AGENDA

Abstracts can be found starting on page 8

ACPHS 8th Annual Research Forum
https://www.acphs.edu/academics/research

Saturday, January 27, 2018

Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208
Gozzo Student Center, Room 201 (broadcast to ACPHS Vermont Campus Room 310)

This is a free 1-day conference, breakfast and lunch included.

This annual conference provides an update on scientific developments on the ACPHS campus and, through invited conference speakers from outside of ACPS, relates these reports to the national context in which pharmaceutical research is proceeding.

8:00 – 8:30
Continental Breakfast
Rite Aid Lounge

8:30 – 8:40
Perspectives on Research at ACPHS

Greg Dewey, PhD, ACPHS President

8:40 – 9:30
Keynote Speaker
“The Business of Science”

Jonathan G. Lasch, PhD
Executive Director
Alfred E. Mann Institute for Biomedical Engineering
University of Southern California, Los Angeles, CA

9:30 – 9:45
Safety First

Shannon R. Magari, ScD, MS, MPH
Colden Corporation, Ballston Lake, NY
AGENDA

9:45 – 10:00  Recognition of Faculty and Staff Services to Office of Research and Scholarly Activity

Shaker A. Mousa, PhD, MBA
ACPHS Vice Provost of Research and Professor, Dept. of Pharmaceutical Sciences
Executive VP and Chairman, Pharmaceutical Research Institute

10:00 – 10:15  ACPHS Chapter of the American Association of Pharmaceutical Scientists (AAPS)

Alexa Hodges, B.S. Class of 2019  President
Chiara Evans, B.S./M.S. Class of 2018  Past-President

10:15 – 11:00  Panel Discussion, “Hematology / Oncology”

Moderator: Shaker A. Mousa

“We have discovered that histone recognition by the ATAD2 bromodomain is modulated by formation of a disulfide bridge: How can disulfide bridge formation be regulated in the nucleus, and throughout the cell cycle?”
Karen Glass, PhD, Associate Professor, ACPHS

“Bladder cancer: Are checkpoint inhibitors the best we can do?”
Badar Mian, MD, AMC Division of Urology, Albany Medical College

“Forget about Opdivo® and Keytruda®—let’s attack immune checkpoints pharmacologically in cancer”
Paul J. Davis, MD, PRI at ACPHS, Dept. of Medicine, Albany Medical College

“Does the discovery & development of PROTACs represent a paradigm shift?”
James M. Gallo, PhD, Professor, ACPHS
AGENDA

11:00 – 11:45  POSTER VIEWING & Networking (list of posters is at the end of this Agenda)
Poster presenters please stand by your poster.
Coffee available in Rite Aid Lounge.

11:45 – 12:35  Keynote Speaker
“7 Reasons to Consider a Career in Industry”

Samantha Schwall, PharmD, RPh
Director, Program and Field Service Operations - Americas
Laerdal Medical, Wappingers Falls, NY

12:40 – 1:45  LUNCH and POSTER VIEWING
Lunch served in Cronin Lounge, 1st floor.

1:45 – 2:30  Infectious Disease Session

Moderator: Meenakshi Malik, DVM, PhD
Associate Professor, Basic and Clinical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

“Vibrio parahaemolyticus Infection: Development of a Novel In vivo Model to Understand the Host-Pathogen Interaction”
Michelle Parent, PhD
Associate Professor, Basic and Clinical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

“Understanding Nrf2 Mediated Restriction of HIV Infection”
John Sharifi, PhD
Assistant Professor, Basic and Clinical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

“Regional Antiibiograms”
Colleen McLaughlin, PhD
Associate Professor, Population Health Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY
AGENDA


Moderator: Tarun Patel, PhD
ACPHS Provost and Vice President of Academic Affairs

“Crosstalk Between Stromal Components and Tumor Cells of TNBC via Secreted Factors Enhances Tumor Growth and Metastasis”
Kideok Jin, PhD
Assistant Professor, Department of Pharmaceutical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

“Irish/American Relations: The American Sailors and the Irish in World War I: Relationships Between the Sailors at the United States Lough Foyle Naval Air Station and the Neighboring Irish in Derry and Donegal”
Margaret Lasch Carroll, PhD
Associate Professor, Department of Humanities and Communication
Albany College of Pharmacy and Health Sciences, Albany, NY

“Phenotypic Screening for Imaging Agents to Assess Chemoresistance of Different Tumors”
Bruce Hay, PhD
Associate Director of Medicinal Chemistry, Pharmaceutical Research Institute
Albany College of Pharmacy and Health Sciences, Albany, NY

“Mass Spectrometry-based Proteomics Resource at ACPHS”
Stanley M. Stevens, Jr., PhD
Associate Professor, Department of Pharmaceutical Sciences
Albany College of Pharmacy and Health Sciences, Colchester, VT

3:15 – 3:30  “Pharmaceutical Industry Team Presentation, Codeine/Gabadine (Nomobuse)”
Nicolas James, Dmitri Aldershoff, Victoria Evolo, Florian Heukensfeldt-Jansen, Mit Gandhi
Albany College of Pharmacy and Health Sciences
Presented by students who completed the ACPHS PHM 324 Pharmaceutical Industry and the Pharmacist’s Role course in Fall 2017—an overview of the pharmaceutical industry that covered: research, development, medical, regulatory, marketing, sales, distribution, legal, ethics and compliance. The course was team-taught by pharmaceutical industry experts.

3:30 – 3:35  Announcement of the 2017 Researcher of the Year

3:35 – 3:45  Closing Remarks
ACPHS President Greg Dewey / ACPHS Vice Provost of Research Shaker A. Mousa
Poster Session

Pharmacotherapy

1. Synthesis of Novel RPE65 Inhibitors for the Treatment of Age-Related Macular Degeneration and Stargardt’s Disease Christopher L. Cioffi, Muthuraman Parthasarathy, Albany College of Pharmacy and Health Sciences, Albany, NY

2. Attitudes and Perceptions Towards Pharmacogenomics Education and Relevance in Pharmacy Practice in Class of 2017 Pharmacy Students in New York and New Jersey Shanice Coriolan, Nimota Arikawe, Arden Moscati, Lisheng Zhou, Stephanie Dym, Seda Donmez, Adinoyi Garba, Sasha Falbaum, Zvi Loewy, Melinda Lull, Maha Saad, Jayne Shtaynberg, Aniwaa Owusu Obeng, Albany College of Pharmacy and Health Sciences, Albany, NY, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, Touro College of Pharmacy, New York, NY, St. John Fisher College, Rochester, NY, D’Youville College School of Pharmacy, Buffalo, NY, Fairleigh Dickinson University, Florham Park, NJ, St. John’s University, Queens, NY, LIU Brooklyn Arnold & Marie Schwartz College of Pharmacy, Brooklyn, NY

3. Medicalization and the Physician: Shaping Identity and Clinical Autonomy Barry DeCoster, Priscilla Hall, Albany College of Pharmacy and Health Sciences, Albany, NY

4. Quality Assessment of Expired Naloxone Products from First-Responders’ Supplies Justin Frey, Schuyler Pruyn, Michael Brodeur, Benjamin Baker, Carla Graichen, Michael Dailey, HaiAn Zheng, Albany College of Pharmacy and Health Sciences, Albany, NY, Albany Medical Center, Albany, NY

-Poster #5 has been withdrawn-

6. Assessment of Time to Clinical Response in Patients with Sepsis Treated Before and After Implementation of a Twice-Daily Blood Culture Follow-up Program Joseph J. Carreno, Rachael Eaton, Faith Babowicz, Katie Toti, Gianna Vitale, Jane Falvo, Ellis Tobin, Ben Lomaestro, Mary George, Albany College of Pharmacy and Health Sciences, Albany, NY, Albany Medical Center Hospital, Albany, NY, Upstate Infectious Diseases Associates, Albany, NY

Molecular Mechanism

7. Disulfide Bridge Formation Contributes to Histone Ligand Recognition by the ATAD2 Bromodomain Chiara Evans, Jamie Gay, Brian E. Eckenroth, Samuel Carlson, Jonathan T. Lloyd, Karen C. Glass, Albany College of Pharmacy and Health Sciences, Colchester, VT, University of Vermont, Burlington, VT

8. Molecular Mechanism of Di-acetyllysine Recognition by the ATAD2B Bromodomain Jonathan T. Lloyd, Jamie C. Gay, Brian E. Eckenroth, Marco Tonelli, Gabriel Cornilesescu, Paul Nguyen, Samuel Carlson, John L. Markley, Karen C. Glass, Albany College of Pharmacy and Health Sciences, Colchester, VT, University of Vermont, Burlington, VT, University of Wisconsin-Madison, Madison, WI

9. Ricin Mediated Programmed Cell Death Cody Kempen, Alexa Hodges, Timothy LaRocca, Albany College of Pharmacy and Health Sciences, Albany, NY
10. Hyperglycemia Potentiates a Shift from Apoptosis to RIP1-dependent Necroptosis  

Payal S. Patel, 1William D. McCaig, 2Nicole L. Shakerley, 2Sergey A. Sosunov, 1Tori A. Smiraglia, 1Matthew A. Deragon, 1Miranda Craft, 1Katharine M. Walker, 1Vadim S. Ten, 1Timothy J. LaRocca, 1Albany College of Pharmacy and Health Sciences, Albany, NY, 2Columbia University, New York, NY

11. Allosteric Activation of Human SIRT6  

Stacia Rymarchyk, Steven Kisaka, Lawrence Urman, Ryan Ayres, Yana Cen, Albany College of Pharmacy and Health Sciences, Colchester, VT

12. Regulation of Mouse Mammary 419II Cancer Stem Cell Proliferation by Bmi-1 and Nanog  

Kayla Stuart, Katherine Sfoglia, Jeffrey Voigt, Albany College of Pharmacy and Health Sciences, Albany, NY

13. Identification and Characterization of Nucleobase Transporters  

Ai Tran, 2Roger Shek, 1Ryota Yokose, 1Marci Wood, 2Jarrod French, 1Yana Cen, 1Albany College of Pharmacy and Health Sciences, Colchester, VT, 2Stony Brook University, Stony Brook, NY

14. Synthesis of Cyclooctyne Containing Probes for Labeling Sirtuins  

Song Zheng, Yana Cen, Albany College of Pharmacy and Health Sciences, Colchester, VT

Infectious Diseases

15. Genetic Basis for Daptomycin Resistance in Methicillin Resistant Staphylococcus aureus  

Jackson Lu, 1Zhuo Ma, 2Ryan Schneider, 1Vincenzo Russo, 2Janice Pata, 2Erica Lasek-Nesselquist, 2Kathleen McDonough, 1Meenakshi Malik, 1Albany College of Pharmacy and Health Sciences, Albany, NY, 2Wadsworth Center, New York State Department of Health, Albany, NY

16. Regulatory Role(s) of ppGpp in Oxidative Stress Response of Francisella tularensis  

Zhuo Ma, 1Madeline Worden, 1Kayla King, 2Chandra Shekhar Bakshi, 1Meenakshi Malik, 1Albany College of Pharmacy and Health Sciences, Albany, NY, 2New York Medical College, Valhalla, NY

17. Structural and Computational Insights into Single Nucleotide Polymorphisms in Cytochrome P450 2C9  

Keiko Maekawa, 2Motoyasu Adachi, 2Yumiko Matsuzawa, 4Qinghai Zhang, 3Ryota Kuroki, 2Yoshiro Saito, 6Manish B. Shah, 1Doshisha Women’s College of Liberal Arts, Kyoto, Japan, 2National Institute for Quantum and Radiological Science and Technology, Ibaraki, Japan, 4The Scripps Research Institute, La Jolla, CA, 5Japan Atomic Energy Agency, Ibaraki, Japan, 6Albany College of Pharmacy and Health Sciences, Albany, NY

18. Role for Host Glycosphingolipid Biosynthesis on the Infectivity of Human Enveloped RNA Viruses  

Simon Ogbamikael, 2Clare Williams, 2Hiram Adames, 2Kouacou Konan, 1Dennis Metzger, 2Eric J Yager, 1Albany Medical College, Albany, NY, 2Albany College of Pharmacy and Health Sciences, Albany, NY

19. Inhibition of HIV Early Replication by the p53 and its Downstream Gene p21  

Binshan Shi, 1Hamayun J. Sharifi, 1Sara DiGrigoli, 1Michaela Kinnetz, 1Katie Mellon, 2Wenwei Hu, 3Carlos M. C. de Noronha, 1Albany College of Pharmacy and Health Sciences, Albany, NY, 2Rutgers the State University of New Jersey, New Brunswick, NJ, 3Albany Medical College, Albany, New York, Albany, NY
20. Applications of New Benzylguanidine Derivative/Nanoparticles in the Treatment of Neuroblastoma
Ozlem Ozen Karakus, Mehdi Rajabi, Dhruba J. Bharali, Shaker A. Mousa, Albany College of Pharmacy and Health Sciences, Albany, NY

21. Formulation and Pharmacokinetics of Diaminopropane Tetraiodothyroaceticacid-conjugated Biodegradable Polymeric Nanoparticles and Anti-angiogenesis Efficacy
Weikun Li, Murat Yalcin, Dhruba J. Bharali, Qinshan Lin, Kavitha Godugu, Shaker A. Mousa, Albany College of Pharmacy and Health Sciences, Albany, NY, Uludag University, Bursa, Turkey, Center for Functional Genomics, University at Albany, Rensselaer, NY

22. The Effects of Sulfated Non-Anticoagulant Heparin Compounds on Cancer Associated Thrombosis
Reham Alzanbaqi, William Ayala, Emily Dzek, Shaniqua Headley, Alassane Kano, Albany College of Pharmacy and Health Sciences, Albany, NY

23. Development of Bioanalytical Method for Pharmacokinetics of a Novel Targeted Anticancer Drug in Rats and Monkeys
Kazutoshi Fujioka, Mehdi Rajabi, Weikun Li, Kavitha Godugu, Thangirala Sudha, Shaker A. Mousa, Albany College of Pharmacy and Health Sciences, Albany, NY

24. Novel Nano-Targeting of Thyrointegrin αvβ3 Receptors for the Modulation of αvβ3 Expression in Different Cancer Cells and Tumors
Kavitha Godugu, Thangirala Sudha, Dhruba J. Bharali, Shaker A. Mousa, Albany College of Pharmacy and Health Sciences, Albany, NY

Pharmaceutical Industry and the Pharmacist’s Role Project (Fall 2017 course at ACPHS)
25. Sulfur Hydroxy Acid Patch
Needa Ahmed, Berry Carlos, Catie Canape, Zheng Hao, Azra Perwaz

26. Temobetta in Glioblastoma
Monica Arquette, Scarlett Cameron, Jacqueline Katz, Dorothy Liu, Breanna Pelski

27. Dorsalat QMT (takynumab) Capital District Biologics
Khush Asghar, Ben Bratek, Yeeun Kim, Jacob Leighton, Leonid Perederey

28. Retin-Aide (eyeteplase 0.5 %)
Kaitlyn Duesler, Ciara Baisley, Victoria Fazio, Meghan Sullivan, Stephen Kim

29. Drug Remodel: Bapineuzumab-Immunotherapy for Amyloid Plaque Build Up in Late Onset Alzheimer Patients
Mohammed Iqbal, Lavinia Salama, Maomita Kundu, Brigette Chiou, Michael Gadelkarim

30. Codeine/Gabadine (Nomobuse)
Nicolas James, Dmitri Aldershoff, Victoria Evolo, Florian Heukensfeldt-Jansen, Mit Gandhi

31. Glutenforall and Celiac Disease
Andriy Krasiy, Sankar Shammugam, Kaylee Peck, Hassan Matar, Chinomso Ogbonna

32. Insulora – Oral Insulin
Elizabeth Pastor, Matthew Daley, Richard Rinaldi, Jaehan Kim
Keynote

The Business of Science
Jonathan G. Lasch, PhD
Executive Director
Alfred E. Mann Institute for Biomedical Engineering
University of Southern California, Los Angeles, CA

What are the pathways from the laboratory to the marketplace, and what are investor expectations for new technologies and technology developers? Where does funding come from, what are the criteria for selecting technologies, and what are the requisite skill sets and resources needed for companies and individuals to successfully develop and commercialize life science products? Why do some ideas receive funding, and others do not? And, what roles can technologists play in these efforts?

Keynote

7 Reasons to Consider a Career in Industry
Samantha Schwall, PharmD, RPh
Director, Program and Field Service Operations - Americas
Laerdal Medical
Wappingers Falls, NY

Have you started thinking about your career? A career is defined as an individual's metaphorical "journey" through learning, work and other aspects of life. Careers are about trial and error, about taking risks, perseverance and about taking pride in every step you make. When making your career choice, think big, factor in what you are passionate about, and be certain to consider Industry. The presentation will demystify the word Industry, showcase the many opportunities, and highlight 7 reasons to consider a career in industry. In the end, your career will be your portfolio of experiences, and it is key that you enjoy your journey.
Safety First
Shannon R. Magari, ScD, MS, MPH
Colden Corporation
Ballston Lake, NY

Ensuring the health and safety of all students, faculty and staff at ACPHS is a top priority. Dr. Magari will recap 2017 efforts and outline our 2018 EHS agenda.

American Association of Pharmaceutical Scientists
Alexa Hodges (President), B.S. Class of 2019
Chiara Evans (Past President), B.S./M.S. Class of 2018
Albany College of Pharmacy and Health Sciences, Albany, NY

AAPS leadership will discuss the value of student research alongside their goals for members and the community this year. Achievements from the past year will also be announced.
**Vibrio parahaemolyticus Infection:**
Development of a Novel *in vivo* Model to Understand the Host-Pathogen Interaction

Michelle Parent, PhD
Department of Basic and Clinical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

*Vibrio parahaemolyticus* serovar O3:K6, and similar serovars, are the most common cause of seafood-related illness in the United States. Infections with this isolate, for those with chronic medical conditions can progress to systemic infection leading to death. The FDA estimates 20% of the population to be classified as having chronic-medical conditions however, it is unknown how many of these individuals are at risk of *V. parahaemolyticus* exposure. Additionally, the CDC reports a 35% increase in *V. parahaemolyticus* in 2015 as compared to 1996-1998 surveillance data, with this species accounting for 64% of all culture confirmed Vibrio infections. Moreover, infections with this pathogen are thought to be grossly underreported. *Vibrio parahaemolyticus* is responsible for most Vibrio outbreaks and related illness in the United States. There is a dearth of literature regarding host immunity to infection with this pathogen, with no literature to date characterizing the murine *in vivo* proinflammatory cytokine or T cell response. Toward that end, my laboratory has recently developed an orogastric murine model of infection for *Vibrio parahaemolyticus*. Thus, providing a mechanism by which we are able to study *in vivo* changes in the immunological environment of the gut.
Understanding Nrf2 Mediated Restriction of HIV Infection
H. John Sharifi, PhD
Department of Basic and Clinical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

Understanding the function of cellular antiviral defenses is important for developing approaches to thwart viral diseases. We have recently reported that Sulforaphane (SFN), a natural compound found in cruciferous vegetables, protected primary human macrophages from HIV infection by activating the cellular transcription factor Nrf2. Because Nrf2 promotes the upregulation of several genes, we hypothesized that one or more of those gene-products is responsible for antagonizing HIV infection. Microarray analysis revealed marked upregulation of the Nrf2-responsive gene, xCT, in primary human macrophages treated with SFN. Subsequent experimentation revealed an inverse correlation wherein higher xCT levels was associated with lower HIV infectivity and lower xCT levels with higher HIV infectivity. Currently our work aims to solidify whether xCT is indeed the Nrf2-responsive agent that acts to block HIV infection and, if so, whether xCT is the end point for antagonizing the virus or a player in a chain of events that ultimately lead to HIV inhibition.
Antimicrobial resistance (AMR) is considered one of the most important threats to global public health. Although control and prevention of AMR is complicated, one touted strategy has been Antimicrobial Stewardship Programs (ASP). ASP are coordinated efforts to optimize antimicrobial use through preventing unnecessary use and, when antimicrobials are necessary, ensure the narrowest spectrum is used for the lowest dose and duration needed to treat the specific infection. During initial empiric treatment for a presumptive bacterial infection, choice of initial antibiotic is often dependent upon the population prevalence of resistant organisms, in addition to patient presentation and history. Antibiograms, also known as cumulative antibiotic susceptibility reports, have been shown to be useful tools in guiding empiric therapy in hospital settings, and are one of the core components of ASP. An antibiogram provides targeted quantitative data on the percentage of specimens exhibiting antimicrobial susceptibility for combinations of organisms and antimicrobial agents. Hospitals compile antibiograms from their clinical isolates, and provide summary and interpretive data to clinicians on a routine basis, most often yearly.

Antibiograms are generally not available in non-hospital settings, where lower volume of isolates and less well defined patient populations can complicate the creation and interpretation of cumulative AMR data. Outpatient health care providers, smaller acute care hospitals, and residential health care facilities, however, could benefit from local cumulative AMR data to guide empiric therapy and improve AMR and patient outcomes. Based on the observation that antimicrobial resistance varies by geography, there has been attention to the idea that AMR data collected across different facilities or outpatient settings can be pooled to create regional antibiograms. These antibiograms have been compiled at the state, regional, and community level from metaanalysis of hospital antibiograms or by pooling data from outpatient settings. The available literature, however, is incomplete with respect to many important questions regarding the sustainability and the potential efficacy of pooled antibiograms for either surveillance, treatment assurance, or AMR prevention programs. This formative evaluation of AMR surveillance and dissemination via regional antibiograms shows that outstanding questions include risks and benefits of using hospital data in non-hospital settings, methodology for collecting and pooling data, optimal geographic or population size of regions, need for stratification by patient, facility, or community risk factors, frequency of updates, and resources needed to initiate and to sustain the programs. This review addresses many of these questions through outlining the minimum requirements for an effective regional antibiogram surveillance program with respect to efficacy for empiric treatment and sustainability as a public health surveillance system.
Crosstalk Between Stromal Components and Tumor Cells of TNBC via Secreted Factors Enhances Tumor Growth and Metastasis

Kideok Jin, PhD

All authors: 1Kideok Jin, 2Niranjan B. Pandey, 2Aleksander S. Popel

1Department of Pharmaceutical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY
2Department of Biomedical Engineering
Johns Hopkins University School of Medicine, Baltimore, MD

Triple negative breast cancer (TNBC) as a metastatic disease is currently incurable. Reliable and reproducible methods for testing drugs against metastasis are not available. Stromal cells may play a critical role in tumor progression and metastasis. We have previously presented evidence of the important roles of interleukin-6 (IL-6) and chemokine (C-C motif) ligand 5 (CCL5) in TNBC tumor growth and metastasis involving crosstalk between cancer cells and stromal lymphatic endothelial cells. In this study, using maraviroc (CCR5 inhibitor) and tocilizumab (anti-IL-6 receptor antibody), we confirmed the IL-6 and CCL5 signaling are key pathways to promote TNBC tumor growth and metastasis. In addition, we discovered that fibroblasts and macrophages secreted IL-8 upon induction by co-culture of TNBC cells such as MDA-MB-231, SUM149, and SUM159 cells. Our data showed that the proliferation of TNBC cells co-cultured with fibroblasts or macrophages was enhanced compared to the monoculture. Furthermore, TNBC cell migration, a key step in tumor metastasis, was promoted by co-culture of fibroblasts or macrophages. Knockdown of the IL-8 receptor, CXCR2 by CRISPR-Cas9 reduces MDA-MB-231 cell proliferation and migration compared to wild type (WT). In a mouse xenograft tumor model, the growth of MDA-MB-231-CXCR2-/- tumor was significantly decreased compared to the growth of tumors from WT cells. In addition, the incidence of thoracic metastasis of MDA-MB231-CXCR2-/- tumors was reduced compared to WT. We found that the auto- and paracrine loop exists between TNBC cells and stroma, which results in enhanced IL-8 secretion from the stromal components. Significantly, inhibition of the IL-8 signaling pathway by Reparixin, an inhibitor of the IL-8 receptor, CXCR1/2, reduced MDA-MB-231 tumor growth and metastasis. Taken together, these findings implicate IL-6, IL-8 and CCL5 signaling as critical pathways in TNBC tumor growth and metastasis via crosstalk with stromal components.
Irish/American Relations: The American Sailors and the Irish in World War I: Relationships Between the Sailors at the United States Lough Foyle Naval Air Station and the Neighboring Irish in Derry and Donegal

Margaret Lasch Carroll, PhD
Department of Humanities and Communication
Albany College of Pharmacy and Health Sciences, Albany, NY

The focus of my research is an investigation of the relationships that developed between the American sailors stationed at the Lough Foyle Naval Air Station on the northern coast of Ireland in World War I between 1918 and 1919 and the Irish people with whom the sailors interacted. The sailors often had evenings free to attend events in Derry and other nearby towns, and had weekends off to explore more of Ireland; they thus had ample opportunities to meet the Irish people and establish relationships with those living near the base. Primary sources indicate that the camp also hosted occasional community events on the base for their Irish neighbors.

My presentation will report on the progress made with my research thanks to a Scholarship of Discovery grant giving me travel and lodging for a week each in Ireland and Washington, DC between July 2016 and July 2017. The Irish side of the investigation involved going to Derry and Donegal and meeting historians, librarians, and reporters with connections to the community, and Irish families whose relatives met the sailors and attended the community events on the base. Finding the Irish families was facilitated by posting notices in church and community newsletters, reading local newspapers from 1918 and 1919, talking to community and university historians, and quite literally knocking on doors in the neighborhoods near the Camp. The American side of the investigation involved working with records at the Naval History and Heritage Command and the National Archives in Washington, DC to gather reports on NAS Lough Foyle and to compile a list of sailors stationed at the Camp. The next step on the Irish front is to contact more families in the vicinity of the base, and on the American front, to contact relatives of the sailors and ask for stories, diaries, letters, photographs, and artifacts that were handed down through the generations.

The result will be profiles of both off-duty American military life and Irish social life at an important time in history: for the Americans, a slice of life during World War I; for the Irish, in relative global isolation until World War I, an interaction with the greater world.
Phenotypic Screening for Imaging Agents to Assess Chemoresistance of Different Tumors

Bruce A. Hay, PhD

All authors: Bruce A. Hay, Thangirala Sudha, Noor S. Z. Kotb, Shaker A. Mousa

Pharmaceutical Research Institute
Albany College of Pharmacy and Health Sciences, Rensselaer, NY

The identification of non-invasive methods to determine therapy choices for cancer patients continues to be a major unmet clinical need. Analysis of biopsy samples can yield valuable information, but obtaining the biopsy sample can be challenging or difficult for the patient, and results can be misleading due to heterogeneity of tumor samples. Imaging agents coupled with their designated imaging method, be it magnetic resonance imaging (MRI) or positron emission tomography (PET), can provide valuable information if the imaging agent binds to a substrate that is present in one type of cancer cells but not another. Unfortunately, it is not simple to identify imaging agents, or leads for imaging agents, that are selective for specific cancer cell types. To identify chemical leads for this application would typically involve the big pharma standard targeted screening approach, where specific, relevant proteins are identified, a binding assay or some other screen is constructed, and as many as one million or more compounds are screened for binding to the protein. Hits from the screen are then potentially converted into clinical candidates in an overall process that usually takes several years minimum from identification of the target protein to clinical candidate. We propose a much faster paradigm, a unique phenotypic screening/photoaffinity labelling approach to identify leads for imaging agents that can discriminate between different cell types, in this case chemoresistant and non-chemoresistant breast cancer cells. The first step is to synthesize a library of specially designed compounds, then incubate them in vitro, one at time, with the 2 different cell types. After photolysis, cell lysis, and dye attachment, we effectively have a dye attached to any protein that bound the initial library compound. PAGE analysis can then determine if there are any proteins that are present in one cell type but not the other that also bind any of the specific library compounds. Library compound/protein pairs that are unique to a specific cell type are leads for the development of imaging agents that can identify this particular cell type in vivo. Project strategy and methods, the synthesis of the specialized compound library, and preliminary screening results will be reviewed.
Mass Spectrometry-based Proteomics Resource at ACPHS

Stanley M. Stevens, Jr., PhD

Department of Pharmaceutical Sciences
Albany College of Pharmacy and Health Sciences, Colchester, VT

Mass spectrometry (MS)-based proteomics has become a powerful, unbiased approach to understand the complex molecular mechanisms underlying fundamental biological processes as well as mechanisms associated with the development and progression of human disease. This approach is an integral component of our research program at ACPHS Vermont, where we are investigating epigenetics changes that occur in various cell and tissue types after chronic alcohol abuse. Specifically, we utilize MS to identify and quantify changes in alcohol-induced histone modifications as well as differential protein expression on a global scale in cell culture and animal models of acute and chronic alcohol exposure. In conjunction with bioinformatics, MS-based proteomic data can be used to not only determine novel proteins and/or pathways that are affected due to a specific physiological or pathophysiological state, but can also predict the activity of potential upstream regulators (e.g., transcription factors) and downstream functional outcomes. The results from proteomic and bioinformatic analysis can provide a detailed mechanistic framework for the development of targeted hypotheses for future studies and will be an innovative resource for ACPHS faculty.
Synthesis of Novel RPE65 Inhibitors for the Treatment of Age-Related Macular Degeneration and Stargardt’s Disease

Christopher L. Cioffi and Muthuraman Parthasarathy

Basic and Clinical Sciences & Pharmaceutical Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

Age-related macular degeneration (AMD) is the leading cause of blindness for individuals aged 60 years or older. There are two forms of AMD: dry (atrophic) and wet (neovascular), with the more prevalent dry form accounting for nearly 90% of all diagnosed cases. There is no FDA-approved therapy for the most prevalent dry form of AMD. Histopathologically, dry AMD represents a slowly progressing neurodegenerative disorder in which specialized neurons (rod and cone photoreceptors) die in the central part of the retina called the macula. Age-dependent accumulation of cytotoxic lipofuscin in the RPE matches the age-dependent increase in dry AMD prevalence and thus is frequently cited as one of potential pathogenic factors contributing to the disease progression. Given that cytotoxic bisretinoids are synthesized from visual cycle retinoids as byproducts of the properly functioning visual cycle, partial pharmacological inhibition of the visual cycle was suggested as a treatment strategy for dry AMD. A critical step in the visual cycle is the conversion of all-trans retinyl ester to 11-cis retinol by the enzyme called isomerohydrolase (IMH). RPE65 represents IMH, which produces 11-cis retinol from all-trans retinyl ester in the RPE. The IMH reaction is rate limiting in the visual cycle function thus making RPE65 an important drug target for partial visual cycle inhibition. RPE65 inhibition was shown to reduce bisretinoid formation in the Abca4−/− mouse model of enhanced lipofuscinogenesis. The majority of known RPE65 inhibitors are retinoids, which generally predicts broad specificity and multiple off-target activities in vivo. There is only one reported non-retinoid RPE65 antagonist (emixustat, a putative retinylamine analogue), which underwent clinical evaluation for dry AMD. Due to its suboptimal pharmacokinetic characteristics and off-target retinal toxicity emixustat does not represent an adequate proof-of-principle molecule for testing the hypothesis of clinical efficacy for RPE65 antagonists. Our lab is designing and synthesizing novel RPE65 inhibitors derived from hit compound CU239, which was identified via an in silico virtual screen of 350,000 compounds using a computational dock model derived from crystallographic bovine RPE65 data. We will present in vitro RPE65 inhibition data of our synthesized compounds, which were screened for RPE65 activity and potency using IMH functional assays conducted by our collaborator at Columbia University. The objective of our project is to conduct hit-to-lead optimization in the structural series exemplified by CU239, with the overall goal of defining the optimized analogs capable of advancing to the IND-enabling studies in the future.
Attitudes and Perceptions Towards Pharmacogenomics Education and Relevance in Pharmacy Practice in Class of 2017 Pharmacy Students in New York and New Jersey

Shanice Coriolan, Nimota Arikawe, Arden Moscati, Lisheng Zhou, Stephanie Dym, Seda Donmez, Adinoyi Garba, Sasha Falbaum, Zvi Loewy, Melinda Lull, Maha Saad, Jayne Shtaynberg, Aniwaa Owusu Obeng

Albany College of Pharmacy and Health Sciences, Albany, NY
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Touro College of Pharmacy, New York, NY
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Purpose: Pharmacogenomics is a rapidly growing discipline in medicine. Despite strong advocacy for curriculum inclusion, pharmacogenomics educational efforts particularly in schools of pharmacy have been inadequate. This study evaluated final year pharmacy students in several colleges and schools of pharmacy in the states of New York and New Jersey on their perceptions towards the importance of pharmacogenomics education; their attitudes on its clinical relevance; and their readiness to use such knowledge in practice.

Methods: We approached eleven schools in the Tri-State area (New York, New Jersey and Connecticut) however only eight schools participated. A 19-question survey was developed and administered via surveymonkey.com to 978 final year pharmacy students from eight schools and colleges of pharmacy in New York and New Jersey. The surveying period lasted between January 23rd and April 17th, 2017. The survey items included questions on demographics; experience with pharmacogenomics education; preparedness to use pharmacogenomics in practice and their perception on the clinical relevance of pharmacogenomics.

Results: A total of 339 students participated in the survey. Approximately 63% of the participants were female. Preliminary findings indicate that 49% received 1 – 3 lectures on pharmacogenomics during their pharmacy school education as compared to 36% who took either a required or an elective course on pharmacogenomics. Moreover, 88% believed that pharmacogenomics is a useful tool for clinicians including pharmacists. Although 75% believed that pharmacogenomics should be covered in detailed in pharmacy curricula, only 42% agreed that pharmacogenomics has been a relevant part of their training. Additional results will be presented once all data has been analyzed.

Conclusions: Preliminary findings suggest that pharmacogenomics educational efforts in pharmacy schools in NY and NJ have made some progress yet more is needed to better equip new practitioners in this age of personalized medicine particularly with the growing acceptance of clinical pharmacogenomics implementation efforts.
Medicalization and the Physician: Shaping Identity and Clinical Autonomy

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In this paper, we examine how physicians are shaped (ethically and metaphysically) by medicalization. By medicalization, we mean, in brief, processes by which human variation and differences become seen as medical conditions through medical identification, surveillance, or treatment. Much of the literature on medicalization has focused on how various conditions become medicalized, or how this work negatively impacts members of power-minority groups (e.g., women, LGBT folks). In this paper, we look at an important lacuna in the literature: how the forces of medicalization shape physicians themselves, ultimately creating agents of medicalization.

Our presentation has two goals. First, we articulate how medical students are shaped by medicalization while in medical schools, training to become physicians. As such, we argue that medicalizing forces and the physician are co-constitutive systems. Second, we argue this has important ethical impact on physicians. In part, these are identity-shaping forces, training students’ virtuous characters as physicians within what MacIntyre would call the "practice" of medicine. While this arguably opens possibilities, it also limits moral character. We argue that by becoming part of the practice of medicine, physicians—even those who are justice-minded—become unable to work toward goals of demedicalization. As such, even justice-minded physicians may be unable to engage in the demedicalization projects as articulated by feminist bioethics. This will have important implications for women’s health and LGBT health.
Quality Assessment of Expired Naloxone Products from First-Responders’ Supplies

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Naloxone is an opioid receptor antagonist that can reverse opioid overdose, which is life-threatening. Since 1970’s, Naloxone products have been developed as injections, and more recently as nasal spray. They have saved many lives at emergency settings, and have been routinely carried by first-responders, including fire fighters, law enforcement officers and emergency medical services (EMS). While public safety supplies are monitored, community naloxone programs give naloxone to the public, who may have expired product on-hand in an emergency. Therefore, this study analyzed the quality and stability of expired Naloxone Solutions for injection, in order to assess their remaining efficacies and potential risks. The samples were collected from EMS or law enforcement supplies, with expiration dates span from 1980 to 2016. Using LCMS methods, the remaining Naloxone were quantified. Possible degradation products were monitored, including Noroxymorphone. All tested samples were found containing more than 90% of labeled amount, with Naloxone degradation correlated with the length of storage over 20 years. Noroxymorphone, the main degradation product of Naloxone, was detected from some older samples, but all less than 1%. Therefore, the risk caused by Noroxymorphone is low, although it is an opioid agonist. Overall, this exploratory quality study suggested that an expired Naloxone Solution for Injection may still be qualified by USP standards. Further risk and benefit evaluation will be conducted to confirm our assessment, with more systematic quality and clinical investigations for other naloxone products on the market.
Assessment of Time to Clinical Response in Patients with Sepsis Treated Before and After Implementation of a Twice-Daily Blood Culture Follow-up Program

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Background: Sepsis is a severe life threatening condition which requires prompt administration of appropriate antibiotics. This study evaluates the effect of a blood culture follow-up program on clinical response in patients with sepsis and concurrent bacteremia or fungemia.

Methods: This was a quasi-experimental study with a double retrospective pre-test and a prospective post-test. Inclusion criteria: admitted to Albany Medical Center Hospital, positive blood cultures, age ≥ 18 y, and suspected or confirmed sepsis. Exclusion criteria: transfer from outside hospital, pregnancy, ANC < 1000/mm³ or polymicrobial septicemia. Pre-test 1 (O1) and pre-test 2 (O2) were 1/1/2013 – 12/31/2013 and 1/1/2014 – 12/31/2014, respectively. The post-test group (O3) was 8/1/2015 – 12/31/2015. In O3, a pharmacist provided prospective audit and feedback for blood culture results twice daily. The primary endpoint was time to sepsis resolution. The secondary endpoints were time to SIRS resolution, time to SOFA resolution, time to pathogen ID, and inpatient mortality. Continuous variables were analyzed using Kruskal-Wallis Test, categorical data were analyzed using Chi-squared test and time-to-event analysis was conducted using stratified Kaplan-Meier curves with log-rank test as appropriate.

Results: 394 patients were enrolled. Median time to the primary endpoint was 4 vs. 3 vs. 3 days in the O1, O2 and O3, respectively (p = 0.02). O3 was associated with a numerically but not statistically improved hazard (95% CI) for sepsis resolution (1.28 [0.92 – 1.77]). Other factors for the primary endpoint were initial ICU admission (0.43 [0.33 – 0.57]), LRTI (0.54 [0.37 – 0.79]), and MDR infection (0.75 [0.57 – 0.97]). Adjusting for these covariates, the intervention was not associated with improved aHR (95% CI) for sepsis resolution (1.25 [0.90 – 1.73]). In a subgroup analysis of four indications (n = 333), the intervention was associated with improved hazard for sepsis resolution (HR [95% CI]: 1.68 [1.08 – 2.62]). In O1, O2 and O3 group median time to SIRS resolution was 4 vs. 2 vs. 3 days (p = 0.02), median time to SOFA resolution was 6 vs. 6 vs. 7 days (p = 0.73), median time to pathogen identification was 2.00 vs. 0.93 vs. 0.99 days (p < 0.001), and inpatient mortality was 13.4% vs. 7.4% vs. 13.1%, (p = 0.17), respectively.

Conclusions: Implementation of a twice-daily blood culture follow-up program did not result in a global benefit for sepsis resolution. Certain indications may benefit from additional blood culture follow-up. Further research is needed to optimize scarce antimicrobial stewardship resources.
Disulfide Bridge Formation Contributes to Histone Ligand Recognition by the ATAD2 Bromodomain

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The ATPase Family, AAA domain-containing protein 2 (ATAD2) bromodomain has canonical bromodomain structure, consisting of four α-helices. ATAD2 is known to be up-regulated in multiple different types of cancer including breast, lung, gastric, endometrial, renal, and prostate cancer. ATAD2 is a co-activator of the androgen and estrogen receptors, as well as MYC and E2F transcription factors. Recently, ATAD2 was shown to read newly synthesized diacetylated marks during DNA replication, and ATAD2 overexpression further increases ATAD2 levels, cell proliferation, and survival genes. Furthermore, up-regulation of ATAD2 is strongly correlated with poor patient prognosis. This makes the ATAD2 bromodomain an innovative target for cancer therapeutics, and several inhibitors are currently in development. Interestingly, the ATAD2 bromodomain contains two cysteine residues near the base of the bromodomain-binding pocket between helices αB and αC. We hypothesized that disulfide bridge formation between residues C1057 and C1079 might regulate the interaction of the ATAD2 bromodomain with its histone ligands. X-ray crystallography confirmed formation of a disulfide bridge in the ATAD2 bromodomain. The role of the disulfide bridge in ATAD2 bromodomain stability was explored through mutagenesis, codon optimization, and expression experiments. To investigate the impact of disulfide bridge formation on histone ligand recognition by the ATAD2 bromodomain, isothermal titration calorimetry was carried out to characterize binding affinities of histone ligands using the ATAD2 bromodomain protein with and without an intact disulfide bridge. This study demonstrates the functional effect of disulfide bridge formation upon histone ligand recognition by the ATAD2 bromodomain, and presents additional structural information, which may prove essential for effective inhibitor development for the treatment of many cancers.
Molecular Mechanism of Di-acetyllysine Recognition by the ATAD2B Bromodomain

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The ATPase family, AAA+ domain-containing protein 2B (ATAD2B) is a nuclear protein that may play a role in the development of neuronal tissues and tumorigenesis. The ATAD2B protein contains a C-terminal bromodomain that is highly homologous to the ATAD2 bromodomain, with 74.7% sequence identity and 94.4% similarity. The ATAD2 bromodomain is an attractive drug target because overexpression of ATAD2 is positively correlated with the progression of multiple cancer types, and poor patient outcomes. Although ATAD2 and ATAD2B are highly conserved, little is known about the function of ATAD2B, or its role in oncogenesis. We hypothesized that the ATAD2B bromodomain would likely be involved in recognition of di-acetyllysine modifications on the histone tail, similarly to its ATAD2 paralog. We identified the acetylated histone ligands of the ATAD2B bromodomain using a combination of isothermal titration calorimetry and nuclear magnetic resonance techniques. Interestingly, the ATAD2B bromodomain has different substrate specificity than the ATAD2 bromodomain, preferentially selecting for the histone H4K5acK8ac ligand. NMR chemical shift perturbation assays and site-directed mutagenesis were used to map out the acetyllysine binding pocket, enabling characterization of residues involved in coordination of mono- and di-acetylated histone ligands by the ATAD2B bromodomain for the first time. In addition, the X-ray crystal structure of the ATAD2B bromodomain in complex with an ATAD2 bromodomain inhibitor was solved at 2.2 Å resolution. This structure revealed that critical contacts required for bromodomain inhibitor coordination are conserved between the ATAD2/B bromodomains, and many of these residues play a dual role in acetyllysine recognition.
Ricin Mediated Programmed Cell Death

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Ricin is a protein toxin derived from the caster bean. In vivo, ricin is seen to show immense cell death in lung tissue, but this has yet to be seen in vitro. We aim to determine the cause of this discrepancy through exploring whether bystander cell death and cytokine co-signaling potentiate the effects of ricin. Here we show that ricin clearly causes significant death to human macrophages (U937 cells), while not having the same effect on human lung epithelial cells (A549 cells) in vitro. We then exposed A549 cells to U937 ricin supernatant which potentiated A549 cell death. Cytotoxicity assays of co-cultured A549 and U937 cells resulted in increased sensitization of A549 cells to ricin. Cytokine co-administration, specifically TRAIL, resulted in increased A549 sensitization suggesting that cytokine signaling may have a large part in the cell death seen in vivo. Furthermore, ricin induced cell death was substantially reduced when ZVAD, a general caspase inhibitor, and other specific caspase inhibitors were added to ricin and TRAIL cytotoxicity assays. This suggests that ricin specifically induces apoptosis. We believe bystander cell death and TRAIL co-signaling plays a vital role in substantial death seen in vivo.
ABSTRACTS: Posters

Hyperglycemia Potentiates a Shift from Apoptosis to RIP1-dependent Necroptosis


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Necroptosis is a type of inflammatory programmed cell death (PCD) that is dependent on kinases RIP1, RIP3 and MLKL. Necroptosis differs from apoptosis, which is dependent on caspases and a non-inflammatory PCD. Activation of necroptosis stimulates glycolysis, producing toxic by-products that induce cell damage such as reactive oxygen species (ROS) and advanced glycation end products (AGEs). Previous work has shown that necroptosis is upregulated in hyperglycemic conditions (LaRocca et al. 2016, J Biol Chem; 291(26):13753-61). These findings suggest that hyperglycemia may induce a shift from apoptosis to necroptosis following extrinsic death receptor-ligand interaction. The current research reflects this hypothesis. Here, we show that hyperglycemia potentiates a shift from extrinsic apoptosis to RIP1-dependent necroptosis. This is observed in different cell types in response to different stimuli of extrinsic apoptosis. The shift is the result of increased levels and activity of RIP1 and decreased levels and activity of executioner caspases in hyperglycemic conditions following stimulation with extrinsic apoptotic stimuli. Although RIP3 does not have any role in the hyperglycemia-induced shift, the enhanced cell death in high glucose conditions was characterized as necroptotic in nature by several cellular markers and the involvement of MLKL. The shift to necroptosis was driven by RIP1 as mutation of this gene using CRISPR-Cas9 caused cell death to revert to caspase-dependent apoptosis in hyperglycemic conditions. Glucose metabolism and involvement of mitochondrial ROS were also essential for promoting the shift to necroptosis. Furthermore, levels of RIP1 (total and phosphorylated) and MLKL increased, while caspase-3 levels decreased, in cerebral tissue from hyperglycemic neonatal mice that had undergone hypoxia-ischemia (HI) brain injury, suggesting that this cell death shift occurs in vivo. This work is significant as it demonstrates a shift from non-inflammatory to inflammatory cell death and is important due the clinical significance of necroptosis in ischemia-reperfusion injury.
Allosteric Activation of Human SIRT6

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Sirtuins, also called Class III HDACs, consume stoichiometric amount of nicotinamide adenine dinucleotide (NAD⁺) to remove acetyl group from lysine residues, and to produce nicotinamide (NAM) and O-acetyl-ADP-ribose (AADPR). A growing body of evidence suggests that sirtuin activities are upregulated during calorie restriction (CR) to extend lifespan in a variety of organisms from yeast to mammals. The compelling idea that sirtuin activity can be increased by small molecule regulators has been intensively pursued with very little success. Here we study the allosteric activation of human SIRT6 by small molecules. We have generated significant preliminary data supporting the feasibility of this approach. Mechanisms leading to the activation were explored. Elucidation of the mechanism of action will provide invaluable information for the structural optimization of the small molecules to achieve improved metabolic stability and target binding affinity. Ultimately, this project has the potential to break new ground on a number of fronts, engineering creative chemical tools for sirtuin regulations, developing novel paradigms for sirtuin functions, and the possibility of generating new therapeutics.
Regulation of Mouse Mammary 419II Cancer Stem Cell Proliferation by Bmi-1 and Nanog

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The Hedgehog (Hh) signaling pathway is linked to cell growth and differentiation in embryonic pattern formation and adult tissue homeostasis, and has been implicated in tumor initiation and growth. Deregulated Hh signaling contributes to etiology of solid tumors, including medulloblastoma and basal cell carcinoma. Hh signaling has also been found to play a role in regulating the growth of tumor stem cells, which have the ability to self-renew and also undergo differentiation. This project focused on regulation of proteins that control cancer stem cell division/differentiation in cells isolated from mouse mammary tumors induced by over-expression of the polyoma T-antigen under the control of the mouse mammary tumor virus promoter (MMTV-PyMT). A cell line (419II cells) exhibiting properties of cancer stem cells was isolated from these tumors using specific stem cell markers (CD44^+CD24^-CD49f^+). The research hypothesis was that 419II cancer stem cells exhibit an active Hh signaling pathway that contributes to regulation of Bmi-1 and Nanog expression. Previous experiments showed that inhibition of Hh signaling with GANT61 treatment inhibited growth of 419II cells. As expected, a reduction in Hh signaling due to GANT61 treatment led to decreased Gli1 expression. Further investigations into the mechanism of GANT61 using Western blotting analyses demonstrated that the expression of both Bmi-1 and Nanog protein was reduced as a result of GANT61 treatment (10 µM for 72 hours). Both Bmi-1 and Nanog are transcription factors which are implicated in regulating cancer stem cell division and differentiation. These transcription factors have also been shown to be regulated by other signaling pathways, including STAT3. To investigate this, 419II cancer stem cells were treated with the STAT3 inhibitor, BBI608 (1 µM for 24 hours). BBI608 inhibited the growth of 419II cancer stem cells by almost 60%, as demonstrated by an MTT assay. To investigate the mechanism of growth inhibition, the effect of BBI608 on Bmi-1 and Nanog expression was analyzed by Western Blotting. BBI608 treatment of 419II cancer stem cells (1µM BBI608 for 24 hours) significantly reduced expression of both Bmi-1 and Nanog. While the data demonstrate that expression of Bmi-1 and Nanog are regulated by multiple signaling pathways, BBI608 was able to alter cell proliferation and gene expression more quickly than GANT61 treatment. The results suggest that drugs which target Bmi-1 and Nanog may reduce the growth potential of mouse mammary stem cells, thereby providing a more effective treatment approach.
Identification and Characterization of Nucleobase Transporters

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Nucleotides, nucleosides and nucleobases are important bioactive molecules. The cellular concentrations of these molecules must be tightly regulated for the viability and success of the organism. The intracellular levels of these compounds are maintained by several complementary processes including de novo biosynthesis, salvage pathway and transport. The focus of this study is the nucleobase transport pathway. Although much is known about the transport mechanism for nucleotides and nucleosides, the knowledge on nucleobase transporters is minimal. The importance of nucleobases in various biological events has magnified the need to understand how they are being transported in and out of the cells.

We have developed a series of bifunctional chemical probes and novel biochemical assays to identify and characterize unknown nucleobase transporters. These results are expected to significantly advance our understanding of overall nucleotide metabolism and the role that nucleobase transport plays in the regulation of this important fundamental process. The additional knowledge and the tools that we developed will have a positive translational impact by enabling us to better define the targeting and pharmacokinetics of currently used antimetabolites and will significantly expand our capacity to discover and further develop novel chemothapeutics that target nucleotide metabolism or downstream processes.
Synthesis of Cyclooctyne Containing Probes for Labeling Sirtuins

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Sirtuins are NAD\(^+\)-dependent protein deacetylases that remove acetyl group from lysine residues. They play critical roles in a variety of cellular events such as DNA repair, metabolic programming and programmed cell death. Sirtuins serve as potential targets for the treatment of cancer and age-related diseases. Recent studies indicate that it is the enzymatic activity rather than the protein abundance that determines sirtuin biological function. Current available techniques cannot evaluate the actual enzymatic activity directly in native biological matrix, stressing the need for an activity-based protein profiling (ABPP) method. ABPP uses small molecule probes to directly investigate the functional state of the enzyme target. Our group has developed a set of ABPP probes that are capable of labeling active sirtuin in a complex mixture of proteins. These probes are thioacetyllysine-based peptides with benzophenone and terminal alkyne groups. Thioacetyllysine serves as the “warhead” to target the active site of active sirtuins. Benzophenone is a photocrosslinking group. The terminal alkyne is considered a “bioorthogonal” group, which can be covalently conjugated to a fluorescent dye or biotin through Cu(I) catalyzed “click chemistry”. The ultimate goal of our research is to use these ABPP probes to monitor the cellular localization and activity of sirtuins in live cells. All of the first generation probes carry the terminal alkyne group. For the “click” conjugation to the fluorophore, Cu(I) catalyst is required. However, Cu catalyst is known to be cytotoxic, which makes the current probes not compatible for live cell imaging. In this project, the Cu-free “click” reaction using cyclooctyne containing probes will be explored. The “click” reaction between cyclooctyne and azide uses ring strain to facilitate the reaction, no catalyst is needed. This reaction is fast, bio-compatible and very selective. This type of Cu-free “click” reaction has been widely used to study biological processes. We have successfully synthesized a series of cyclooctyne containing probes using several independent strategies.
Genetic Basis for Daptomycin Resistance in Methicillin Resistant *Staphylococcus aureus*

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The extensive use of daptomycin for treating complex methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the last decade has led to the emergence of daptomycin-resistant *Staphylococcus aureus* strains. An understanding of the molecular mechanisms underlying the daptomycin resistance is required for identifying new targets for potential antimicrobial development. Even though the genomic studies have provided information about the mutations associated with daptomycin resistance, they do not provide crucial information regarding the order and hierarchy of genetic changes leading to daptomycin resistance and the relative importance of these mutations in the evolution of daptomycin resistance. In the present study, we established a continuous culture bioreactor model in which *S. aureus* strain N315 was exposed to increasing doses of daptomycin (0, 6, 10, and 14 μg/ml) and samples were collected every 24 hours for 14 days. Minimum inhibitory concentrations (MICs) were determined using broth microdilution and E-test method. The samples were then whole genome sequenced to map the stepwise acquisition of resistance genes. Our results indicate that the bioreactor model successfully recapitulated previously published clinically relevant mutations involved in daptomycin resistance while also implicating new mutations which are currently being further validated by bioinformatics analysis. The development of daptomycin resistance in N315 strain was associated with mutations in genes encoding proteins with two main functions: i. that increase the charge of the cell membrane (membrane peptide resistance factor); and ii. that alter cell membrane phospholipid content (cardiolipin synthase). To summarize, we used a bioreactor model to understand the evolution of genetic changes responsible for daptomycin resistance which will ultimately help in the identification of new targets for potential antimicrobial development.
Regulatory Role(s) of pp(p)Gpp in Oxidative Stress Response of Francisella tularensis

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Francisella tularensis (Ft) is an important Gram-negative facultative intracellular human pathogen responsible for causing tularemia. It is also classified as a category A agent by the CDC based on its possible use as a bioterror agent. Although the molecular basis for the high infectivity and virulence of Ft is not well understood, the pathogenicity of Ft is mainly dependent on its ability to persist and replicate in phagocytic cells. To survive and replicate inside the cells, Ft has to resist the attack of host-generated reactive oxygen and nitrogen species. Multiple antioxidant enzymes that are important defense factors against oxidative stress have been identified and implicated in the pathogenesis of Ft in multiple studies. Our previous study has demonstrated that some of these antioxidant enzymes are regulated by a LysR family transcriptional regulator, OxyR. In the present study, we further explore the regulation of the oxidative stress response by stringent response molecules pp(p)Gpp produced by RelA and SpoT proteins of Ft. We generated a series of Ft LVS mutant strains including a relA gene deletion mutant (∆relA), a relA/spoT double gene mutant (∆relA/spoT) and their corresponding transcomplements. These mutant strains were characterized for their sensitivity towards oxidants by generating growth curves, by disc diffusion and bacterial killing assays; for their ability to survive in macrophages, and for their virulence in mice. Results from these studies indicate that while RelA alone does not contribute to virulence attributes of Ft, both the RelA and SpoT of F. tularensis play an important role in providing resistance against oxidative stress, intramacrophage survival and virulence in mice. Further studies employing molecular and biochemical approaches to elucidate the global regulatory roles of stringent response messengers pp(p)Gpp in regulation of gene expression responsible for oxidative stress resistance of Ft are currently underway.
Structural and Computational Insights into Single Nucleotide Polymorphisms in Cytochrome P450 2C9

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Deceased

Xenobiotic metabolizing cytochrome P450 (CYP) enzymes constitute the major enzyme family in drug metabolism with increasing importance in pharmacogenetics, and more recently to pharmacogenomics. Single nucleotide polymorphisms, a single base pair variation in a DNA sequence that results in amino acid substitution in CYPs are major determinants of inter-individual variability in drug response leading to drug-drug interactions and adverse reactions. The highly polymorphic CYP2C9 metabolizes over 15% of clinical drugs currently available that include ibuprofen, warfarin, tolbutamide, glimepiride, losartan, and diclofenac. Many of the sixty CYP2C9 alleles reported until now exhibit significantly altered activities toward various drugs compared to the wild type (WT). Despite the extensive functional and structural characterization of various CYP enzymes from multiple species, the structural basis of genetic polymorphisms is still lacking. The crystal structures of human CYP2C9 and its two important polymorphic variants, *3 (I359L) and *30 (A477T), in complex with an angiotensin II receptor antagonist drug losartan were determined. The WT and the *30 complex showed binding of three molecules of losartan, one in the active site, another at the peripheral site, and the third in the access channel. Whereas the *3 complex illustrated binding of two losartan molecules and lacked the third molecule in the access channel. The distal I359L substitution in the *3 variant remarkably affected orientation of many residue side chains crucial for substrate interaction and altered the binding of losartan in the active site. The *30 variant with T477A substitution illustrated hydrogen-bonding interaction with the sidechain of Q214, which reoriented markedly compared to the WT complex. Furthermore, molecular modeling and docking studies revealed the residues crucial for substrate specificity in CYP2C9. The results provide structural and computational insights into altered catalytic activity of the CYP2C9 variants and have important implications for understanding polymorphisms in CYP-mediated drug metabolism.
Role for Host Glycosphingolipid Biosynthesis on the Infectivity of Human Enveloped RNA Viruses

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Though host lipids have long been known to be critical structural component of viral envelopes, recent studies have revealed that host lipids play critical roles in the entry, genome replication, assembly, and release of several clinically important viruses. Influenza A viruses cause the highly-contagious respiratory infection known as the flu, a significant cause of morbidity and mortality worldwide annually. Zika virus, a member of the Flavivirus genus, is responsible for the recent widespread epidemic of Zika fever in Central and South America that has been associated with serious birth defects and neurological illnesses. Though agents of disparate human diseases, both viruses are enveloped single-stranded RNA viruses whose life cycles appear to be intimately connected with cellular lipids. The glycosphingolipids glucosylceramide and lactosylceramide, products of the cellular enzymes glucosylceramide synthase (GCS) and lactosylceramide synthase (B4G5), are enriched in the Golgi complex and membrane lipid rafts- sites known to be involved in the entry, protein synthesis, and budding of both influenza and flaviviruses. Data from our studies suggest that both viruses are dependent on GCS activity, and the glucosylceramide its produces, for the generation of mature, infectious virus particles. Additionally, our data suggest that both viruses are capable of co-opting GCS enzymatic activity to facilitate the production of viral particles. Further understanding of the shared requirement for glycosphingolipids and defining the importance of GCS enzymatic activity in the life cycles of influenza and Zika viruses may result in the development of broad-spectrum antiviral therapies targeting both pathogens.
Inhibition of HIV Early Replication by the p53 and its Downstream Gene p21

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Background: The tumor suppressor gene p53 has been found to suppress HIV infection by various mechanisms, but the inhibition of HIV at an early stage of replication by host cell p53 and its downstream gene p21 has not been well studied.

Method: VSV-G pseudotyped HIV-1 or HIV-2 viruses with GFP or luciferase reporter gene were used to infect HCT116 p53+/+ cells, HCT116 p53−/− cells and hMDMs. The infections were detected by flow cytometry or measured by luciferase assay. Reverse transcription products were quantified by a TaqMan real time PCR. siRNA knockdown experiments were applied to study potential roles of p53 and p21 genes in their restriction to HIV infection. Western blot experiments were used to analyze changes in gene expression.

Results: The infection of HIV-1 was inhibited in HCT116 p53+/+ cells in comparison to HCT116 p53−/− cells. The fold of inhibition was largely increased when cell cycle switched from cycling to non-cycling status. Further analysis showed that both p53 and p21 expressions were upregulated in non-cycling HCT116 p53+/+ cells and HIV-1 reverse transcription was subsequently inhibited. siRNA knockdown of either p53 or p21 rescued HIV-1 reverse transcription from the inhibition in non-cycling HCT116 p53+/+ cells. It was identified that the observed restrictions by p53 and p21 were associated with the suppression of RNR2 expression and phosphorylation of SAMHD1. These observations were confirmed by using siRNA knockdown experiments. In addition, p53 also inhibited HIV-2 infection in HCT116 p53+/+ cells and siRNA knockdown of p21 increased HIV-2 infection in hMDMs. Finally the expressions of p53 and p21 were found to be induced in hMDMs shortly after HIV-1 infection.

Conclusions: The p53 and its downstream gene p21 are important restriction factors that interfere with HIV early stage of replication in non-cycling cells and hMDMs.
Applications of New Benzylguanidine Derivative/Nanoparticles in the Treatment of Neuroblastoma

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Neuroblastoma (NB) is a type of cancer that forms in certain types of nerve tissue. Metaiodobenzylguanidine (MIBG) and its radioactive iodine (I-131) derivative are used in diagnostic imaging and therapy of NB because of its high transport affinity and accumulation into NB. The purpose of this study was to synthesize and characterize a novel benzyl guanidine (BG) derivative, which has a similar active group like MIBG, and its polymer-conjugated analogue PLGA-PEG-BG for the synthesis of nanoparticle (NP) formulations for delivery of chemotherapy to NB and glioblastoma cell lines for comparison.

We tested the effects of BG conjugated to PLGA-PEG (PLGA-PEG-BG) versus MIBG in NB tumors implanted in nude mice. Treatment with PLGA-PEG-BG resulted in significant suppression of NB tumor growth (P <0.01) and tumor viability (P <0.05) compared to control and more effective NB growth inhibition than that of MIBG at the same dose regimen.

PLGA-PEG-BG can be synthesized as NPs and encapsulate a dye like Rhodamine 6G/Cy5 for in vitro uptake studies or a chemotherapy agent for in vivo biodistribution studies. The in vitro uptake of PLGA-PEG-BG NPs encapsulating Rhodamine 6G (PLGA-PEG-BG-Rh-6G-NPs) was examined with confocal imaging and showed a significant uptake of the NPs in glioblastoma U87 cell line compared to NB cell lines. The in vivo uptake studies of these PLGA-PEG-BG-Rh-6G-NPs as well as PLGA-PEG-BG-NPs encapsulated with a chemotherapy agent are in progress. In conclusion, PLGA-PEG-BG NPs might provide a novel Nano delivery system for chemotherapy and radiotherapy.
Formulation and Pharmacokinetics of Diaminopropane Tetraiodothyroaceticacid-conjugated Biodegradable Polymeric Nanoparticles and Anti-angiogenesis Efficacy

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Angiogenesis, the development of new blood vessels, is crucial for tumor growth. An established tumor needs nutrients and oxygen from the blood in order to grow and spread, and then several angiogenic factors are induced to promote the growth of new blood vessels. If the growth of blood vessels is blocked, the tumor will shrink or even disappear. Several anti-angiogenic agents (for example, bevacizumab and sorafenib) have been approved by the FDA for their contribution to survival improvement when combined with chemotherapy or radiation. A new anti-angiogenic agent, diamino tetraiodothyroacetic acid (DAT), is a thyroid hormone derivative and can regulate multiple vascular growth factors and control proliferation of tumor cells. However, DAT as a thyroid hormone derivative may influence gene expression after it transports across cellular membranes.
The Effects of Sulfated Non-Anticoagulant Heparin Compounds on Cancer Associated Thrombosis

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Pancreatic cancer is the fourth leading cause of cancer related deaths in both males and females in the United States. Research demonstrates that a frequent cause of mortality in cancer patients is due to venous thromboembolism (VTE). Tumor aggressiveness and increasing metastatic potential correlate with mortality risk. Surgical removal of the tumor and chemotherapy leave cancer patients at risk for VTE and other thrombosis complications. To combat thrombosis complications, heparin and low molecular weight heparin (LMWH) are used in therapy for cancer patients. Unfortunately, these drugs are limited in use due to an increased risk of bleeding complications for the patient. According to recent studies the development of different types of non-anticoagulant heparin (NACH) provide an imitative heparin excluding the side effect of increased bleeding. In our experiment, we investigated the effects of sulfated non-anticoagulant low molecular weight (S-NACH) on cancer associated thrombosis using human pancreatic cancer cells, SUIT2. S-NACH in the presence of low levels of TFPI exhibits an anti-thrombotic effect as evident from the increased clotting time and suppressed clot formation in the TEG assay. Additionally, S-NACH suppressed pancreatic cancer cell proliferation.
Development of Bioanalytical Method for Pharmacokinetics of a Novel Targeted Anticancer Drug in Rats and Monkeys

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Targeted anticancer drugs have been developed based on multiple chemical scaffolds, including conjugates of nanoparticles and active drugs. P-bi-TAT is a novel targeted anticancer drug, which is a conjugate of polyethylene glycol (P) with bis-triazole tetraiodothyroacetic acid (triazole tetrac, TAT). We developed a bioanalytical method for P-bi-TAT with liquid chromatography-tandem mass spectrometry in electrospray ionization (ESI) positive mode using a biphenyl column. We used collision-induced dissociation (CID) and multiple reaction monitoring (MRM) mode, and quantified P-bi-TAT with an internal standard method using a derivative of tetrac, DATE-05, as an internal standard. The sample preparation from plasma was solid-phase extraction using OASIS HLB columns with 80% acetonitrile in water. The quantification limit for P-bi-TAT was 30 ng/mL.

We applied the bioanalytical method for the determination of pharmacokinetic parameters of P-bi-TAT in plasma from rats and cynomolgus monkey administered a single subcutaneous dose at 100 mg/kg and 25 mg/kg, respectively. Results were: Tmax: 6 and 6 h; Cmax: 225 and 216 μg/mL; T1/2: 8.1 and 13 h; AUC (0-48 hours): 3564 and 3144 μg/mL*h.

In conclusion, a validated bioanalytical method was developed for Pharmacokinetic and Toxicokinetic studies in animals and in human trials.
Novel Nano-Targeting of Thyrointegrin αvβ3 Receptors for the Modulation of αvβ3 Expression in Different Cancer Cells and Tumors

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Over-expression of αvβ3 integrins in various tumor tissues plays a key role in tumor cell proliferation, tumor growth, angiogenesis, and metastasis. These processes are effectively inhibited with high affinity thyrointegrin αvβ3 targeted delivery system having efficient uptake by the target tumor and its microenvironment. We synthesized a thyrointegrin αvβ3 integrin antagonist Diamino propane tetrac (DAT), which has the chemical name of \( 4\{-4\{-3\{-3\{-poly\{2\-(2-hydroxyacetotoxy)propanamido)aminopropoxy\}-3,5-diiodophenoxy\}-3,5-diiododophenyl\}acetic acid \). DAT was conjugated Poly (lactic-co-glycolic acid) (PLGA) via covalent bonding followed by the assembly of the nanoparticulate formulation (NDAT). A cell-based adhesion assay and an enzyme-linked sorbent assay with purified receptor verified that NDAT has much higher binding affinity and specificity to αvβ3 integrin than tetrac, which was confirmed with molecular docking. In vitro studies with different cancer cells that express αvβ3 integrins quantitated with flow cytometry and western blots demonstrated potent suppression of αv and β3 expression by NDAT. NDAT suppressed the expression αv and β3 subunits in human cancer cell lines and in tumors implanted in nude mice as shown with qRT-PCR analysis. Our in vivo tumor targeting studies showed the efficacy of NDAT in inhibition of solid tumor growth and tumor-associated angiogenesis. In conclusion, we demonstrated the targeting affinity and blockade of αvβ3 integrin-mediated function by a novel polymeric NDAT, which restrained the activity of the most aggressive and metastatic cancer cells within different tumors.

**Figure 1** (Left) Cyclic polypeptide RGDVF bound to αvβ3 (PDB code: IL5G). Metal ions Mn\(^{2+}\) are depicted as spheres (yellow); (Right) Structure of Nano-diamino-tetrac (NDAT). Tetrac is covalently bound via an ether bond involving its outer ring hydroxyl group to a linker. The diamino-linker via an amide bound is joined to the PLGA (poly[lactic-co-glycolic acid]) nanoparticle. Five to 8 tetrac molecules are bound to each 150 nm nanoparticle.