ASP 2021 Symposium

June 8, 2021 • 11:00 am - 5:00 pm Eastern Time

A Celebration of Theresa Busch's 20th Anniversary at the University of Pennsylvania

CONFERENCE PROGRAM

SCHEDULE-AT-A-GLANCE

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June 8, 2021 • 11:00 am - 5:00 pm EST

Time (EST)	Session
11:00 am – 11:05 am	Alec Greer (CUNY) - Introduction
11:05 am – 11:10 am	Costas Koumenis (Vice Chair of Research and Director of the Research Division, Radiation Oncology, University of Pennsylvania)
11:10 am – 11:30 am	Sandra Gollnick (Roswell Park) - PDT and Tumor Immunity
11:30 am – 11:50 am	Bin Chen (University of the Sciences) - Targeting ABCG2 to enhance 5-aminolevulinic acid (ALA) for tumor imaging and therapy
11:50 am – 12:10 pm	Timothy Zhu (University of Pennsylvania) - Light dosimetry for pleural PDT using a real-time navigation system
12:10 pm - 12:20 pm	**Break**
12:20 pm – 12:40 pm	Tayyaba Hasan (MGH and Harvard University) - Dramatic Reduction of distant pancreatic metastases in immunodeficient mice using local PDT with nab-paclitaxel
12:40 pm – 1:00 pm	Sherri McFarland (University of Texas at Arlington) - Metallodrug photosensitizers for photodynamic therapy
1:00 pm – 1:50 pm	**Lunch break**
1:50 pm - 2:10 pm	Jonathan Celli (University of Massachusetts, Boston) - Modeling tumor-microenvironment interactions in pancreatic cancer for development of biophysics-informed photomedicine strategies
2:10 pm - 2:30 pm	Huang-Chiao Huang (University of Maryland) - Photodynamic Modulation of Bidirectional Drug Transport Across the Blood-Brain Barrier
2:30 pm - 2:50 pm	Srivalleesha Mallidi (Tufts University) - Functional and molecular photoacoustic Imaging guided photodynamic therapy
2:50 pm - 3:10 pm	Imran Rizvi (University of North Carolina) - Flow-Induced Carboplatin Resistance in a 3D Model for Ovarian Cancer: Targeted PDT and Combinations
3:10 pm - 3:30 pm	Gal Shafirstein (Roswell Park) - Light Dosimetry Guided Interstitial PDT for Locally Advanced Cancer
3:30 pm - 3:40 pm	**Tea break**
3:40 pm - 4:00 pm	Bryan Q. Spring (Northeastern University) - Development of multiplexed microendoscopy to guide precision cancer medicine
4:00 pm - 4:20 pm	Keith Cengel (University of Pennsylvania) -
4:20 pm - 4:40 pm	Yi Hong Ong (University of Pennsylvania) - Blood Flow-Informed Photodynamic Therapy (BFI-PDT) Improves Therapeutic Efficacy
4:40 pm - 4:50 pm	Gwendolyn Cramer (University of Pennsylvania) - Surgery for mesothelioma induces immunosuppression that limits photodynamic therapy efficacy
4:50 pm - 5:00 pm	Theresa Busch (University of Pennsylvania) - Try, Try Again and other lessons on scientific research from A. A. Milne's Hundred Acre Wood

ABSTRACTS

PDT and Tumor Immunity

Sandra Gollnick, Riddhi Falk-Mahapatra, Kimberly Ramsey
PDT Center, Roswell Park Comprehensive Cancer Center

Over the last decades the interest in PDT as an enhancer of anti-tumor immunity and our understanding of the mechanisms by which PDT enhances anti-tumor immunity have dramatically increased. In this talk, we will look back on the studies that laid the foundation for our understanding of how PDT enhances anti-tumor immunity, the limitations of PDT as an adjuvant and provide an update on current advances and therapies that take advantage of PDT enhancement of immunity.

Targeting ABCG2 to enhance 5-aminolevulinic acid (ALA) for tumor imaging and therapy

Bin Chen
University of the Sciences

Aminolevulinic acid (ALA) is a prodrug that is converted in the heme biosynthesis pathway to protoporphyrin IX (PpIX) for photodynamic therapy (PDT) and fluorescence-guided tumor detection and resection. Although ALA has been approved for the treatment of skin lesions and guiding surgical resection of gliomas, clinical outcomes of ALA applications are not satisfactory due to issues such as low tumor PpIX production, high PpIX fluorescence heterogeneity, and low tumor to normal fluorescence contrast. As the substrate of ABCG2 transporters, PpIX fluorescence in tumor cells is highly dependent on ABCG2 expression and activity in tumor cells. Pharmacological inhibition of ABCG2 activity has been shown to enhance ALA-PpIX fluorescence in tumor cells, representing a promising therapeutic enhancement strategy for the use of ALA for tumor imaging and targeting. Particularly, we showed that some FDA-approved small molecule kinase inhibitors significantly increased ALA-PpIX fluorescence and PDT response in both tumor cells and animal tumor models. These clinically used kinase inhibitors maybe used for enhancing 5-aminolevulinic acid (ALA) for tumor imaging and therapy by inhibiting ABCG2 activity.

Light dosimetry for pleural PDT using a real-time navigation system

Timothy Zhu
University of Pennsylvania

Uniform light fluence distribution for patients undergoing photodynamic therapy (PDT) is critical to ensure predictable PDT outcomes. However, current practice when delivering intrapleural PDT uses a point source to deliver light that is monitored by multiple isotropic detectors placed within the pleural cavity to assess its uniformity. We have developed a real-time infrared (IR) tracking camera to follow the movement of the light point source and the surface contour of the treatment area. The calculated light fluence rates were matched with isotropic detectors using a two-correction factor method and an empirical model that includes both direct and scattered light components. Our clinical trial in HPPH- and Photofrin- mediated pleural PDT demonstrated that it is feasible to use an IR camera-based system to track the motion of the light source during PDT and its use to quantify the uniformity of light distribution, which deviated by a standard deviation of 18% and 10%, respectively, from the prescribed light dose. The tracking wand design was improved for Photofrin, which happened after the HPPH.

Dramatic Reduction of distant pancreatic metastases in immunodeficient mice using local PDT with nab-paclitaxel

Mike Pigula, Zhiming Mai, Sriram Anbil, M. Myung-Gyu Choi, Tayyaba Hasan
Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, St Mary's Hospital, Catholic University Seoul

Despite advances in drug development, pancreatic adenocarcinoma (PDAC) remains a stubbornly difficult disease to treat. Surgical resection, the only potentially curative option, is suitable for only 20% of the patients diagnosed with this disease. Unfortunately, 80% of patients are ineligible for surgery due to the presence of distant metastases at the time of diagnosis. For these patients, only systemic chemotherapy options are offered and outcomes of all are dismal. We describe a photodynamic therapy (PDT) based approach that, in combination with the first-line chemotherapeutic nab-paclitaxel, effectively addresses distant metastases in 3 separate orthotopic models of pancreatic cancer. We demonstrate that photodynamic therapy combined with chemotherapy inhibits the eventual development of metastases in models of early stage PDAC, and reduces the burden of already established distant metastases in late stage models of disease while maintaining effective control over primary tumor growth. Our findings suggest that it may be possible to leverage the systemic anti-tumor effects of PDT to treat advanced cancer, and potentially re-classify patients with previously inoperable disease as surgical candidates. Potential mechanisms, in the absence of a robust immune system remains somewhat speculative and will be discussed.

Metallodrug photosensitizers for photodynamic therapy

Sherri McFarland
The University of Texas at Arlington

Modeling tumor-microenvironment interactions in pancreatic cancer for development of biophysics-informed photomedicine strategies

Jonathan Celli
University of Massachusetts Boston

The tumor microenvironment influences disease progression not only through both paracrine crosstalk and biophysical interactions which implicate the altered mechanical microenvironment of solid tumors. This may be particularly relevant to tumors of the pancreas, which are associated with stiff fibrotic stroma that limits drug delivery and plays prominent tumor-promoting roles. Our lab uses in vitro 3D tumor models and patient derived organoids in conjunction with soft condensed matter physics methods that allow us to quantify dynamic changes in extracellular matrix mechanics in relation to phenotypic traits of tumor and stromal, and in response to therapy. Here I will present recent work examining the impact of PDT on the mechanical and transport properties of extracellular matrix in pancreatic 3D tumor-fibroblast co-culture models. We find that pre-treatment with verteporfin-based PDT increases nanoparticle penetration and enhances payload of an RNA-medicine agent delivered via nanocarrier to tumor cells embedded in this model stroma environment. Our results also show that direct photodestruction of tumor-associated fibroblasts also improves tumor response to PDT. More broadly, the methods integrated here comprise a research platform for screening PDT and chemotherapy strategies targeting biophysical tumor-stroma interactions in pancreatic cancer and other solid tumors.

Photodynamic Modulation of Bidirectional Drug Transport Across the Blood-Brain Barrier

Collin Inglut, Barry Liang, Huang-Chiao Huang
University of Maryland College Park, University of Maryland Baltimore

The blood-brain barrier (BBB) is a significant obstacle for drug delivery to brain tumors. The strength of the BBB in protecting brain cancer from exposure to circulating drugs is maintained by not only the intact tight junctions between endothelial cells, but also a broad range of drug efflux transporters on endothelial and cancer cells. We showed that photodynamic priming could break down the barrier to get drugs into brain tumor cells, but also prevent drug efflux mediated by ATP-bind cassette (ABC) transporters. Leveraging nanotechnology and imaging, we unraveled the molecular impact of photodynamic priming on tight junction proteins and ABC efflux transporters in vitro. We also demonstrated that nanotechnology-assisted photodynamic priming improves the selective drug penetration in rat brains, with minimum to no damage in normal tissues. The translational potential and the new nanoplatform developed here will also be discussed in the presentation.

Functional and molecular photoacoustic Imaging guided photodynamic therapy

Srivalleesha Mallidi
Tufts University

For personalizing effective treatment strategies it is paramount to understand the dynamic changes in the microenvironment as the tumor adapts or surrenders to a therapeutic insult. Towards this goal, we present the utility of non-invasive 3D ultrasound guided functional and molecular photoacoustic imaging (PAI) to understand the tumor functional and molecular heterogeneity in addition to predicting local recurrence. Photoacoustic imaging, as a nomenclature suggests, involves generation of acoustic signals by irradiating tissue with nanosecond laser pulses and it offers functional information with high sensitivity on par with optical imaging at deeper penetration depths. In the first part of the talk, I will present utility of PAI for monitoring photodynamic therapy (PDT), a photochemistry-based treatment modality, with 3D atlas of the changes in tumor blood oxygen saturation (endogenous contrast) and its correlation to tumor recurrence. In the second part of the talk, I will present utility of PAI in obtaining molecular maps of cancer biomarkers such as epidermal growth factor receptor (EGFR), with dye-antibody conjugates(exogenous contrast). Finally I will present long term strategy and directions on pushing the envelope of ultrasound-guided PAI as an important preclinical and clinical tool in tumor diagnosis, selection of customized patient-specific treatment, monitoring the therapeutic progression and overall treatment outcome.

Flow-Induced Carboplatin Resistance in a 3D Model for Ovarian Cancer: Targeted PDT and Combinations

Imran Rizvi
The University of North Carolina at Chapel Hill, North Carolina State University

Advanced-stage epithelial ovarian cancer is the leading cause of death from gynecologic malignancies and is most frequently associated with the production of ascites, the abnormal accumulation of fluid due to disease or abnormal pathology. Increasing evidence suggests that ascites promotes disease progression, facilitates the spread of tumor cells, and portends the poorest outcomes. An understudied area remains understanding the impact of physical stress (e.g. due to fluid flow) on treatment failure. Recent findings on flow-induced shear stress and resistance to platinum-based chemotherapy in 3D models for ovarian cancer will be presented. The role of targeted photodynamic therapy (PDT) and PDT-based combinations will be discussed.

Light Dosimetry Guided Interstitial PDT for Locally Advanced Cancer

Gal Shafirstein
Roswell Park

Development of multiplexed microendoscopy to guide precision cancer medicine

Bryan Spring
Northeastern University

This talk will introduce multiplexed, video fluorescence microendoscopy to guide targeted therapies by imaging tumor spatial heterogeneity and the tumor immune microenvironment within surgical margins.

Blood Flow-Informed Photodynamic Therapy (BFI-PDT) Improves Therapeutic Efficacy

Yi Hong Ong, Joann Mille, Min Yuan, Malavika Chandra, Mirna El Khatib, Sergei A. Vinogradov, Mary E. Putt, Timothy C. Zhu, Keith A. Cengel, Arjun G. Yodh, Theresa M. Busch
University of Pennsylvania

PDT is well known to induce fluctuations in tumor blood flow during illumination across various treatment protocols. The extent and time-course of PDT-induced vascular damage can critically impact therapeutic effect. Functional deterioration of tumor blood vessels after light delivery is favorable as it deprives remaining tumor cells of oxygen and nutrients. Conversely, therapeutic effects can be compromised when vascular damage manifests as temporary ischemia during light delivery. Under these circumstances, a resultant decrease in oxygen supply during PDT can reduce reactive oxygen species generation and limit cell kill.

In this study, we demonstrated a novel blood-flow-informed PDT (BFI-PDT) platform that aims to conserve tumor perfusion during PDT. BFI-PDT modulates tumor blood flow during illumination by dynamically adjusting the choice of irradiance based on real-time measurement of PDT-induced vascular response. In preclinical murine models, BFI modulation of light delivery improves PDT efficacy compared to standard treatment with continuous high irradiance, while limiting treatment times to less than those needed for continuous illumination at low irradiance. This contribution introduces BFI-PDT as a platform for personalized light delivery in PDT, documents the design of a clinically-relevant instrument, and establishes the benefits of BFI-PDT with respect to treatment outcome and duration.

Surgery for mesothelioma induces immunosuppression that limits photodynamic therapy efficacy

Gwendolyn M. Cramer, Richard W. Davis IV, Astero Klampatsa, Shirron Carter, Joann Miller, Keith A. Cengel, Theresa M. Busch
Perelman School of Medicine, University of Pennsylvania

Lung-sparing radical pleurectomy with intraoperative photodynamic therapy (PDT) promisingly extends survival for patients with malignant pleural mesothelioma (MPM). Nevertheless, most patients treated with this multimodal approach go on to develop local tumor recurrence, so it is crucial to determine potential mechanisms that prompt treatment failure and identify mitigation strategies. Surgery in the absence of PDT is known to induce inflammation, and we have seen in our preclinical models of murine MPM treated with simulated surgery (tumor injury without cytoreduction) followed by Photofrin-PDT that surgery diminishes the curative potential of PDT. To further explore the mechanisms by which surgically induced inflammation might diminish PDT efficacy, we have used these murine MPM tumor injury/PDT models to determine key leukocyte players in the development of local tumor response and establishment of long-term systemic tumor control. Using flow cytometry-based immunophenotyping and functional studies focusing on myeloid-derived suppressor cells and T cells, we have found distinct patterns of innate and adaptive inflammatory cells in tumors, tumor draining lymph nodes, and spleens of MPM tumor bearing animals. Overall, these studies suggest that surgically mediated modulation of immune cell trafficking and functionality prior to PDT leads to a systemic suppression of PDT-induced anti-tumor immune response. Targeted inhibition of these molecular or cellular signals of surgically induced inflammation can potentially restore PDT efficacy in the intraoperative setting.

Try, Try Again and other lessons on scientific research from A. A. Milne's Hundred Acre Wood

Theresa Busch
University of Pennsylvania

Hundred Acre Wood, the creation of famous children's book author A.A. Milne, was home to numerous mantras for mindfulness such as "think, think, think" and "they always take longer than you think" that are readily applied to the trials and tribulations of a career in scientific research and the experiments that build its body of knowledge. In my travels along varied paths of scientific inquiry that transverse the Wood of my academic career, the forks and branches of these roads have often converged on a few thematic clearings of research focus. Among these clearings, our investigations of dose rate in radiotherapy sit at the intersection of both intentionally laid trails and meandering footpaths that weave their way through studies of the therapeutic and mechanistic benefits of low fluence rate in photodynamic therapy of tumors to our more recent inquiries into the normal tissue sparing high dose rate of FLASH radiotherapy. Taking our work in radiotherapy dose rate as an example, I seek to recognize the value of committed mentors, enthusiastic collaborators and good friends in the ongoing maturation of our research. These individuals respond to the query in the Wood - " Do you think you could very kindly lean against me, 'cos I keep pulling so hard that I fall over backwards." To all participating in this symposium, I genuinely extend "thanks for noticing me" and look forward to continuing and new collaborations that forge paths forward in the science that defines our Wood.