogenic protein stimulation.

In vivo methods use a mouse model with B16F10 melanoma tumors on the right flank, with two endpoints – 5 days post treatment for NanoString and 3x size for regrowth analysis. Mice will be used in the following cohorts: control, mNP only, mNP/3x8GY, mNP/15GY, mNP/ heating/3x8GY, and mNP/ heating/15GY. Genetic/ RNA analysis techniques include western blotting to quantify protein expression and NanoString to quantify RNA expression differences.

Results: Using a monolayer of cells does not generate heat, and thus there was limited differences in protein expression, with the exception of phosphorylated ERK. However, by pelleting the cells for treatment, slight heat was able to be generated with larger differences in protein expression, especially in p27, p21, calreticulin, and mdm2; all of which are important cell cycle or immunogenic proteins in cancer. In vivo experiments are currently being completed, with NanoString and efficacy results expected soon.

Conclusion: Radiation treatment alone is thought to induce an immune response, but by combining with mNP heating the immune response may be much greater. Here we demonstrate differences between the individual treatments versus when they are combined and gain insight into the pathways involved in the elicited immune response.

THUR 12

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: GLOBAL PERSPECTIVE ON RATIONALE AND RESULTS TO DATE

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Background

An increasing concern for improved management of peritoneal dissemination and local recurrence of cancers that occur within the abdomen and pelvis has been expressed by both surgeons and medical oncologists. This condition was, in the past, regarded as a universally fatal manifestation of cancer dissemination. It has been associated with early death and a miserable quality of life in those patients manifesting peritoneal dissemination and the progression of peritoneal metastases.

Methods

In the past 30 years a marked conceptual change in the possibilities to prevent or treat peritoneal metastases has occurred. Currently, management strategies for this condition from a large number of abdominal and pelvic cancers exist. A comprehensive approach that involves cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) is the current standard of care.

Results

It has become imperative for the multidisciplinary team (MDT) to consider options for prevention and treatment of peritoneal metastases. The primary and recurrent cancers that must have special attention by the MDT if peritoneal metastases is present include appendiceal cancer (Lancet Oncology 2006;7:69-76), malignant peritoneal mesothelioma (J Oncol Pract 2016;12(10):928-35), colon cancer (Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 2.2017), ovarian cancer (N Engl J Med 2018;378(3):230-240), gastric cancer (Sugarbaker PH, et al. Regional Chemotherapy: Possibilities for Prevention and Treatment of Peritoneal Metastases from Gastric Cancer. Management of Gastric Cancer. SMGroup. www.smgebooks.com), or rare malignancies (Goere D, et al. Int J Hyperthermia 2017;533:528-33).

Conclusions

Systemic chemotherapy alone is not optimal management of selected patients with peritoneal metastases. Cytoreductive surgery with HIPEC must be considered.

THUR 13

CYTOREDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEALCHEMOTHERAPY (HIPEC): SINGLE-CENTER EXPERIENCE

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Background. With standard treatment plan, abdominal cancers with peritoneal carcinomatosis (PC), prognosis is very poor. Due to its significant, but acceptable, morbidity and mortality, and high cost, this comprehensive management plan requires good patient selection.

Methods This was a retrospective single centre study and patients with advanced and recurrent abdominal cancer with PC treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) were included in the study.

Results This analysis included all patients (n = 319, 246 female, 73 male) with PC from various primary tumors: primary ovarian 83, recurrent ovarian 102, primary colorectal 48 recurrent colorectal 38, mesothelioma 8, pseudomyxoma 35, adenosarcoma 2 and gastric cancer 3 who were treated in our institution between 1996 and 2018. The mean age was 56 years (23–79). The median duration of surgery was 4 h and 58 min (3 h 30 min – 6 h 49 min). Median blood loss was 589 milliliters (280–1530 ml). Morbidity rate was 24/319 (7,5%); Dindo-Clavien grade III/IV complications (11/319; 3,4%). Mortality rate was 1/316 (0.3%) in our study population.

Conclusions Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can significantly influence overall and disease-free survival in selected patients with peritoneal carcinomatosis of various tumor entities. We were able to demonstrate the feasibility, efficacy, and safety of CRS + HIPEC in patients suffering from PC.

THUR 14

HIPEC, TUMOR ORGANOIDS, AND PERSONALIZED MEDICINE

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Introduction: Precision medicine could benefit from personalized models where patient specific chemotherapy efficacy can be tested prior to initiation of treatment.

Methods: Biospecimens obtained during CRS/HIPEC procedures, were transferred to the laboratory, washed with saline, antibiotic, and red blood cell lysis buffer. Biospecimens were minced, dissociated, and incorporated into an ECM-based hydrogel system and biofabricated into patient-specific tumor organoids. Cells were not sorted for tumor cells, as to preserve tumor heterogeneity, including stroma and immune cell components. Following establishment of organoid sets, multiple chemotherapy drugs were screened in parallel. Quantification of live/dead staining and metabolism assays, recorded which chemotherapies were most effective in killing cancer cells for a particular patient. Maintenance of cancer type phenotypes were confirmed using IHC antibody staining.

Results: 14 biospecimens from 8 patients were applied for organoid development between November 2016 and May 2017. Take rate (successful establishment of viable organoid sets) was 75%. Average time from organoid development to chemotherapy testing was 5 days. Primaries examined were low and high grade appendiceal cancer, epithelioid mesothelioma and papillary cystic mesothelioma. All tumor organoids were tested with different chemotherapy lines and and exhibited response that was either similar to the patient response or within the variability of the expected clinical response. LGA organoids showed no response to any chemotherapy agent screens.

Conclusion: Development of 3D tumor organoids is feasible in rare tumors and tumors with low cellularity. Tumor organoid biofabrication allows for individual patient tumor, immune cells and stroma to remain viable for personalized drug screening prior to initiation of treatment.

THUR 15

ENHANCED RECOVERY PROTOCOL (ERP) IMPROVES OUTCOMES IN PATIENTS UNDERGOING CYTOREDUCTIVE SURGERY (CRS) AND INTRAOPERATIVE HEATED INTRAPERITONEAL CHEMOTHERAPY (HIPEC) FOR PSEUDOMYXOMA PERITONEII (PMP)

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Introduction

Patients with pseudomyxoma peritonei (PMP) often require extensive cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) and have high post-operative narcotic use and length of stay. Enhanced Recovery Protocols (ERP) are evidence based interventions aimed at improving outcomes. Currently there are no reports of using ERP in this patient population.

Methods

ERP was developed for patients with PMP treated at a tertiary academic center by a single surgeon with CRS and HIPEC. 24 consecutive patients were reviewed. Primary outcome was narcotic use measured in PO morphine equivalents.

Results

24 consecutive were reviewed. 10 patients were in the pre-ERP cohort (Mean age 57.8, 6 females) and 14 patients were in the post ERP cohort (Mean age 59.2, 10 female). Median narcotic use measured in PO morphine equivalents was significantly lower in the post- ERP cohort (240 mg vs. 17 mg ($p = 0.012$)).

Conclusion

Application of ERAS protocol is feasible and safe in patients undergoing CRS and HIPEC for PMP with significant reduction in post-operative narcotic utilization. In the future this may ultimately result in improved outcomes and decreased lengths of hospitalization.

THUR 16

RESPONSE TO LAPAROSCOPIC HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY AS AN INDUCTION CHEMOTHERAPY IN PATIENTS WITH UNRESECTABLE PERITONEAL SURFACE MALIGNANCIES

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Introduction

Induction Chemotherapy is a method to enable complete resection with reducing tumor burden in unresectable or locally advanced cancers. In this study, the results of laparoscopic hyperthermic intraperitoneal chemotherapy as induction chemotherapy were reported in patients with peritoneal surface malignancies.

Method

Between 2013-2018, diagnostic laparascopy was performed to 138 patients. Fourteen of 138 patients were not able to achieve complete cytoreduction. Laparoscopic hyperthermic intraperitoneal chemotherapy were performed in these patients. The results of these procedures were evaluated.

Results

Fourteen patients underwent laparoscopic hyperthermic intraperitoneal chemotherapy. The mean age of the patients was 53.8 ± 8.75 (32-74). Eleven patients were female, 3 were male. The average duration of the procedure was 2 hours 30 minutes ± 1 hour 16 minutes. Eight patients with peritoneal metastasis were originated from stomach cancer, 4 were from colon cancer, one was from bile ducts,one was from peritoneal mesotheliomaand one was from over cancer. Intraperitoneal implantable port was placed to all patients. Systemic and intraperitoneal chemotherapy was give for four cycles and the patients were evaluated with computarized tomography. The peritoneal cancer index (PCI) was decreased in 3 (37.5%) patients with gastric carcinoma, in one with over carcinoma (100%) and in one with peritoneal mesothelioma (100%). Cytoreductive surgery and HIPEC were performed in 5 (35%) out of 14 patients. Early and late complications were not detected. Ascites were controlled in all patients. Disease free survival was 3-11 months (± 3.14) and total survival was 8.9 ± 3.28 months.

Discussion

Laparoscopic hyperthermic intraperitoneal chemotherapy and intraperitoneal chemotherapy can prolong survival as well as control ascites and reduce tumor burden in patients with peritoneal surface malignancies.

THUR 17

INFECTIOUS COMPLICATIONS AFTER CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

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Background: The aim of this study was to review the postoperative and infectious complications and determine the risk factors associated with infections in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods: Between October 2007 and December 2013 patients who underwent CRS and HIPEC with a curative intent were included in the study. "The Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance System" definitions were used to identify postoperative nosocomial infections.

Results: One hundred and sixty-nine CRS and HIPEC were performed. Overall 155 complications were seen in 82 (48.5%) patients. Grade 3-4 morbidity rate was 25.5% (n=43). Seventy infections occurred in 47 patients. Surgical site infection was the most common infectious complication. The most common microorganism isolated from the cultures was Escherichia coli. Age (OR:1.039, CI: 1.006-1.073), the mean total number of staff scrubbing in the surgery (OR:2.241, CI: 1.415-3.548), and intensive care unit stay (OR:1.325, CI: 0.953-1.842) were independent risk factors for infectious complications.

Conclusions: Infectious complications are the most important cause of perioperative morbidity and mortality in CRS and HIPEC. As well as patient and tumor characteristics, surgeon/center-related factors play an important role on infectious morbidity. Patients with peritoneal carcinomatosis should be considered as a complex oncologic group at high risk of infectious complications.

Key words: Oncology, infection, peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy, morbidity

THUR 18

300 CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY PROCEDURES : THE NATIONAL CANCER CENTRE SINGAPORE EXPERIENCE

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INTRODUCTION:

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are increasingly being utilised in the treatment of peritoneal metastases. We provide a review of a high-volume Asian institute's experience and survival outcomes with this procedure.

METHODS:

Data were prospectively collected from 300 consecutive CRS and HIPEC procedures performed in a single institution between April 2001 and December 2017. Our primary endpoints were overall survival (OS) and disease-free survival (DFS), and secondary endpoints were morbidity and mortality.

RESULTS:

77.3% of patients were Chinese, 3.7% were Malay, 4.3% were Indian and 14.7% were of other ethnicities. Primary tumours were colorectal (34.7%), ovarian and primary peritoneal (31.6%), appendiceal (23.7%), mesothelioma (4.3%) and others (5.7%). The median peritoneal cancer index (PCI) was 10, and 87.2% of patients achieved a completeness of cytoreduction score (CC) of 0. High-grade morbidity occurred in 19.7% of cases, and there were no 30-day mortalities. At 5-years, the OS was 47.6% and DFS was 24.4%. The only factor associated with improved OS on multivariate analysis was the PCI score ($p = 0.023$).

CONCLUSIONS:

The combined treatment of CRS and HIPEC is beneficial and is associated with reasonable morbidity and mortality in Asian patients with PC from colorectal, ovarian, appendiceal, primary peritoneal and mesothelioma primaries. The extent of peritoneal disease is the most important prognostic factor for survival.

THUR 19

DOES THE CHEMOTHERAPY FOR HEATED INTRAPERITONEAL CHEMOTHERAPY MATTER?

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Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is an established therapy for peritoneal surface malignancies; however, the optimal chemotherapeutic agent to use in HIPEC is not clear. We will evaluate current clinical trials comparing outcomes in cohorts receiving various chemotherapies for peritoneal surface malignancies.

THUR 20

A SURGEON'S PERSPECTIVE ON CHOOSING A CHEMOTHERAPY AGENT FOR HIPEC. EVOLUTION FROM MITOMYCIN C TO CARBOPLATIN

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My first HIPEC (then IPHC), was performed December 1991 at Wake Forest University Baptist Medical Center in Winston-Salem, NC. Much thought went into drug selection at that time. Several considerations narrowed the field of agents considerably. A Japanese study using Mitomycin C (MMC) documented their experience combined with heat in an intra-operative IP perfusion setting for patients with gastric cancer. Since there was essentially no American clinical experience and no animal studies, MMC was the drug presented to our IRB. It was eventually approved, and was adopted for our clinical research program. The perfusion device was "jury rigged" by our perfusionists and was limited by our equipment to 39.5 degrees Celsius. An FDA perfusion device with higher temperature capability was not available before 2000. We continued to give thought to an alternative agent, as MMC can be quite problematic. It was cytotoxic, clearly was very irritating to the peritoneal cavity, caused extensive adhesions in most patients, and we suspected that it prolonged postoperative ileus and, thereby, hospital stay. A short trial using high dose Cisplatin with thiosulfate was deemed too toxic. When Oxaliplatin became available, it was not used because of the original cost ($16k wholesale for one dose). Enter pharmacogenetics. Our group investigated activation of MMC, which occurs in cells. The gene responsible, NQ01, is not infrequently mutated at bp609. Heterozygous mutations resulted in significantly decreased MMC activation in our laboratory studies and, in our series, were associated with decreased long-term survival. If this mutation was identified with pre-operative testing, an alternative was required. After extensive deliberation and consultation, Carboplatin was selected and has ultimately replaced MMC in our HIPEC program for all pathologies. The rationale for this, our current treatment regimen, and our experience will be reviewed.

THUR 21

EARLY AND LONG-TERM OUTCOMES OF CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAOPERATIVE INTRAPERITONEAL CHEMOTHERAPY IN PATIENTS WITH PERITONEAL SURFACE MALIGNANT DISEASES

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Introduction

Cytoreductive surgery (CRS) and Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC) are accepted as a treatment option in patients who are diagnosed with Peritoneal Surface Malignancies (PSM) originated from colon, rectum and ovary. In this study, we present the early and late outcomes of patients with PSM admitted to the treatment center of PSM Turkey.

Methods

The results of patients operated until 2013-2018 have been evaluated.

Results

One hundred twenty four patients were treated with 126 CRS and HIPEC procedures. The mean age of the patients was 54.9 ± 8.75 (34-72) and 83.9% (104) were female and 16.1% (20) were male. Average duration of the procedure was 9 hours 30 minutes ± 2 hours 56 minutes. The majority of the tumors were of colorectal (53.2%) and over (35.5%) origin. Mean Peritoneal Cancer Index was 16.89 ± 11.46 and mean blood loss was 677.82 and 282.1 ml. All patients underwent cytoreductive surgery and HIPEC were followed up in intensive care unit. Those who had a peritoneal cancer index below 10 were directly exposed. In all patients, there was a low magnesium level were detected postoperatively. One patient had cardiac insufficiency related death, 1 patient had intracranial hemorrhage related death, Grade IV-V complication was 1.61% and 5 patients had postoperative pneumonia, Grade II complication (4.03%), late parastomal hernia in one patient, and incisional hernia in 2 patients were detected. The mean duration of hospital stay was 8.6 ± 2.1 days. Disease-free survival was 17.52 months and overall survival was 20.25 months.

Discussion

Cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy can be an option to treat patients with peritoneal surface malignancies with acceptable mortality and morbidity rates. Fellowship seems to be essential to complete learning curve for optimum successful surgery and to prevent complications. Cytoreductive surgery and HIPEC also seems to be extend survival and life expectancy in patients with PSM. The length of hospital stay can be prolonged due to the height of creatinine and nasocomial pneumonia.

THUR 22

LIQUID BIOPSY IN PERITONEAL CARCINOMATOSIS: ROLE OF EXOSOMES

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Gastric and colorectal cancers have a high likelihood of spread to the peritoneal surface, which manifests as peritoneal carcinomatosis. Peritoneal carcinomatosis is typically associated with dismal prognosis. Aggressive multimodality treatment that consists of systemic therapy, cytoreductive surgery and intraperitoneal chemotherapy has been shown to improve survival in patients with peritoneal carcinomatosis. However, the overall medial survival still remains poor. Current diagnostic studies are not capable of predicting an individual patient's risk of peritoneal carcinomatosis or detect peritoneal carcinomatosis at an early stage.

Liquid biopsy utilizing serum markers is a promising approach to identify patients at increased risk for peritoneal carcinomatosis and to detect peritoneal carcinomatosis at an early stage before it becomes detectable by imaging. To that end, serum exosomes have emerged as an important method of communication utilized by cancer cells to communicate with the target cells and create a pre-metastatic niche. Exosomes are membrane bound nano-vesicles produced by cells. They carry molecular information unique to the parent cell and have been shown to be an important mode of intercellular communication. Cancer cells have been shown to secrete more exosomes than do their normal counterparts. Exosomes are found in blood, saliva, ascitic fluid, breast milk, cerebrospinal fluid, and urine. Proteins and miRNAs carried in cancer-derived exosomes are implicated in epithelial- mesenchymal transition, aggressiveness, and invasiveness. Exosomes are also resistant to degradation at normal conditions, which make them an attractive target for liquid biopsy.

Exosome- proteomic profiling and miRNA analysis have identified unique targets that are promising as blood-based biomarkers. Current work in our laboratory have identified miRNAs and proteins that are specifically up and down-regulated in serum exosomes of patients with peritoneal carcinomatosis compared to exosomes from patients with non-metastatic colorectal cancer and liver metastasis. Further work is ongoing to evaluate the individual proteins and miRNAs role in cancer survival, metastasis, and progression.

THUR 23

A POTENTIAL ROLE FOR CARCINOEMBRYONIC ANTIGEN IN MEDIATING INFLAMMATION AND ANGIOGENESIS IN PSEUDOMYXOMA PERITONEI.

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Pseudomyxoma Peritonei (PMP) is a cancer characterized by peritoneal dissemination of mucinous tumors derived from a primary appendiceal neoplasm. Our previous studies have suggested a role for carcinoembryonic antigen (CEA) in promoting colon cancer metastasis to the liver. In addition, we have also shown the importance of cytokines IL6, IL8, IP10 and MCP1 to the inflammatory PMP tumor microenvironment. The present study was undertaken to define a biological role for CEA in regulating inflammatory and angiogenic responses within the peritoneum in PMP.

Matched ascites and sera were collected from PMP patients during cytoreductive surgery. Ten chemokines/cytokines, C-reactive protein (CRP) and CEA were measured in sera and in ascites from PMP patients ($n=32$) using Milliplex immunoassays. Statistical analysis was performed using Wilcoxon rank test, Mann Whitney U test and bivariate analysis. Macrophages were isolated from peritoneal fluids obtained post operatively from drain fluids by attachment to a plastic substrate, and the effect of CEA on cytokine/chemokine production measured.

In PMP patients, CEA levels were higher in ascites than in serum [1054 vs. 98 ng/ml,$p<0.001$] and were positively correlated to all ten cytokines we examined ($R=0.52$,$p=0.004$). In contrast, CEA expression correlated only with IFNg in serum ($R=0.43$,$p=0.022$). CEA expression correlated with CRP both in serum ($R=0.59$, $p=0.001$) and in ascites ($R=0.518$, $p=0.005$). The cytokines, IL6 and IL8, were elevated in ascites but not in serum. In vitro, IL6, IL8, IP10 and MCP1 expression levels were increased within 24 hours in macrophages exposed to CEA. Expression of VEGF, TNFa and IFNg was increased within 3 hours of CEA treatment and remained elevated at 24 hours.

Elevated CEA expression and its positive correlation to both pro-inflammatory and pro-angiogenic cytokines including VEGF, IL-6, IL-8, TNF- and MCP-1in ascites but not in serum provide correlative evidence for a biological role for CEA within the peritoneal tumor microenvironment. These results considered together with our in vitro studies with peritoneal macrophages support our hypothesis that CEA is a critical regulator of tumor-stromal communication and a mediator of inflammatory and possibly angiogenic responses within the peritoneal microenvironment in PMP patients.

THUR 24

IS CRS & HIPEC A SAFE AND EFFECTIVE PALLIATIVE TREATMENT STRATEGY IN PATIENTS WITH REFRACTORY SYMPTOMATIC PERITONEAL METASTASIS?

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INTRODUCTION

Although the number of patients treated with HIPEC is increasing, majority of patients referred for treatment have often already received chemotherapy and experienced disease relapse. A subset of these patients is often referred with symptomatic disease and no longer has any viable treatment options. In this study we wanted to investigate the outcomes in patients who were treated with HIPEC in a palliative setting.

METHODS

A retrospective analysis was performed identifying patients who had failed at least two lines of chemotherapy and/or had experienced symptomatic progression before referral to therapy. Patients with symptomatic disease including ascites, obstruction, and pain were identified.

We reviewed the charts for sites of histologic tumor type, LOS, perioperative complications, perioperative mortality, peritoneal recurrence, overall recurrence, and overall survival.

RESULTS

There were no post operative deaths and complication occurred in 22% of the patients. Palliation was achieve in 91% of patients. The average LOS was 9 days. Forty-three percent of patients survived for a year or longer and the observed median survival was 9 months. Thirty percent of patient did not experience peritoneal progression but 75% of these patients did develop developed progressive nodal/systemic disease.

CONCLUSION

CRS/HIPEC can be performed safely in the palliative setting in a symptomatic, heavily treated patient population. Observed overall survival reported in this small series is comparable/better than those reported with third line systemic therapy with 43% of patients surviving for more than 12 months, but majority of these patients would not have been offered any systemic therapy because of symptoms. Patient with symptomatic disease should be referred to peritoneal center for consideration for CRS with HIPEC as it can palliates symptoms in over 90% of patients, can provide a bridge for patients to receive additional systemic therapy, and result in meaningful life extension.

THUR 26

THE ESSENTIALS OF MAGNETIC FLUID HEATING EVALUATION

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Background: Magnetic fluid heating has great potential in the fields of thermal medicine and cryopreservation. However, variations with experimental parameters, analysis methods, and experimental error make it difficult to directly compare measurements between laboratories. We propose creating a standard for assessing heating capability or specific absorption rate (SARv) of newly developed materials, such as iron-oxide nanoparticles, to allow direct comparison among laboratories.

Methods: The impact of fitting method (Time-Rise or Box-Lucas) and parameters (i.e. time point selection) was assessed through simulation and a retrospective analysis of SARv fitting of previously published data [1 – 3]. The simulations compared six heating scenarios representative of published data with SARv in the range of 0.01 to 10s of W/mL. Random noise ranging from 0 – 10 oC was applied to each simulated dataset. Then, SARv was calculated for each system using both Time-Rise and Box-Lucas fitting with evaluation times ranging from 5 – 250 s. The simulations were used to assess the accuracy and precision of the calculated results. The retrospective analysis was used to assess the precision of the analysis methods. Twelve different methods for defining the evaluation time were compared for the Time-Rise method. Three different methods for defining the evaluation time were compared for the Box-Lucas fitting method.

Results: The calculated SARv values ranged from 0.00035 – 17.3 W/mL. For the highest accuracy and precision, Time-Rise fitting should be used on datasets having short evaluation times and greater variation, while Box-Lucas is preferred for datasets having less/low variation and long evaluation times. For materials or conditions exhibiting low heating rates, accurate and precise measurements are challenging, therefore, we recommend using international union of pure and applied chemistry (IUPAC) standards to define a lower limit of SARv. Specifically, we need to account for a noise floor for ΔT measurement as a multiple of where is defined as the background root-mean square noise of the experimental setup without heating. Conclusion: When publishing SARv, the experimental noise and method of data analysis should be reported in addition to the field strength and frequency. Importantly, different inductive coil systems will generate different noise, irregardless of the sample tested, which must be factored into a robust SARv estimate.

References:

[1] Etheridge et. al., Ann. .Biomed. Eng. (2013). 41(1): p. 78-88.

[2] Hurley et. al., Mol. Pharm. (2016). 13(7): p. 2172-83.

[3] Bordelon et. al., J. App. Phys. (2011). 109(12): p. 124904.

THUR 27

TITLE: MRI MONITORING OF THERMOEMBOLIZATION

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Introduction: Thermoembolization is a pre-clinical transarterial intervention for solid tumors. It combines an ablative focal reaction with a pH change and embolus. In this investigation, the proposed injection is an electrophile, dichloroacetyl chloride (DCACl), mixed in mineral oil. DCACl hydrolyzes with water or reacts with other nearby nucleophiles. In the reacting milieu, the intervention quickly produces acid wherever the DCACl is hydrolyzed, enhancing the therapy's effect. Furthermore, there is evidence that the dichloroacetate (DCA) resulting from hydrolysis can undermine Warburg metabolism, a hallmark of cancer. In order to translate thermoembolization to the clinic, MRI is proposed to characterize the procedure via thermal imaging and T1 and R2* properties.

Methods: Fresh porcine kidneys were harvested, cleared with saline, and heparinized. For each kidney, the renal artery was sutured to a canula with two fluoroptic temperature probes being inserted into one of the kidney's poles and the interpolar region. Temperature probes measured once per second, starting 5 minutes before and 20 minutes post injection. The injection was 4 mL of 5 M DCACl, infused in about 30 seconds.

Before and after DCACl injection, anatomic MRI images were acquired. More importantly, a multi-echo fast gradient-recalled echo (MFGRE) pulse sequence acquired information related to changes in chemical shift, amplitude, and T2 That data indicated the manifestation of heat in time and space.

Results: The MRI's MRFGE sequence indicated very large temperature increases, especially in regions appearing to be vasculature, on the order of 25°C. Elsewhere in the parenchyma, the increases ranged from 5-10°C. The MR thermometry indicated temperatures remained elevated for the remainder of MR temperature monitoring. According to the temperature probes, the temperature increased by 5°C over 1 minute and remained elevated for the remainder of the probe measurement (20 more minutes). After the kidney was removed from the MR scanner, its appearance was mottled with lesions; within 12 hours, the entire kidney appeared damaged.

Conclusions: As indicated by MR monitoring and resulting tissue damage, thermoembolization may be a potent embolic and ablative therapy. The prolonged temperature elevation was surprising and needs further characterization. Nonetheless, the MR and temperature probes recorded temperature increases for the remaining length of measurement.

THUR 28

MR THERMOMETRY: NEW MR SCANNERS – NEW CHALLENGES

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Introduction: Magnetic Resonance thermometry with 1.5 T scanners during RF-induced regional hyperthermia has been in clinical use since 2001. Since that time several generations of MR scanners have been introduced with significant improvements for diagnostic imaging. These improvements are affecting MR thermometry.

Methods: State-of-the-art MR scanners with a 70 cm bore facilitate the use of larger hyperthermia applicators. When the body coil of the MRI system is used for MR thermometry the signal is lower than in scanners with a 60 cm bore. More sensitive digital receivers compensate for the lower signal but they are also more sensitive to the RF signal of the hyperthermia system.

The load from the water bolus of the hyperthermia system and the applicator within the MRI bore causes a slight mismatch of the body coil.

Despite the 70 cm bore opening, the field-of-view (FOV) of the modern MRI scanners is still only 50 – 55 cm. In contrast to diagnostic use, the hyperthermia applicator needs space under the patient for the water bolus. System-specific fixtures in the lower part of the bore prohibit matching the center of the hyperthermia applicator with the sweet spot of the MRI. Therefore the fat references used for B0 field drift compensation are at the outer edge or outside the FOV.

Most recent MRI scanners offer dock-able carts for special purposes (e. g. HIFU or surgical use). These carts are useable for the hyperthermia applicator and patient support.

Results: More filtering between the hyperthermia system and the receiver of modern MRI systems is needed to get undisturbed MR images for MR thermometry. The reduced image quality caused by the mismatch of the body coil is still sufficient for MR thermometry. The position of the fat references of the hyperthermia applicator inside the 50 cm FOV allow drift correction of the B0 field. The use of specialized dock-able carts for the hyperthermia systems reduce the space needed inside the MRI examination room and facilitate a quick change between hyperthermia and diagnostic use.

Conclusion: MR thermometry is possible with state-of-the-art 1.5 T MR scanners. Further improvements of the image quality could be achieved by integrating a MR receiving coil in the hyperthermia applicator.

THUR 30

FEASIBILITY OF HEATING BRAIN TUMORS USING A 915 MHZ ANNULAR PHASED ARRAY WITH 72 DIPOLE ANTENNAS IN A 3-RING CONFIGURATION

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Background: Hyperthermia at temperatures from 40-45°C is known to improve the radiation response of tumor cells, including in brain tumors. However, current strategies to heat deep-seated targets in brain are primarily invasive and existing deep HT applicators do not have appropriate frequency, geometry, and number of sources to focus at depth. This study evaluates the feasibility of heating brain tumors using a novel 915 MHz annular phased array with 72 dipole antennas in a 3-ring configuration.

Methods: The proposed applicator consists of 3 rings of 24 water-coupled dipole antennas ($30\times5mm^2$) enclosed in a cylindrical frame with 22 or 26cm (diameter) and 13cm (length). We used a multiphysics software that couples electromagnetic, thermal, and fluid dynamics physics to simulate heating patterns in brain, including natural convection induced in the cerebrospinal fluid (CSF). Simulations were performed in a multilayer anatomical head model. The antenna focus was characterized in terms of 50% SAR isovolume. The 3D steering was implemented using phase path difference methods. Tumor targets were inserted into the model with 2-5cm diameter and variable blood perfusion, including a necrotic core and a surrounding rim of high-perfused tissue. Tissue properties were based on the IT'IS Database V3.1 with added temperature dependent blood perfusion that increases 1.5 (2.5)-fold at 45°C in the tumor (healthy brain) tissues.

Results: The larger array diameter (26cm vs 22cm) generates a more focused SAR profile with ellipsoid shape ($4\times2\times2cm^3$ vs $5\times2\times2cm^3$) while reducing superficial power deposition by 60-70%. Power deposition is enhanced near larger pockets of CSF, though natural convection diffuses the extra heating. The focal volume can be centered anywhere within the skull and shifted laterally to cover larger tumor volumes. Heating of realistic tumor models with necrotic centers to a minimum of 40°C is demonstrated for practical tumor perfusion cases, while sparing surrounding well-perfused healthy tissues.

Conclusion and future directions: Feasibility of heating realistic brain tumors with necrotic cores to 40-45°C with a 72-antenna phased array is demonstrated with numerical simulations. Ongoing studies indicate the ability to group antennas so that only 8-12 amplifiers are required to make the antenna array construction feasible.

THUR 31

CONVERGENT TOXICITY OF HYPERTHERMIC AND OSMOTIC STRESS SENSITIZES HCC CELLS BY INHIBITION OF HSF1

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Introduction: Susceptibility of cancer cells to hyperthermia induced cell death is determined by a balance between the therma dose and the cytoprotective heat shock response. Orchestrated by a master transcription factor, Heat shock factor 1 (HSF1), heat shock response restores cellular homeostasis by producing inducible heat shock proteins such as HSP70 and HSP27. Therefore, overcoming the heat shock response has become an increasingly important therapeutic strategy in interventional oncology. We previously reported that combining hyperosmolarity and mild hyperthermia with thermochemical ablation was more toxic to HepG2 and Hep3B cells than either treatment alone. In this study, we demonstrate that hyperosmolarity sensitizes human HCC cell lines to hyperthermia induced cell death by inhibiting HSF1.

Methods: Four human hepatocellular carcinoma cell lines, HepG2, Hep3B, SNU398, and SNU449 (all obtained from ATCC) were cultured in a CO2 incubator at 37°C or at 43°C for mild hyperthermia (2 hours). HSF1 inhibitor iHSF1115 was a gift from Dr. Richard Voellmy (HSF Pharmaceuticals SA). 200mM (400mOsm) sodium acetate was added for 2 hours for osmotic stress alone or with concomitant heat shock. Total RNA was recovered by Qiagen total RNA isolation kit and mRNA levels of HSPA1A (HSP70) and HSPB1 (HSP27) (normalized to 18S) were measured by qPCR. Total protein lysates were prepared and protein levels of HSF1, HSF1 S326, HSP60, HSP90, HSP70, and HSP27 were examined by Western blots. The alamar blue assay was employed to evaluate cell viability.

Results: Phosphorylation of HSF1 at S326 increased in all 4 cell lines treated with hyperthermia while the total protein levels of HSF1 remained relatively unchanged. Adding sodium acetate to cells treated with hyperthermia significantly decreased both total and phosphorylated HSF1 protein levels in all 4 cell lines compared to those treated with hyperthermia alone. mRNA levels of two HSF1 target genes, HSPA1A and HSPB1, were also significantly decreased in samples treated with combined stress. Consistently, protein levels of HSP70 and HSP27 were higher in hyperthermia treated cells but unchanged in cells treated with combined stress when compared to no-treatment control. HSP60 and HSP90 proteins levels remained the same in all treatments. An HSF1 inhibitor, iHSF1115, also augmented hyperthermia induced cell death in SNU449 and HepG2 cells.

Conclusions: Preliminary results indicate that hyperosmotic stress compromised the cytoprotective heat shock response by decreasing expression of HSF1 and its downstream target genes.

THUR 32

GALECTIN-1 INHIBITION OVERCOMES ACQUIRED RADIATION AND ASSOCIATED HYPERTHERMIA RESISTANCE IN LUNG CANCER

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Despite being the leading cause of cancer-related deaths worldwide, lung cancer survival rates have been stagnant during the past 30 years. Here we induced radiation resistance in A549 non-small cell lung cancer cell by repeated exposures of clinically relevant fractionated radiation (25 fractions of 2.2 Gy). The newly generated cell line, A549-RR, acquired radiation resistance as defined by increased cell viability, colony formation, and 3D sphere formation after radiation in vitro, as well as reduced tumor growth inhibition by radiation in vivo. Interestingly, A549-RR also developed resistance to hyperthermia alone as determined by clonogenic cell survival (42°C for 60 minutes). However, when cells were exposed to an additional 2 Gy radiation, hyperthermia at 42°C diminished the acquired radiation resistance. Mechanistically, this resistance was mediated through galectin-1 signaling, as pharmacological intervention by galectin-1 inhibitor PTX008 overcame this acquired resistance. Overall these results suggest that radiation resistance can be overcome by concurrent hyperthermia or galectin-1 inhibition and that these interventions might be interconnected.

THUR 33

COMPARING TUMOR RESPONSE TO PHOTON IRRADIATION AND HYPERTHERMIA WITH THAT SEEN FOLLOWING IRRADIATION WITH CARBON IONS ALONE

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Introduction: Combining hyperthermia with protons has been suggested to have the same anti-tumor effect as carbon ions. Our current pre-clinical studies were designed to investigate whether hyperthermia combined with photon irradiation could be just as effective as carbon ions.

Methods: A C3H mammary carcinoma growing in the right rear foot of female CDF1 mice was used in all experiments. Using non-anaesthetised animals, treatments were performed when tumors had reached 200 mm^3 in size. These involved immersing the tumor bearing leg in a water bath maintained either at 25°C for radiation (240 kV X-rays) alone or with heating at 41.5-43°C for 60 minutes. The radiation was applied either in the middle of the heating period (simultaneous treatment), or 4-hours prior to heating (sequential treatment). The percentage of mice showing local tumor control 90 days after treatment with graded radiation doses was recorded and following logit analysis of the radiation dose response curve, the TCD50 value (radiation dose causing tumor control in 50% of mice) was estimated.

Results: Radiation alone resulted in a TCD50 value of 54 Gy. This was decreased by heating, such that the therapeutic enhancement ratios (TER, ratio of TCD50 values for radiation alone to radiation and heat) increased with heating temperature. With a simultaneous treatment, the TER values were calculated to be 1.6, 1.9, 2.4 and 3.5 following heating at temperatures of 41.5, 42.0, 42.5 and 43°C, respectively. For a sequential treatment, these respective heating temperatures resulted in somewhat lower TER values of 1.2, 1.3, 1.5, and 1.8. Carbon ions in the same tumor model has previously been reported by us to produce a TCD50 value that was 1.5 times lower than that seen with photons (Sørensen et al., Acta Oncol., 2015;54:1623-30).

Conclusions: Photons and hyperthermia can induce the same local tumor control as carbon ions, but the temperature at which this equivalent response occurs depends on the radiation and heat sequencing. For a truly simultaneous treatment, one only needs a mild hyperthermia temperature of 41.5°C, but in a sequential schedule, temperatures at 42.5°C and above are required.

Supported by grants from the Danish Cancer Society and the Danish Council for Independent Research: Medical Sciences.

THUR 34

HYPERTHERMIA-MEDIATED DRUG DELIVERY INDUCES BIOLOGICAL EFFECTS AT THE TUMOR AND MOLECULAR LEVELS THAT IMPROVE CISPLATIN EFFICACY IN TRIPLE NEGATIVE BREAST CANCER

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Introduction: Triple negative breast cancer is an aggressive disease that accounts for at least 15% of breast cancer diagnoses, and a disproportionately high percentage of breast cancer related morbidity. Intensive research efforts are focused on the development of more efficacious treatments for this disease, for which therapeutic options remain limited. The high incidence of mutations in key DNA repair pathways in triple negative breast cancer results in increased sensitivity to DNA damaging agents, such as platinum-based chemotherapies. Hyperthermia has been successfully used in breast cancer treatment to sensitize tumors to radiation therapy and chemotherapy. It has also been used as a mechanism to trigger drug release from thermosensitive liposomes.

Methods: In this study, mild hyperthermia is used to trigger release of cisplatin from thermosensitive liposomes in the vasculature of human triple negative breast cancer tumors implanted orthotopically in mice. The *in vitro* sensitivity of the cell lines to cisplatin and hyperthermia alone and in combination was characterized extensively using enzymatic assays, clonogenic assays, and spheroid growth assays. Relative expression of several heat shock proteins and the DNA damage repair protein BRCA1 were assayed at baseline and in response to hyperthermia both *in vitro* and *in vivo*.

Results: The heat-triggered liposomal formulation of cisplatin resulted in significantly delayed tumor growth and improved overall survival compared to treatment with either non-thermosensitive liposomes containing cisplatin or free cisplatin, as was observed in two independent tumor models (i.e. MDA-MB-231 and MDA-MB-436). Heat-triggered drug delivery significantly increased drug concentrations within the tumor, while hyperthermia was also able to degrade BRCA1 and increase CDDP sensitivity. Evaluation of correlations between the *in vitro* and *in vivo* results served to identify the *in vitro* approach that is most predictive of the effects of hyperthermia *in vivo*.

Conclusion: Interestingly, delivery of cisplatin in thermosensitive liposomes in combination with hyperthermia resulted in the most significant tumor growth delay, relative to free cisplatin, in the less cisplatin-sensitive cell line (i.e. MDA-MB-231). This work demonstrates that thermosensitive cisplatin liposomes used in combination with hyperthermia offer a novel method for effective treatment of triple negative breast cancer.

THUR 35

BREAST CANCER TREATMENT IN BALB/C MICE WITH MAGNETIC FLUID HYPERTHERMIA AND ITS MOLECULAR MECHANISMS

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Introduction

Magnetic fluid hyperthermia (MFH) is a promising method in cancer therapy using magnetic nanoparticles (NPs) which can generate heat during exposure to an alternating magnetic field (AMF). In this study, we assessed the effect of MFH on mechanisms of apoptosis in the murine cell line (MC4-L2) and the treatment of breast tumor in BALB/c mice using four generation dendrimer coated iron oxide nanoparticles (G4@IONPs).

Method and material

Immediately after MFH, the viability of cells was assessed in all groups (MFH+NPs, only MFH, only NPs, control) by MTT assay. In order to determine the number of apoptosis and mRNA copies for Bax and Bcl-2 in the cells after MFH, TUNEL assay and RT-PCR were performed, respectively. 1 × 106 MC4-L2 cells were subcutaneously injected in the right inguinal flank of the female mice. The mice (tumor volume > 50 mm3) were exposed to an AMF (12 kA/m, 300 kHz) three times during twenty minutes after intertumoral injection of 5mg G4@IONPs. The temperature of tumor and mice body was monitored via an infrared thermometer (FLIR Systems). Tumor volume was measured during 28 days after MFH. Histopathology, Immunohistochemical staining, TUNEL and caspase assays were performed in the liver and tumor tissues.

Results

Cell viability percentage only in the group of MFH+NPs decreased significantly. The number of apoptotic cells and Bax/Bcl-2 ratio in MFH+NPs increased significantly. MFH led to significantly reduce the tumor volume 28 days after the treatment compared with that in control mice (saline injection without MFH). Tissue destruction obviously was seen in tumor histopathology of treated mice. CD31 and CD34 as angiogenesis markers decreased in treated tumors without any change in the liver. Apoptosis significantly increased in treated tumor tissues based on TUNEL and caspase-3 activity.

Discussion

Apoptosis is a genetically programmed process for the elimination of damaged or redundant cells. Based on our results, MFH could activate both intrinsic (Bax/Bcl-2) and extrinsic (caspases-3) pathways of apoptosis in breast cancer cells and tumor. MFH can be considered as an anti-angiogenesis treatment for breast cancer because of decreasing the CD31 and CD34. All adverse effects were only seen in the treated tumors, not healthy tissues, which represented an acceptable localized treatment. More research is needed to assess MFH with an anticancer drug-loaded G4@IONPs for a multimodality treatment of breast cancer.

THUR 36

COMBINED MILD HYPEROSMOTIC AND HYPERTHERMAL STRESSES OVERCOME THE CELL SURVIVAL MECHANISMS OF MULTIPLE HUMAN HEPATOCELLULAR CANCER CELL LINES

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Abstract

Purpose: Thermochemical Ablation (TCA) is a multiplexed, minimally-invasive, image-guided method of tissue ablation. TCA is based on the local application of exothermic acid/base neutralization reactions that cause tumor tissue destruction.

Other tumor ablation methods such as radiofrequency ablation (RFA) or cryoablation are frequently incomplete and tumor recurrence is quite common. It is thus plausible that at the margins of a TCA-treated lesion, the concentration of salt would be low, and the hyperthermia would be both mild and relatively short compared to the core of the lesion, potentially allowing for tumor recurrence to occur. Here, we assessed the effects of mild hyperosmotic and hyperthermic stresses on various hepatocellular cancer (HCC) cell lines in vitro.

Materials and Methods: Viability of human HCC cell lines, specifically Hep3B, HepG2, SNU449, and SNU398 was assessed after in vitro exposure to increasing concentrations of sodium acetate –NaOAc–, and Sodium Chloride –NaCl– (0-400mM) for 24h at 37C. A subset of cells was also exposed to hyperosmotic conditions concurrently with a sublethal heat shock of 43C for 3h at the beginning of the treatment.

Results: The magnitude of the effect of individual and combined stresses on cell viability varied significantly among all the lines tested. We found that in HepG2 and Hep3B cells without thermal stress, NaCl induces a greater loss of viability than NaOAc at concentrations >100mM. In contrast, the effect of both salts on SNU449 and SNU398 was quite comparable. Additionally, the response to thermal stress alone was mild in Hep3B and SNU449 cells while it was very robust in HepG2 and SNU398, whose viability after the heat shock alone decreased to <20%. Importantly, all 4 cells were very sensitive to the combined stresses, and a potent additive effect was particularly evident for the combination of NaCl (>100mM) and heat.

Conclusion: Simultaneous thermal and osmotic stresses show evidence of an additive effect on liver cancer, and the magnitude of the effect is likely to be determined by the genomic landscape of the tumor cells and their microenvironment. Our results suggest that the marginal zone of a TCA-treated tumor should display significant signs of cytotoxicity, and thus TCA may prove effective in reducing the incidence of local recurrences rates in HCC.

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