



ALBANY COLLEGE OF PHARMACY
AND HEALTH SCIENCES

ACPHS Seventh Annual Research Forum

<http://www.acphs.edu/academics/research>

Saturday, January 28, 2017

**Albany College of Pharmacy and Health Sciences
106 New Scotland Avenue, Albany, NY 12208
Gozzo Student Center, Room 201**

This is a free 1-day conference, lunch included, rsvp not necessary.

This annual conference provides an update on scientific developments on the ACPHS campus and, through invited conference speakers, 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

Welcome Message



Greg Dewey, PhD, ACPHS President

8:40 – 9:15

Keynote Speaker

“Advancing Medicines for Tomorrow: Pressures, Paradigms and Progress – the Roles of Science and Collaboration”



*Keith Horspool, PhD
Vice President, Material and Analytical Sciences
Boehringer Ingelheim, Ridgefield, CT*

AGENDA

9:15 – 9:30

Safety First



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

9:30 – 9:40

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*

9:40 – 9:50

ACPHS Chapter of the American Association of Pharmaceutical Scientists (AAPS)



*Chiara Evans, BS/MS of Pharmaceutical Sciences Class of 2018
President, ACPHS Chapter AAPS*

9:50 – 11:00

Panel Discussion, “Oncology: Current Trends”

Moderator: Shaker A. Mousa

James Gallo, PharmD, PhD, Professor & Dept. Chair, Pharmaceutical Sciences, ACPHS

Paul J. Davis, MD, Pharmaceutical Research Institute, ACPHS and Albany Medical College

Stewart Sell, MD, Wadsworth Center, New York State Department of Health, Albany, NY



J. Gallo



P.J. Davis



S. Sell

- I. How Quantitative Systems Pharmacology (QSP) May Help Cancer Precision Medicine (Gallo)
- II. Novel Strategies in Cancer Management—Role of $\alpha\text{v}\beta\text{3}$ Antagonist Targeting in Glioma and Other Cancers (Davis)
- III. Cancer Stem Cell and Impact of Immunotherapy (Sell)

AGENDA

11:00 – 11:45

POSTER VIEWING & Networking

*Poster presenters please stand by your poster.
Coffee available in Rite Aid Lounge.*

11:45 – 12:20

Keynote Speaker

“The Value of Innovation”



Nathan Tinker, PhD

Executive Director

NewYorkBIO

12:20 – 2:30

LUNCH and POSTER VIEWING

Lunch served in Cronin Lounge, 1st floor.

2:30 – 3:30

Oral Session, “Ten Minute Talks”

Moderator: Tarun Patel

ACPHS Provost and Vice President of Academic Affairs



***“Novel Non-Retinoid RPE65 Isomerase Antagonists for
the Treatment of Age-Related Macular Degeneration and
Stargardt Disease”***

Christopher Cioffi, PhD

Assistant Professor, Basic & Clinical Sciences

Albany College of Pharmacy and Health Sciences

AGENDA



“Quantifying the Minimum Adherence Threshold Associated with the Development of Reverse Transcriptase Resistance Mutations Among HIV-infected Veterans’ Affairs Patients Receiving Antiretroviral Therapy”

*Jenna Yager, Doctor of Pharmacy Candidate Class of 2017
Albany College of Pharmacy and Health Sciences*



“Healthcare, Alliances, and Virtues in the Women’s Health Movement: An Initial Study of the Our Bodies, Ourselves Archives”

*Barry DeCoster, PhD
Assistant Professor, Humanities & Communication*

*Wendy Parker, PhD
Associate Professor, Population Health Sciences
Albany College of Pharmacy and Health Sciences*



***“Pharmaceutical Industry Team Presentation”
ResuClick: A Reloadable, Reusable Epinephrine Auto Injector as an Answer to the Current Epinephrine Market Monopoly***

*Megan Ward, Doctor of Pharmacy Candidate Class of 2019
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. It was an overview of the pharmaceutical industry and 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 Blythe Award

3:35 – 3:45

Closing Remarks

ACPHS President Greg Dewey / ACPHS Vice Provost of Research Shaker A. Mousa

Poster Session

Basic & Translational Research

Effects of Ischemia/Reperfusion on Citrate Synthase and SERCA Activity in the Rabbit Urinary Bladder Treated with Ganoderma Lucidum

^{1,2}Connor M. Callaghan, ¹Catherine Schuler, ¹Robert E. Leggett, ³Alpha D-Y Lin, ^{1,2}Robert M. Levin

¹Stratton VA Medical Center, Albany, NY; ²Albany College of Pharmacy and Health Sciences, Albany, NY;

³Taichung Poh-Ai Hospital of Zhengzhou University, Taipei, Taiwan

The Functional Characterization of the BRPF3 Bromodomain

Chiara Evans, Jaime Gay, Karen C. Glass

Albany College of Pharmacy and Health Sciences, Colchester, VT

Investigating the Role of Disulfide Bridge Formation on Histone Recognition

Jamie Gay, Samuel Carlson, Karen C. Glass

Albany College of Pharmacy and Health Sciences, Colchester, VT

Novel Probes for Sirtuins: A Chemical Biology Approach

¹Elysian Graham, ¹Stacia Rymarchyk, ¹Marci Wood, ²Kangling Zhang, ³Hening Lin, ¹Yana Cen

¹Albany College of Pharmacy and Health Sciences, Colchester, VT; ²University of Texas Medical Branch,

Galveston, TX; ³Cornell University, Ithaca, NY

Reversal of Anticoagulant Activities of Heparin and its Derived Low Molecular Weight Heparin by Poly-L-Lysine: Comparative Study with Protamine Sulfate

Jaehan Kim, Vandhana Muralidharan-Chari, Shaker A. Mousa

Albany College of Pharmacy and Health Sciences, Albany, NY

Biological Function and Histone Recognition of Family IV Bromodomain-containing Proteins

Jonathan T. Lloyd, Amanda Poplawski, Mulu Y. Lubula, Samuel Carlson, Jamie Gay, Karen C. Glass

Albany College of Pharmacy and Health Sciences, Colchester, VT

Structural Insights into Recognition of Acetylated Histone Ligands by the BRPF1 Bromodomain

¹Mulu Y. Lubula, ²Brian Eckenroth, ¹Samuel Carlson, ¹Amanda Poplawski, ³Maksymilian Chruszcz,

²Sylvie Doublet, ¹Karen C. Glass

¹Albany College of Pharmacy and Health Sciences, Colchester, VT; ²University of Vermont, Burlington, VT;

³University of South Carolina, Columbia, SC

The Link Between Tissue Hypoxia and Calcinosis in Systemic Sclerosis

¹Mitchell Miller, ²Lee Shapiro, ^{1,2}Jessica Farrell

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Steffens Scleroderma Center at The Center for Rheumatology, Albany, NY

Evaluation of Procoagulant Compounds with Thromboelastography

Bridget Price, John Geurds, Ebunoluwa Iluyomade, Shaker A. Mousa

Albany College of Pharmacy and Health Sciences, Albany, NY

POSTERS

High Glucose Potentiates a Shift From Apoptosis to Necroptosis

¹Nicole L. Shakerley, ¹Tori A. Smiraglia, ¹Payal S. Patel, ¹Katharine Walker, ¹Miranda Craft, ²Sergey Sosunov, ²Vadim Ten, ¹Timothy J. LaRocca

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Columbia University, New York, NY

Novel Probes for Nucleobase Transporters

¹Ai Tran, ¹Marci Wood, ¹Ryota Yokose, ²Jarrod B. French, ¹Yana Cen

¹Albany College of Pharmacy and Health Sciences, Colchester, VT; ²Stony Brook University, Stony Brook, NY

The Mediation of Prostaglandin E, D and F_{2α} in Centrally Injected Arachidonic Acid-induced Cardiorespiratory Effects

Murat Yalcin

Uludag University, Bursa, Turkey

The Key Role of Central Thromboxane A₂ on Central Cardiorespiratory and Neuroendocrine Regulation

Murat Yalcin

Uludag University, Bursa, Turkey

Drug Design & Delivery

Towards Better Structure-Based Models of P-Glycoprotein Efflux of Drugs

Stefan Balaz

Albany College of Pharmacy and Health Sciences, Colchester, VT

Design and Synthesis of Dual-functional Nucleobase Analogs for Labeling Nucleobase Transporters 1Ai

¹Ai Tran, ²Jarrod B. French, ¹Yana Cen

¹Albany College of Pharmacy and Health Sciences, Colchester, VT; ²Stony Brook University, Stony Brook, NY

Health Outcomes

The Impact of Care Coordination on Provider Satisfaction in Lynch Syndrome Survivors and Preivors

¹Allison M. Burton-Chase, ¹Kelsey Hennig, ¹Alec LeBorgne, ¹Rebecca Chu, ²Lisa Campo-Engelstein, ¹Wendy Parker

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Albany Medical College, Albany, NY

Health-Related Quality of Life in Lynch Syndrome Patients

Kirsten M. Donato, Wendy M. Parker, Shannon McCormick, Thomas O'Grady, Allison M. Burton-Chase

Albany College of Pharmacy and Health Sciences, Albany, NY

Disparities in Hypertension Among Women with Chronic Kidney Disease

Wendy M. Parker, Kirsten M. Donato, Daryl Nnani, Darren Grabe

Albany College of Pharmacy and Health Sciences, Albany, NY

Lynch Syndrome Survivors and Preivors as Educators in Their Health Care Provider Relationships

¹Kelsey Hennig, ¹Rebecca Chu, ¹Barry DeCoster, ¹Alec LeBorgne, ¹Wendy Parker, ²Lisa Campo-Engelstein,

¹Allison M. Burton-Chase

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Albany Medical College, Albany, NY

Evaluation of an Adjusted Body Weight-Based Vancomycin Dosing Guideline

¹Emily Falli, ¹Amilee Poucher, ²Christina L. Lombardi, ¹Daniella Ferri, ^{1,2}Monique R. Bidell

¹St. Peter's Hospital, Albany, NY; ²Albany College of Pharmacy and Health Sciences, Albany, NY

Infectious Diseases

Assessment of Institutional Fluoroquinolone Use for Uncomplicated Infections

¹Steven J. Brown, ²Steven M. Lane, ^{1,2}Monique R. Bidell

¹St. Peter's Hospital, Albany, NY; ²Albany College of Pharmacy and Health Sciences, Albany, NY

Modeling the Genetic Basis for the Development of Antimicrobial Resistance

¹Jackson Lu, ¹Zhou Ma, ¹Sally Catlett, ²Amit Pai, ³Janice Pata, ³Kathleen McDonough, ¹Meenakshi Malik

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²University of Michigan, Ann Arbor; ³Wadsworth Center, New York State Department of Health, Albany, NY

Characterization of the Role of Transcriptional Regulator AraC of *Francisella tularensis*

¹Zhuo Ma, ²Dina Marghani, ²Chandra Shekhar Bakshi, ¹Meenakshi Malik

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²New York Medical College, Valhalla, NY

xCT as a Novel Restriction Factor of HIV Replication

¹Hunter Martin, ¹H. John Sharifi, ²Carlos de Noronha

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Albany Medical College, Albany, NY

The Suppression of HIV Early Replication by Tumor Suppressor p53

Sara DiGrigoli, Mark Paquette, Michaela Kinnetz, John Sharifi, Binshan Shi

Albany College of Pharmacy and Health Sciences, Albany, NY

Molecular Regulation of Host Inflammation During Influenza A Virus Infection

Rachel Visconti, Eric J. Yager

Albany College of Pharmacy and Health Sciences, Albany, NY

Identification and Characterization of Unknown Antioxidant Defense Mechanisms of *Francisella tularensis*

¹Madeline Worden, ¹Zhuo Ma, ²Chandra Shekhar Bakshi, ¹Meenakshi Malik

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²New York Medical College, Valhalla, New York

Impact of Host Glycosphingolipid Biosynthesis on Influenza Virus Infectivity

¹Clare Williams, ¹Hiram Adames, ²Shrivali Banerjee, ³Marie Pluvoise-Philip, ⁴Kouacou Konan, ¹Eric J. Yager

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Albany Academy for Girls, Albany, NY;

³Albany High School, Albany, NY; ⁴Albany Medical College, Albany, NY

Nanomedicine

Anti-CD24 Nano-targeted Delivery of Docetaxel for the Treatment of Prostate Cancer

¹Dhruba J. Bharali, ¹Thangirala Sudha, ¹Huadong Cui, ²Badar Mian, ¹Shaker A. Mousa

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Albany Medical College, Albany, NY

Self-assembly of Green Tea Catechin Derivatives Nanoparticles for Oral Lycopene Delivery

Weikun Li, Melamangalam S Jayaraman, Dhruba J. Bharali, Shaker A. Mousa

Albany College of Pharmacy and Health Sciences, Albany, NY

Targeted Delivery of Paclitaxel and Doxorubicin to Cancer Xenografts via the Nanoparticle of Nano-diamino-tetrac

¹Thangirala Sudha, ¹Dhruba J. Bharali, ^{1,2}Murat Yalcin, ^{1,3}Noureldien H. E. Darwish, ^{1,2}Melis Debreli Coskun, ¹Kelly A. Keating, ⁴Hung-Yun Lin, ^{1,5}Paul J. Davis, ¹Shaker A. Mousa

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Uludag University, Bursa, Turkey;

³Mansoura University, Mansoura, Egypt; ⁴Taipei Medical University, Taipei, Taiwan; ⁵Albany Medical College, Albany, NY

Targeted Delivery of Cisplatin to Tumor Xenografts via the Nanoparticle Component of Nano-diamino-tetrac

¹Thangirala Sudha, ¹Dhruba J. Bharali, ^{1,2}Murat Yalcin, ^{1,3}Noureldien H. E. Darwish, ^{1,2}Melis Debreli Coskun,

¹Kelly A. Keating, ⁴Hung-Yun Lin, ^{1,5}Paul J. Davis, ¹Shaker A. Mousa

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Uludag University, Bursa, Turkey;

³Mansoura University, Mansoura, Egypt; ⁴Taipei Medical University, Taipei, Taiwan; ⁵Albany Medical College, Albany, NY

Activity of Nanoparticulate Tetraiodothyroacetic Acid (Nanotetrac; Nano-diamino-tetrac) Against Preclinical Models of Glioblastoma

¹Thangirala Sudha, ¹Dhruba J. Bharali, ^{1,2}Noureldien H. E. Darwish, ³Stewart Sell, ⁴Aleck Herbergs, ^{1,5}Paul J. Davis, ¹Shaker A. Mousa

¹Albany College of Pharmacy and Health Sciences, Albany, NY; ²Faculty of Medicine, Mansoura University, Mansoura, Egypt; ³Wadsworth Center, New York State Department of Health, Albany, NY; ⁴Cleveland Clinic, Cleveland, OH;

⁵Albany Medical College, Albany, NY

Oncology

Development of Bioanalytical Method for Pharmacokinetics and Biodistribution of Novel Targeted Anticancer Drugs

Kazutoshi Fujioka, Mehdi Rajabi, Kavitha Godugu, Thangirala Sudha, Shaker A. Mousa

Albany College of Pharmacy and Health Sciences, Albany, NY

Improved Efficacy of Temozolomide (Temodar) Against Glioma by Nanotargeting Using Tetraiodothyroacetic acid (Tetrac)

Conor McCallion, Dhruba J. Bharali, Weikun Li, Sudha Thangirala, Kavitha Godugu, Shaker A. Mousa

Albany College of Pharmacy and Health Sciences, Albany, NY

The Effect of GANT61 on Mouse Mammary Tumor Stem Cells

Kayla Stuart, Jeffrey Voigt

Albany College of Pharmacy and Health Sciences, Albany, NY

POSTERS

Pharmaceutical Industry and the Pharmacist's Role Project (Fall 2016 course at ACPHS)

Nano-Diamino Propane Tetrac in the Management of Glioblastoma Multiforme

Thomas Bullis, Jordan Armeli, Giuliana Campo, Arianna Burton, Kwasi Ameyaw
Albany College of Pharmacy and Health Sciences, Albany, NY

Hicu-Gone: A Prospective Anti-Hiccup Medication

Jennifer Chen, Stephanie Cho, Kiera Clark, Shanice Coriolan, Patricia Drake
Albany College of Pharmacy and Health Sciences, Albany, NY

Diabest: The Revolutionary Antidiabetic Agent Combining a GLP-1 RA and a DPP-IV Inhibitor

Daniel Ghaly, Mina Girgis, Patrick Forlenza, Gabrielle Fernandes, Megan Gerken
Albany College of Pharmacy and Health Sciences, Albany, NY

Efficacy of Nano-formulated Temozolomide in Glioblastoma Multiforme Treatment

Jasim Shohan, William Smith, Tyler Stone, Mary Suttie, Barbara Tambasco, Shiraz Umar
Albany College of Pharmacy and Health Sciences, Albany, NY

Renerva: Potential Huntington's Disease Treatment

Kevin Le, Ariana Kalamaras, Mohsan Iftikhar, Melina Huynh, Matt Hoeffner
Albany College of Pharmacy and Health Sciences, Albany, NY

Development of Lipaxa® (gavicaserin) a More Specific Serotonergic Weight Loss Medication Also Indicated in Younger Populations

Jeffrey MacDonald, Coral Mahay, Brianna Lopez, Mei Cui Lu, Shaheedul Sami, Gavin Leung
Albany College of Pharmacy and Health Sciences, Albany, NY

Snoozeon: A Summary of a Blockbuster Insomnia Medication

Ali Nasser, Samantha Parente, Emily Ewell, Chukwuma Onumonu, Tom O'Brien
Albany College of Pharmacy and Health Sciences, Albany, NY

Complevir: a Long-Term Solution to the Global Pandemic of HIV

Mit Patel, Christopher Patterson, Nirvana Prashad, Nana Prempeh
Albany College of Pharmacy and Health Sciences, Albany, NY

eyeMAC for Macular Degeneration

James Mango, Yahya Rasouly, Kelsey Ross, Donya Rowe, Sarah Ruby, Karim Shama
Albany College of Pharmacy and Health Sciences, Albany, NY

ResuClick: A Reloadable, Reusable Epinephrine Auto Injector as an Answer to the Current Epinephrine Market Monopoly

Nick Vachon, Alexa Valentine, Amber Van-Heusen, Megan Ward, Ashia Wright
Albany College of Pharmacy and Health Sciences, Albany, NY

Advancing Medicines for Tomorrow: Pressures, Paradigms and Progress – the roles of science and collaboration



Keith Horspool, Ph.D.

Vice President, Material and Analytical Sciences
Boehringer Ingelheim
Ridgefield, CT

Keith Horspool is Vice President of Material and Analytical Sciences at Boehringer-Ingelheim, Ridgefield, CT. His department develops and applies scientific methods and tools to generate improved product and process understanding and robustness. This is a new organization and the goal is to apply physical/material sciences-based approaches (e.g. crystal engineering, structural analyses, physical characterization, predictive modeling) throughout the duration of the drug development and commercial lifespan of a product supporting the implementation of effective, cost efficient processes for the manufacture of drug product and drug substance.

Prior to joining BI, Keith worked at Pfizer and Astra Zeneca. He has 30 years' experience during which he has managed preformulation, product development, drug delivery and materials science. He has a B.Sc., in Pharmacy, a Ph.D., in Pharmaceutical Chemistry.

Healthcare is undergoing extraordinary changes due to unprecedented cost pressures combined with the growing demand for new treatments and advances in new technology that offer profound ways to enable future advances in drug discovery and development. Various themes underlying potential new directions for the pharmaceutical/biotech industry require strong collaboration with academia, patients, regulatory authorities and partners in other industries that possess expertise in areas that will drive innovation and new paradigms that enable more efficient and effective progression of new modalities and their supply to the market. The opportunities are immense and reflect the exciting possibilities for pharmaceutical scientists to engage on cutting-edge concepts that will impact next generation healthcare for patients worldwide. The presentation will provide a view on certain areas, past, present, and future, relevant for shaping pharmaceutical/biotech strategies to accelerate new therapies through development and how healthcare solutions will influence future medical outcomes.

Safety First



Shannon R. Magari

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 2016 efforts and outline our 2017 EHS agenda.

The ACPHS Chapter of the American Association of Pharmaceutical Scientists



Chiara Evans

President, ACPHS Chapter AAPS

Highlighted will be the who, what, and why of the ACPHS Chapter of the American Association of Pharmaceutical Scientists (AAPS). Events held by the ACPHS AAPS during the academic year will be presented, as well as how AAPS plays a role in encouraging ACPHS students to engage in research on campus.

The Value of Innovation



Nathan Tinker, PhD

Executive Director
NewYorkBIO

Nathan Tinker has been Executive Director of NewYorkBIO since 2007. As Executive Director, Nathan serves as a spokesman and advocate for the state's industry. He comes to the Association with a deep knowledge and awareness of the industry and its unique strengths in New York and he has more than 20 years of experience in working with both global and emerging technology companies.

Immediately prior to joining NewYorkBIO, Nathan served as Executive Director of the Sabin Vaccine Institute Cancer Vaccine Consortium and as the Director of the Nanotechnology and Biotechnology Practice at Antenna Group. Before that, Nathan was Co-Founder and Executive Vice President of the NanoBusiness Alliance, the national trade association for nanotechnology. Nathan began his career in market research and communications, serving such clients as Apple, eSpeed, Sprint, Cantor Fitzgerald, DaimlerChrysler, Yahoo!, CSX, and many others.

Our industry is under attack, from politicians, media, and the public, which has always had a love-hate relationship with the biopharmaceutical industry, going back to the 1800s. But today it's more intense and it's coming from more directions. And today the stakes are demonstrably higher that short-sighted policy changes will endanger innovation and hope. The fact is that we as an industry need to tell our story better. We need a consistent narrative—the true story about the miracles we've accomplished, the staggering unmet medical needs we face, and the economic realities that face our business. We need to tell the story of the Value of Innovation.

Novel Non-Retinoid RPE65 Isomerase Antagonists for the Treatment of Age-Related Macular Degeneration and Stargardt Disease



Christopher L. Cioffi

Department of Basic and Clinical Sciences
Department of 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 55 years or older in the developed world. Nearly 11 million people in the United States are affected, and this patient population is projected to increase to approximately 22 million. Globally, annual health care costs exceed \$300 billion and the total number of AMD patients is estimated to reach 288 million by 2040. 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. Dry AMD represents a slowly progressing neurodegenerative disorder in which rod and cone photoreceptors die in the central part of the retina (macula) due to an accumulation of toxic bisretinoids and lipofuscin in the retinal pigment epithelium (RPE). Moreover, excessive accumulation of lipofuscin is the sole causative factor of macular dystrophy in autosomal recessive Stargardt disease (STGD). Currently, there is no FDA-approved therapy for dry AMD or STGD. It has been hypothesized that inhibition of bisretinoid formation in the RPE may delay the progression of dry AMD and suppress degenerative processes in STGD. One approach under investigation is modulation of the visual cycle via partial inhibition of the isomerohydrolase RPE65 isomerase, which converts all-*trans* retinyl ester to 11-*cis* retinol within the RPE. Retinoid-based antagonists of RPE65 isomerase have been reported to reduce bisretinoid formation in the *Abca4*^{-/-} transgenic mouse model of enhanced lipofuscinogenesis. Furthermore, the non-retinoid RPE65 isomerase antagonist emixustat (ACU-4429) produced a dose-dependent and reversible suppression of rod photoreceptor sensitivity in patients with geographic atrophy in a Phase IIa clinical trial (ENVISON-CLARITY). However, suboptimal pharmacokinetic (PK) characteristics and observed off-target retinal toxicity has rendered emixustat less than optimal for chronic administration. Thus, the identification of a new class of RPE65 isomerase antagonists with improved PK, efficacy, and safety profiles is of high importance. Our medicinal chemistry team, in collaboration with Columbia University and the University of Oklahoma, will rationally design and develop novel RPE65 isomerase antagonists utilizing a hit compound identified from an *in silico* screen campaign as a springboard for our drug design efforts. Our team will implement and execute a medicinal chemistry work plan through hit-to-lead and lead optimization campaigns in order to identify novel drug-like RPE65 isomerase antagonists that exhibit improved ADME, DMPK, and safety profiles relative to emixustat and are worthy of advancement into drug development, IND-enabling study assessment, and clinical trials.

Quantifying the Minimum Adherence Threshold Associated with the Development of Reverse Transcriptase Resistance Mutations among HIV-infected Veterans' Affairs Patients Receiving Antiretroviral Therapy



¹Jenna Yager, ²John Faragon, ^{1,3}Nimish Patel

¹Albany College of Pharmacy & Health Sciences, Albany, NY

²Albany Medical Center, Albany, NY

³Samuel S. Stratton Veterans' Affairs Medical Center, Albany, NY

Purpose: Poor adherence (ADH) to antiretroviral therapy (ART) can lead to deleterious patient outcomes including development of resistance among patients infected with human immunodeficiency virus (HIV). The primary objective of this study was to quantify the minimum ADH threshold associated with development of reverse transcriptase (RT) resistance mutations. The secondary objective was to determine if the minimum adherence threshold was independently associated with development of RT resistance mutations.

Methods: A retrospective cohort study, utilizing repeated subject sampling, was conducted among patients receiving care at the Upstate New York Veterans' Healthcare Administration between 2000 and 2013. Inclusion criteria were: 1) age ≥ 18 years, 2) diagnosis of HIV infection, 3) receipt of ≥ 3 ART medications from ≥ 2 classes for ≥ 3 months, and 4) availability of pre- and post-treatment resistance tests. Data obtained from patients' medical records included: demographics, history of HIV infection, antiretroviral history, genotypic test results and dispensing records. Medication ADH was captured using pharmacy refill records to calculate medication possession ratios as a percentage. The outcome of interest in this study was new mutations in RT as indicated by genotypic test results. Classification and regression tree (CART) analysis was performed to identify the minimum ADH threshold associated with development of incident RT mutations.

Results: Among the 65 included subjects, mean \pm standard deviation (SD) age was 49.2 ± 8.7 years. Subjects were primarily male (98.5%). Distribution of ART regimens was: protease inhibitor-based (40.0%), followed by mixed class (≥ 3 ART classes, 30.8%), non-nucleoside reverse transcriptase inhibitor-based (26.2%) and integrase strand transfer inhibitor-based regimens (3.1%). Mutations in RT were observed in 25 (38.5%) patients. The CART-derived ADH threshold associated with development of RT mutations was 80.5%. Patients above this threshold were less likely to develop RT mutations than those below (13.6% versus 51.2%, $p=0.003$). In multivariate analyses, ART ADH $\geq 80\%$ (adjusted odds ratio: 0.15, 95% confidence interval: 0.04–0.60, $p=0.007$) was independently associated with development of RT mutations after adjustment for regimen type and number of non-ART medications.

Conclusions: Patients with an ART ADH threshold of $\geq 80\%$ were significantly less likely to develop RT resistance mutations than patients below this threshold. After adjustment of confounding factors, ART ADH $\geq 80\%$ was independently protective against developing RT resistance mutations.

Healthcare, Alliances, and Virtues in the Women's Health Movement: An Initial Study of the *Our Bodies, Ourselves* Archives



¹Barry DeCoster and ²Wendy Parker

¹Department of Humanities and Communication
Albany College of Pharmacy and Health Sciences, Albany, NY

²Department of Population Health Sciences
Albany College of Pharmacy and Health Sciences, Albany, NY

The goals and methods of the Women's Health Movement aimed to transform health care, most notably with the objective of creating a collective understanding of women's bodies while resisting medicalization within modern medical care. We studied the work of the Boston Women's Health Book Collective (BWHBC) as a specific example of wider trends and goals of the Women's Health Movement. Our interdisciplinary, archival project analyzed the conception of, researching of, and writing of *Our Bodies, Ourselves*, a revolutionary text in women's health written by the BWHBC. *Our Bodies, Ourselves* was designed to achieve two goals: to allow women to be lay knowers about their own bodies, and to guide physicians on the specific needs of women's health. In writing this original text, though, the BWHBC members were forging new relationships, and relationships have moral dimensions' worthy of attention. Why did the women trust one another? How and with whom did they collaborate? Did they enact virtuous selves allowing both individually self-preserving and collectively empowering collaborations? Collaboration and interdisciplinary work is difficult. For those who are marginalized and/or powerless in various ways, alliance building and collaboration is necessary for survival. These oppressive forces may limit us as individuals, restrict the values we hold, or how we develop virtuous traits. This difficulty in navigating collaboration requires a certain kind of self, a particular attitude. This project sought to find evidence in the BWHBC archives to understand how virtue was or was not a part of the words and documented materials affiliated with the women's health movement in the 1970s. Were the women's health movement ideal of "knowledge is power" and the goal of patient empowerment results of successful collaborations? Do threads of these collaborations exist in the contemporary patient provider relationship? Our conceptual analysis and what we learned from the archives led to a second phase of the project, which we will highlight briefly in our talk. We interviewed eleven people, a mixture of OBGYNs, midwives, and women who have given birth to discover how facets of collaboration are enacted in contemporary healthcare. The interviews helped to identify and clarify the goals and methods of collaboration involved in childbirth, as well as important disconnects and clear differences in how diverse providers approach patients and patient care. Our research was funded by the ACPHS Scholarship of Discovery Grant "The Collaborative Self Virtues for Seeking and Building Alliances in Health Care," 2015-2016.

ResuClick: A Reloadable, Reusable Epinephrine Auto Injector as an Answer to the Current Epinephrine Market Monopoly



Nick Vachon, Alexa Valentine, Amber Van-Heusen,
Megan Ward, Ashia Wright

Pharmaceutical Industry and the Pharmacist's Role Project*
Albany College of Pharmacy and Health Sciences, Albany, NY

Rationale. Between 2008 and 2015, the price of EpiPen® (Mylan Pharmaceuticals), a drug that is used to treat anaphylaxis from allergen exposure, jumped from \$100 to over \$600 in cost to the patient. Due to the increase in cost, both patients and healthcare providers are being left without the device or turning to purchasing epinephrine multi-dose vials and syringes instead of purchasing the autoinjector pen. While there have been many similar devices that have been developed (such as Auvi-Q® by Kaleo Pharmaceuticals) and generic epinephrine products that have entered and been taken off the market, there is a lack of an epinephrine autoinjector that aims to reduce negative patient outcomes by reducing burden and cost to the patient. ResuClick, an epinephrine autoinjector designed around this idea, aims to become the solution to this long-standing health issue. **Research, Clinical, and Development.** The development of this device would require outsourcing development engineering with numerous companies due to needing to redesign the available technology to be suitable for the goals of the ResuClick device. Cost and production time would be greatly decreased because of the technologies that are already available for similar devices such as insulin pens and syringes. **Regulatory.** The purpose of Regulatory Affairs during the development and launch of ResuClick is to ensure that the product follows necessary regulations and procedures in place by the Food and Drug Administration. A 501(K) application submission would need to be filed with the Center for Devices and Radiological Health to ensure the device follows medical device regulations. In addition, an Abbreviated New Drug Application would need to be filed with the Food and Drug Administration to allow for accelerated review of the drug to be placed on the market. **Marketing and Sales.** ResuClick would be marketed towards outpatient settings and community pharmacies and primary care physicians, where promotional focus would be on the ease of the device, the reduced cost burden to both patients and healthcare providers, as well as demonstrating that ResuClick is a breakthrough within the epinephrine autoinjector market by allowing choice for all individuals. **Medical Affairs.** The Medical Affairs team would provide independent medical education to both healthcare providers and patients for the correct assembly and usage of the device through publication, research, call centers, Frequently Asked Questions sheets, and formulary dossier. **Ethical Decision Making.** The purpose of this department is to collaborate with other departments and various professionals to make sure that all parts and individuals that are involved with the development, launch, and product lifecycle of ResuClick follow moral and ethical standards. This would include oversight of all departments involved with ResuClick as well as current and future patients who may use ResuClick.

* Presented by students who completed the ACPHS PHM 324 Pharmaceutical Industry and the Pharmacist's Role course in Fall 2017. It was an overview of the pharmaceutical industry and covered: research, development, medical, regulatory, marketing, sales, distribution, legal, ethics and compliance. The course was team taught by pharmaceutical industry experts.

Effects of Ischemia/Reperfusion on Citrate Synthase and SERCA Activity in the Rabbit Urinary Bladder Treated with Ganoderma Lucidum

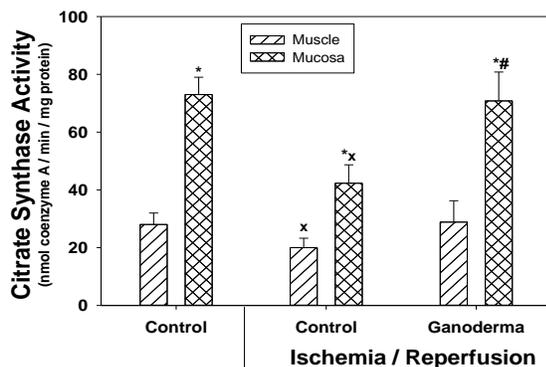
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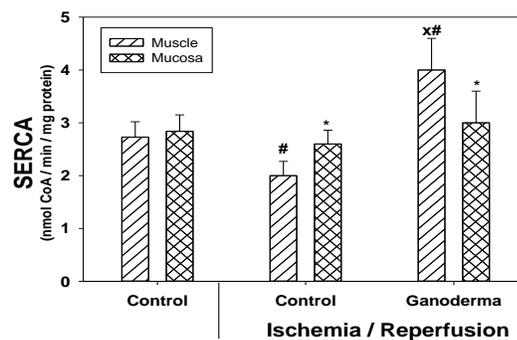
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The ability of the Chinese natural product “Ganoderma Lucidum (GL)” to protect against oxidative stress was studied using an in-vivo model of Ischemia / Reperfusion (I/R) in the rabbit urinary bladder. The goal was to correlate bladder contractility and compliance with the enzyme activities of Citrate Synthase and SERCA to analyze the biochemical changes associated with mitochondrial function and calcium regulation. Three groups of 6 adult male NZW rabbits each were divided as follows: Group 1 consisted of control rabbits; Group 2 of rabbits that received bilateral ischemia; and Group 3 of rabbits undergoing bilateral ischemia and fed a suspension of GL by gavage daily for 2 weeks prior to surgery and for 4 weeks following surgery. Bilateral ischemia was performed by clamping the vesicular arteries for 2 hours (ischemia) and then removing the clamps and allowing the rabbits to recover for 4 weeks (reperfusion). In a previous study utilizing the same tissues, GL was found to significantly protect optimal contractility and compliance of the bladder when exposed to oxidative stress compared to the control group. This was associated with increases in the activities of both Citrate Synthase and SERCA, supporting the importance of mitochondria and calcium regulation in maintaining normal bladder physiology. The mechanism for GL is likely complex and multifactorial but at least one factor appears to be through combating oxidative stress, possibly as a free radical scavenger, thereby maintaining cellular membrane integrity. Further studies are warranted to better understand the role that other enzymes and cellular processes play in the beneficial effects of GL.



* = Significantly different from Muscle
x = Significantly different from Control
= significantly different from Control I/R, p < 0.05



* = Significantly different from Muscle,
x = Significantly different from Control I / R
= Significantly different from Control, p < 0.05

The Functional Characterization of the BRPF3 Bromodomain

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Bromodomains are epigenetic readers of post-translational modifications, namely acetylated lysines¹. The bromodomain-PHD finger 3 (BRPF3) protein is a part of the bromodomain superfamily sub-family IV, which also contains its paralogs, BRPF1 and BRPF2/BRD1². Each of these proteins contain a bromodomain, a PZP region, and a PWWP domain. While much is known about BRPF1 and BRPF2, there has been little investigation into BRPF3. Currently, no structural information is available for the BRPF3 bromodomain, and its histone ligands have not been characterized. BRPF3 is part of a complex with the histone acetyltransferase bound to ORC1 (HBO1), and is important for guiding the chromatin remodeling functions of HBO1³. HBO1 and BRPF3 play a role in regulating DNA replication and embryo development. Mutations of BRPF3 are associated with bile duct cancer, pediatric leukemia, and adult medulloblastoma⁴. Insight into the mechanisms behind its function as a histone reader domain are imperative to understanding its role in the HBO1 HAT complex, and will be essential to assist in the design of therapeutic agents for these diseases in the future. In this study we identified conditions to optimally express and purify the BRPF3 bromodomain, and used isothermal titration calorimetry to detect acetylated histone ligands recognized by this bromodomain.

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Investigating the Role of Disulfide Bridge Formation on Histone Recognition

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ATAD2a is a highly conserved chromatin-regulation gene that contains an AAA+ ATPase domain and a bromodomain. Current research has shown that ATAD2a functions as an oncogene, and ATAD2a is highly over-expressed in a variety of aggressive carcinomas. Working in cooperation with additional signaling systems (likely cell-cell contacts and growth factors) and acting as a co-factor for transcription of the MYC oncogene, ATAD2a overrides the normal cell cycle and initiates cell transformation and uncontrolled growth. Once activated in a transformed cell, ATAD2a initiates a positive feedback loop, leading to amplified production of ATAD2a, its co-regulators, and Myc (Boussouar et al., 2013). As a proto-oncogene, ATAD2a is required during DNA replication as a reader of newly synthesized histone marks, suggesting an integral role in replication-coupled chromatin reassembly (Koo et al., 2016).

The ATAD2a bromodomain is composed of 128 amino acid residues, which form into a conserved bundle of four alpha helices that shape the bromodomain-binding pocket. Bromodomain proteins function as epigenetic readers that recognize acetylated histone tails to facilitate the transcription of target genes. Interestingly, the ATAD2a bromodomain contains two cysteine residues located just outside of the bromodomain binding pocket and form a disulfide bridge. Protein instability has been a significant obstacle to our investigations on the structure and function of the ATAD2a bromodomain, and in the literature this has been mitigated by the addition of reducing agents to prevent oligomerization of ATAD2a bromodomains via free cysteine residues. However, our research suggests that formation of this disulfide bridge directly impacts the shape of the binding pocket, and regulates the affinity of the ATAD2a bromodomain for acetylated histone ligands. Understanding the structural impact of correct disulfide bridge formation on the function of the ATAD2a bromodomain will be essential to support the design of effective ATAD2a bromodomain inhibitors, and may provide a means to interrupt the runaway amplification cycle of ATAD2a in malignant cancer cells.

Novel Probes for Sirtuins: A Chemical Biology Approach

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Sirtuins, also called Class III HDACs, consume stoichiometric amounts of nicotinamide adenine dinucleotide (NAD⁺) to remove acetyl group from lysine residues and to produce nicotinamide and *O*-acetyl-ADP-ribose. This intriguing class of enzymes has been implicated in regulating various cellular events and has also been suggested to mediate the beneficial effects of calorie restriction (CR). Sirtuins have been intensely pursued by academia and pharmaceutical industry as therapeutic targets.

However, controversies on sirtuin biology also peaked during the last few years because of conflicting results from different research groups. This is partly because these enzymes have been discovered recently, and the intricate interaction loops between sirtuins and other proteins make the characterization of them extremely difficult. One of the daunting tasks is to correlate sirtuin activity to disease pathogenesis. Current molecular biology and proteomics techniques report protein abundance rather than active sirtuin content. Innovative chemical tools that can directly probe the functional state of sirtuins are desperately needed.

We have been taking a highly integrative approach to interrogate the functional state of sirtuins in complex biological samples. Our preliminary results demonstrate the feasibility of this strategy. We have obtained a set of powerful chemical probes that are capable of assessing the active content of sirtuins in model systems. In complex native proteome, the probe should selectively “highlight” the active sirtuin components. Combined with mass spectrometry based proteomics analysis, this strategy should unveil the functional profile of sirtuins under different physiological and pathological conditions. This will provide information on how abnormal enzyme activity will contribute to disease progression. Furthermore, cell permeable probes will also be employed in cellular imaging study. It will enable the simultaneous detection of functional state and localization and empower the direct analysis of sirtuin function in response to cellular and environmental cues.

Reversal of Anticoagulant Activities of Heparin and its Derived Low Molecular Weight Heparin by Poly-L-Lysine: Comparative Study with Protamine Sulfate

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Heparin is used extensively as an anticoagulant and is administered as unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for the prevention and treatment of deep vein thrombosis and pulmonary embolism. It is also used during invasive angiographic or cardiopulmonary bypass surgeries to prevent thromboembolic disorders. Protamine sulfate (PS) is being used to neutralize the effects of UFH after invasive surgical procedures. Although PS is effective and relatively safe, serious adverse reactions have occurred. In addition, PS can only partially reverse the effects of LMWHs. We studied the neutralizing effects of three different molecular weights of poly-L-lysine (PLL-1K, PLL-4K, and PLL-15K) as possible alternatives to PS toward UFH, LMWHs (tinzaparin and fraxiparin), fondaparinux, and rivaroxaban using an aPTT assay. While both PLLs and PS did not reverse the anticoagulation mediated by fondaparinux and rivaroxaban, PLL-15K was the most effective in neutralizing UFH and LMWHs as compared to PS. Thus, this study reveals that PLL-15K might be a suitable alternative to PS as an antidote for UFH and LMWHs.

Biological Function and Histone Recognition of Family IV Bromodomain-containing Proteins

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Bromodomain proteins function as epigenetic readers that recognize acetylated histone tails to facilitate transcription of target genes. There are approximately 60 known human bromodomains, and these are split into 8 sub-families based on structural conservation. The bromodomain-containing proteins in family IV consist of 7 members (BRPF1, BRPF2, BRPF3, BRD7, BRD9, ATAD2a, and ATAD2b). The bromodomains of each of these proteins recognize and bind acetyllysine residues on histone tails protruding from the nucleosome. However, the histone marks recognized by each bromodomain protein, can be very different. Our research revealed that the BRPF1 subunit of the MOZ histone acetyltransferase (HAT) recognizes histone acetylated at H2AK5ac, H4K12ac, H3K14ac, H4K8ac and H4K5ac¹. While the bromodomain of BRD7, a member of the SWI/SNF complex, was shown to preferentially recognize histones H3K9ac, H3K14ac, H4K8ac, H4K12ac and H4K16ac². The bromodomains of BRPF2 and BRPF3 are very similar in amino acid sequence, and function as part of the HBO1 HAT complex, but there is limited data on which histone ligands they bind³. Similarly, there is little known about the histone targets of the BRD9 and ATAD2b bromodomain proteins. Interestingly, the ATAD2a bromodomain was recently shown to preferentially bind to H4K5acK12ac in newly synthesized histones following DNA replication⁴. ATAD2 is a co-activator of the estrogen and androgen receptors, and has also been shown to stimulate MYC and E2F-dependent cell proliferation. Additionally, ATAD2a is overexpressed in a range of cancers including lung, breast, and prostate cancer, as well as ovarian and hepatocellular carcinoma. However, despite the physiological importance of the family IV bromodomains, little is known about how they function at the molecular or atomic level. Here, we summarize our understanding of how family IV bromodomains recognize and select for acetyllysine marks by providing the molecular details of ligand binding, which will be critical for the development of new therapeutic interventions targeting these bromodomains.

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Structural Insights into Recognition of Acetylated Histone Ligands by the BRPF1 Bromodomain

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In humans, translocation of the monocytic leukemia zinc-finger (MOZ) histone acetyltransferase (HAT) protein is associated with a subtype of acute myeloid leukemia (AML) with a particularly poor outcome. MOZ forms tetrameric complexes with ING5 (inhibitor of growth 5), hEAF6 (human Esa1-associated factor-6-ortholog), and the bromodomain-PHD finger protein 1 (BRPF1). BRPF1 contains a unique combination of domains typically found in chromatin-associated factors, which includes PHD fingers, a bromodomain and a PWWP (Pro-Trp-Trp-Pro) domain. Bromodomains are evolutionary conserved structural motifs generally known to recognize acetylated lysine on the histone tail. Previous studies revealed that the BRPF1 bromodomain preferentially binds to the H2AK5ac, H4K12ac and H3K14ac histone peptides. However, the molecular mechanism driving recognition of the acetylated histone tails by the BRPF1 bromodomain has not been elucidated. In this study we used X-ray crystallography to determine the structures of the BRPF1 bromodomain in complex with the H2AK5ac and H4K12ac histone peptide ligands. These structures revealed that a network of H-bond and hydrophobic contacts coordinate the acetyllysine moiety and make specific contacts to flanking residues in the histone tail. We also identified two ordered water molecules in the binding pocket, which mediate coordination of the acetyllysine moiety. To gain a better understanding of the molecular mechanism driving specificity, we also carried out site-directed mutagenesis in combination with isothermal titration calorimetry (ITC) studies. These studies indicated that the two most important contacts for ligand coordination include the highly conserved N83 residue, which contacts the acetyllysine directly via H-bond, as well as F89, which creates a critical hydrophobic contact with the histone tail and shapes the bromodomain binding pocket wall. Circular dichroism (CD) spectroscopy studies performed on each of the wild-type and mutant proteins demonstrated that the mutations introduced into the BRPF1 bromodomain did not cause any significant change in the overall structure, or unfolding of the mutant proteins as evinced by the observed less than 6% change in α -helical content. The work presented here is important for unraveling the role of the BRPF1 bromodomain in modulating the genomic binding targets of the MOZ HAT, and its potential as a therapeutic target in MOZ-related leukemias.

The Link Between Tissue Hypoxia and Calcinosis in Systemic Sclerosis

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Purpose: Systemic sclerosis (SSc) is characterized by three main aspects: autoimmunity, vasculopathy, and fibrosis. Calcinosis is a complication in SSc which is most frequently seen at the fingertips. Decreased density of small blood vessels in SSc results in multiple regions of tissue hypoxia and induction of hypoxia-inducible factor-1 (HIF-1), which has a role in activation of osteoclasts and bone resorption. We hypothesize it has a role in calcinosis as well.

Methods: An extensive literature review was performed, examining the link between hypoxia and calcinosis. There is limited data published on the relationship between calcinosis and hypoxia. This necessitates evaluation of other disease states and using associations to elucidate the mechanisms involved.

Results: Key associations have been noted between calcinosis and acro-osteolysis, digital ulcers, osteoporosis, and pulmonary arterial hypertension. These manifestations are each related to hypoxia and/or HIF-1, providing support of its role in calcinosis. Calcinosis in SSc is dystrophic. We hypothesize that the calcium in calcinosis arises from enhanced bone resorption. Ultrastructural and crystallographic analysis of calcinosis revealed that the major constituent of the deposits is hydroxyapatite, further supporting the notion that the source of the calcium is bone. In an unpublished case report, a patient with SSc and pulmonary fibrosis was prescribed treprostinil, a potent vasodilator. After approximately 6 months of therapy, she noted dramatic reduction in her calcinosis, confirmed on imaging. This provides some evidence supporting the relationship between hypoxia and calcinosis in SSc.

Conclusion: Calcinosis is related to chronic hypoxia and acro-osteolysis in the setting of SSc. This results in the creation of a hypoxic and hypothermic microenvironment in the digits, favoring bone resorption, and calcium deposition. Chronic hypoxia and induction of HIF-1 promote bone resorption and is the suspected source of the calcium in calcinosis. Therefore, examination of bone mineral density and degree of hypoxia in the digits may be a predictor for calcinosis in SSc.

Evaluation of Procoagulant Compounds with Thromboelastography

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Hemostatic agents play an important role in reestablishing hemostasis in pre-hospital situations when there is hemorrhage or traumatic injury. Despite medical advances, hemorrhagic shock is still the main cause of battlefield mortality and the second most prevalent cause of mortality in civilian trauma. In an effort to create a more efficient hemostatic agent capable of creating a stronger clot in less time when compared to the current procoagulant topical medications, we are testing new hemostatic agents developed with the use of nanotechnology. Unfortunately, when testing the new hemostatic agents with the thromboelastography (TEG) assay we found that the new nanofiber products do not appear to be more efficient hemostatic agents. Further testing is required to determine if this is a limitation of testing because matrix formation ability was limited.

High Glucose Potentiates a Shift from Apoptosis to Necroptosis

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Necroptosis is an inflammatory programmed cell death (PCD) pathway that is distinct from caspase-dependent apoptosis, which is non-inflammatory. The signaling is driven by three kinases: RIP1 (initiator kinase), RIP3, and MLKL. Downstream of RIP1, RIP3, and MLKL necroptosis stimulates glycolysis leading to accumulation of reactive oxygen species (ROS) and advanced glycation end products (AGEs). These ROS and AGEs damage the cell leading to cellular lysis underscoring the central role of glucose in necroptosis. Previously, we showed that hyperglycemia upregulates necroptosis and that hypoxia-ischemia brain injury is exacerbated in hyperglycemia due to necroptosis. That work also showed that hyperglycemia inhibits apoptosis while promoting caspase-independent cell death. This suggested that hyperglycemia may shift apoptosis to necroptosis. Here, we show that this hypothesis is likely the case. Using two different stimuli of extrinsic apoptosis, TNF- α and Fas ligand (FasL), we demonstrate that cell death shifts from caspase-dependent apoptosis to RIP1-dependent necroptosis in hyperglycemic conditions. Results are supported by the fact that phosphatidylserine exposure (marker of apoptosis) decreases in hyperglycemic conditions while membrane permeability (marker of necroptosis) increases. The shift to necroptosis was coincident with increased levels of the central necroptosis kinases and was not associated with decreased caspase activity. The shift to necroptosis also involved ROS and changes in intracellular calcium signaling. That hyperglycemia induces a shift from apoptosis to necroptosis represents a shift from non-inflammatory to inflammatory death in this condition. We believe that this phenomenon may play a role in the exacerbation of ischemic brain injuries during hyperglycemia.

Novel Probes for Nucleobase Transporters

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The transport of purine and pyrimidine nucleobases is central to nucleotide metabolism and essential for the delivery of numerous therapeutics, yet the proteins and mechanisms that govern this process are poorly understood, particularly in humans. Nearly all organisms express several classes of proteins that selectively transport nucleobases, both actively and passively, into and out of cells. In humans, however, no specific nucleobase transporters have yet been identified. The only known human proteins that accept nucleobases as substrates do so with low affinity and by an unknown mechanism. In addition, the observed nucleobase transport kinetics in human cells cannot be accounted for by this single class of transporters. The identification and characterization of nucleobase transporters has been significantly hindered by the lack of specific and accurate tools. Thus, there is a critical need to develop tools for the study of nucleobase transport and to use these tools to determine the identity, substrate specificity and mechanisms of human transport proteins involved in this process.

In this project, we will take a highly integrative chemical biology approach to capture and characterize unknown nucleobase transporters and receptors in humans. We have developed a series of bifunctional nucleobase analogs that are effective in tagging and isolating potential nucleobase transporters. Novel biochemical assays will also be developed to enable the facile and accurate characterization of transport kinetics and substrate specificity. We expect these new tools to significantly expand the scope of our current capabilities for drug discovery and development of nucleotide antimetabolites.

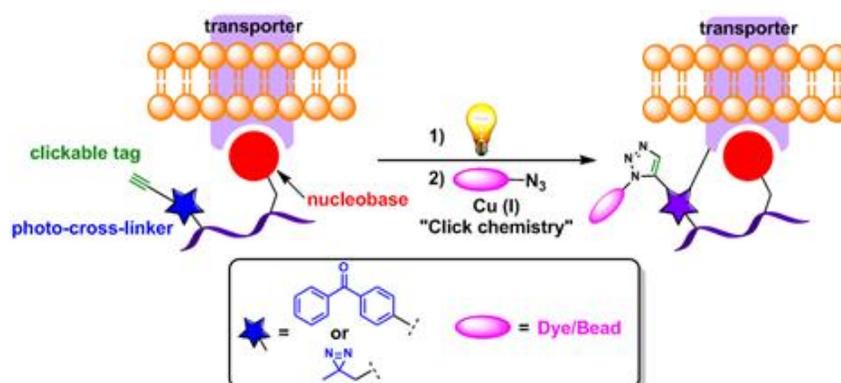


Figure 1. Schematic representation of the labeling of transporters using bifunctional probes.

The Mediation of Prostaglandin E, D and F_{2α} in Centrally Injected Arachidonic Acid-induced Cardiorespiratory Effects

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Purpose of the study: Recently we reported that centrally injected arachidonic acid (AA) led to pressor and bradycardic responses on cardiovascular system and hyperventilation effect on respiratory system by activating cyclooxygenase (COX) to thromboxane A₂ (TXA₂) signaling pathway. No previous studies have been found to report either partial or complete mediation of other centrally effective COX metabolites such as prostaglandin (PG) D, PGE and PGF_{2α} alongside TXA₂ in the AA-evoked cardiorespiratory effects so far. Therefore, the present study was designed to investigate the possible effects of centrally injected AA on cardiorespiratory parameters and the mediation of the central PGD, PGE and PGF_{2α} in AA-induced cardiorespiratory effects in rats.

Methods: Experiments were performed in male Sprague Dawley rats. AA (0.5 μmol) was injected intracerebroventricularly (i.c.v.) and cardiorespiratory parameters were recorded. To show mediation of the central PGD, PGE and PGF_{2α} in AA-evoked cardiorespiratory effects, pretreatment with DP/EP prostanoid receptor antagonist, AH6809 (10 and 20 μg; i.c.v.) or FP prostanoid receptor antagonist, PGF_{2α} dimethyl amine (PGF_{2α}DA) (30 and 50 μg; i.c.v.) was carried out 5 min before AA (0.5 μmol) treatment, and the cardiorespiratory parameters were recorded.

Results: Central administration of AA caused pressor and bradycardic responses on cardiovascular system and hyperventilation and increase in partial oxygen pressure (pO₂) and decrease in partial carbon dioxide pressure (pCO₂) effects on respiratory system in rats. Pretreatment with different doses of AH6809 or PGF_{2α}DA partially blocked the cardiorespiratory and blood gases changes induced by AA.

Conclusions: The current data propose that centrally injected AA produces pressor and bradycardic responses on cardiovascular system and hyperventilation and increase in pO₂ and decrease in pCO₂ effects on respiratory system. As a result of evoked hyperventilation, central treatment with AA might cause an increase in pO₂ and a decrease in pCO₂. Interestingly activation of central PGD, PGE and PGF_{2α} receptors is partly involved in the pressor, bradycardic, hyperventilation and blood gases responses of the centrally injected AA in rats.

The Key Role of Central Thromboxane A₂ on Central Cardiorespiratory and Neuroendocrine Regulation

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Thromboxane A₂ (TXA₂) is one of the biologically active products of prostaglandin synthesis metabolism and is synthesized in the central nervous system and plays critical role as a neuromodulator or neurotransmitter in various brain-controlled activities. In the current presentation, the key role of TXA₂ on central cardiovascular, respiratory and neuroendocrine regulation under normal and stimulated conditions were reviewed.

Previously we reported that intracerebroventricularly injected TXA₂ causes an increase in blood pressure by activating central TXA₂ receptors in normotensive and hypotensive rats and also that central TXA₂ is involved in central regulation of blood pressure especially in hypotensive conditions. Moreover, central endogenous TXA₂ is mediated in the melittin, a phospholipase A₂ (PLA₂) activator, arachidonic acid (AA), CDP-choline, a choline donor, or orexin -evoked pressor response under normal and stimulated conditions. The central TXA₂ plays active role in the respiratory control. Because centrally injected AA induced hyperventilation along with increase in pO₂ and the decrease in pCO₂ which is mediated by the activation of central TXA₂ signaling pathway. The activation of central TXA₂ signaling pathway also mediated centrally administered CDP-choline, a choline donor, -induced hyperventilation effects. Our previous reports also explained that central TXA₂ signaling pathway can activate neuroendocrine regulation. Because central treatment with AA stimulated hypothalamic–pituitary–gonadal axis in male rats by activating central TXA₂ signaling pathway. As well as central TXA₂ could cause increase in plasma catecholamine, vasopressin and renin in normotensive and hemorrhaged hypotensive rats, and the activation of the central TXA₂ signaling pathway is the one involved in this melittin or AA -induced increase in plasma catecholamine, vasopressin and rennin levels.

In summary, those reports could be interpreted that TXA₂, an AA metabolites, has potential role in central nervous system as a neuromodulator or neurotransmitter on central cardiorespiratory and neuroendocrine regulation under normal and stimulated conditions.

Towards Better Structure-Based Models of P-Glycoprotein Efflux of Drugs

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ABC-cassette efflux pumps intercept numerous drug molecules entering the cells through the membrane bilayer at the internal interface and return them back in a complex, ATP-driven process. The efflux affects pharmacokinetics in the brain and other organs, and contributes to multiple drug resistance of cancer cells. Molecular details of the ABC-pumps actions and their relationship to drug structure are crucial for rational development of ABC-pump inhibitors as well as for minimizing the susceptibility of new drugs to the efflux. Despite almost 40 years of intensive study, the mechanistic details of the efflux process remain rather sketchy, relevant quantitative data for the vast majority of drugs are surprisingly sparse, and, consequently, the drug development process in this area has been slow and inefficient. We are using the most frequently studied efflux pump, P-glycoprotein (ABCB1 - Pgp) multidrug transporter.

Numerous published models relating drug structures to their Pgp-mediated efflux exhibit low descriptivity and predictivity. Main reasons for this weak performance are: (1) the lack of mechanistic detail considering only the first drug-Pgp binding step, and (2) the inability to quantitatively account for the drug presence at the internal bilayer interface, which determines the extent and location of drug binding in the Pgp entry site. The first issue is being ameliorated using at least two drug-Pgp binding steps: the initial binding to the inward-facing Pgp from the internal bilayer interface and the final binding step to the outward-facing Pgp, which precedes the release of the drug into the extracellular aqueous phase. To obtain the relevant data, we are developing novel planar and spherical asymmetric bilayer systems, in which reconstituted Pgp is uniformly oriented, and experimental conditions can be controlled on both sides of the bilayer. The second issue is addressed using drug distribution in bilayer strata predicted by our unique structure-based system. Measured efflux kinetics for Pgp substrates/inhibitors with varying intrabilayer distribution is being analyzed using a kinetic model comprising both relevant steps of drug efflux. The binding affinities for both key steps in the kinetic model are linked to computational atomistic models of human Pgp in a bilayer in the inward-facing and outward-facing conformations, containing bound drugs. The structural models are using published X-ray structures optimized with the biophysical constraints by targeted MD simulations. For a set of inhibitors/substrates, the binding affinities of both steps are correlated with drug structure using our validated multimode, multi-species modification of the Linear Response (LR) approach. Substitution of the LR models of individual steps into the kinetic models generates comprehensive structure-based model of Pgp efflux and passive transport. Pgp efflux or inhibition are beneficial in selected regions and detrimental in the rest of the body. The resulting models will improve preclinical drug development of selective Pgp inhibitors and design of other drugs by providing guidelines to avoid Pgp binding, while instilling limited distribution to both drug categories.

Design and Synthesis of Dual-functional Nucleobase Analogs for Labeling Nucleobase Transporters

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In humans, nucleotides are essential metabolites, and are regulated by complementary salvage and de novo biosynthetic pathways. The transport of nucleobases to cells is an important step to build up nucleotides, and is critical for cell survival. Many chemotherapeutic agents (anticancer, antiviral, antiarrhythmia, and antihypertensive drugs) enter human cells via nucleobase transporter as a primary pathway. 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. However, no specific human nucleobase transporter has yet been identified. By identifying and characterizing nucleobase transporters, the knowledge on how nucleobase transport contributes to nucleotide metabolism will be significantly expanded. This knowledge can be further exploited to improve the delivery and efficacy of chemotherapeutics.

Our initial effort has been focused on the design and synthesis of dual functional nucleobase analogs. These chemical probes have three components including 1) a purine or pyrimidine “warhead” to target the active site of nucleobase transporter protein; 2) a photoactivatable functional group to crosslink the probe to the target protein upon irradiation; and 3) a terminal alkyne moiety for “click-chemistry” mediated conjugation to reporters (fluorescent dye or biotin). Benzophenone was chosen in the preliminary study because of its easiness in synthesis and good quantum yield in photoactivation. However, the steric bulkiness of benzophenone might hinder the interaction between probe and target protein. By reducing the size of the photoaffinity group, we may uncover probes with preference to other nucleobase binding proteins, and improve labeling efficiency as well. In the current project, chemical probes containing diazirine group have been synthesized. Diazirine is a widely used photoactivatable group due to its small size, chemical stability and high reactivity of the carbene species generated upon irradiation. These novel chemical probes will be utilized to target and capture human nucleobase transporter proteins.

The Impact of Care Coordination on Provider Satisfaction in Lynch Syndrome Survivors and Preivors

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Background: Lynch syndrome (LS) is a hereditary cancer syndrome which predisposes individuals to several early-onset cancers, including endometrial and colorectal cancer (CRC). Effective patient-provider relationships may influence adherence to the complex screening and surveillance regimen recommended for LS survivors and preivors, however little is known about the patient-provider relationship in this population.

Methods: Multiple domains of the patient-provider relationship, including care transitions, health care utilization, interpersonal skills, and perceived health care provider (HCP) knowledge of the patient and LS, were assessed using a mixed methods approach (online survey followed by a semi-structured, in-depth telephone interview).

Results: The survey (n=57) and follow-up interview (n=55) included LS survivors and preivors who were assessed on their current HCP relationships and the factors that could improve those relationships, as well as the impact those relationships had on adherence to their medical management regimen. Participants were predominantly female (74%) and white (95%) with a mean age of 44 years (range 21-68). The sample included 25 (44%) preivors and 32 (56%) survivors. Preivors most commonly identified their gastroenterologist (44%) as their care coordinator, with “themselves” (16%) as the second most common response. Survivors most commonly identified their oncologist (44%) as their care coordinator followed by their gastroenterologist (19%). Qualitative interview data indicated that the most prominent factor in determining HCP satisfaction ratings in this population is care coordination. Specifically, patients who believe that their care is well-coordinated reported high levels of provider satisfaction; those who reported that their providers are either not coordinating their care or who are doing it poorly report low levels of provider satisfaction. However, LS survivors and preivors use the term “care coordination” to represent multiple aspects of the patient-provider relationship. Specifically, this term was used to indicate provider knowledge of LS, effective communication with and among HCPs, appropriateness of recommendations, reminders for screenings, the thoroughness of the provider, utilization of available resources, time spent with the patient, and the provider’s investment in the patient’s care.

Conclusions: The results suggest that care coordination plays a key role in provider satisfaction in LS survivors and preivors, however there is a significant amount of variability in terms of patient expectations for well-coordinated care. Further research is needed to assess these multiple domains of care coordination and to develop interventions targeting these aspects of the patient-provider relationship.

Health-Related Quality of Life in Lynch Syndrome Patients

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Background: Lynch Syndrome (LS) is an autosomal dominant cancer syndrome caused by germline mutations in mismatch repair genes or an *EPCAM* deletion, accounting for approximately 2-4% of all colorectal cancers (CRC). In addition to CRC risks, women with LS have an increased risk for ovarian and endometrial cancer. The measurement of quality of life in colorectal cancer patients provides valuable information about the burden of disease and is associated with longer survival.

Methods: Participants completed a mailed self-administered questionnaire that assessed demographics, clinical characteristics, patient satisfaction, health care utilization, health behaviors and screening, and psychosocial variables. Participants were CRC survivors with LS or sporadic cancer who were matched on age, sex, race/ethnicity, cancer stage, geography, and time since diagnosis using a case-control design. Participants with LS were recruited from patient registries at The University of Texas MD Anderson Cancer Center (MD Anderson) (n=33) and through social media (n=42); sporadic CRC participants were recruited from patient registries at MD Anderson (n=75). Analysis for this paper is limited to those that responded completely for all measures (n=145).

Results: In LS patients, the mean Health Related Quality of Life score was 84.8 (11.9) compared to sporadic patients mean score of 85.8 (16.7). The mean Physical Well Being (GP) for LS patients was 23.8 (4.1) compared to 23.2 (4.9) for sporadic. Interestingly, LS patients had lower mean scores compared to sporadic in all other categories including Health Related Quality of Life Colorectal, Social Family Well Being, Emotional Well Being, and Functional Well Being, with no significance between groups.

Discussion/Conclusion: In conclusion, HRQOL is imperative to survivorship of colorectal patients in general, but specifically in LS. Although we expect there to be significances between the LS group and sporadic group regarding well being and health related quality of life, this suggests that more analysis needs to be done to further understand the differences in survivorship between groups. More research needs to be completed to explore the relationship between HRQOL, treatment regimens, and health outcomes.

Disparities in Hypertension Among Women with Chronic Kidney Disease

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Background/Purpose: Chronic kidney disease (CKD) affects more than 10% of the US population. Diabetes mellitus and hypertension are the leading pathways to CKD. Cardiovascular disease is the leading cause of death in women and chronic kidney disease is a rapidly growing and debilitating chronic disease with long term health consequences and high costs of care. Women with cardiovascular disease or cardiovascular disease risk factors are less likely than men to receive recommended preventative therapies. This disparity is greater in women from lower socioeconomic classes as well as minorities. Research has shown that women often have worse blood pressure control than men. This project seeks to update the existing literature on sex differences in hypertension treatment to understand factors that might point to the lack of control of hypertension in women that lead to early CKD or rapid CKD progression.

Methods: Data was obtained through the National Center for Health Statistics' National Health and Nutrition Examination Survey (NHANES). This survey assesses the health and nutrition of children and adults in the United States. Persons 18 years or older from NHANES data in 2007-2012 were included in this analysis (n=17,970). SAS Institute software 9.4 (Cary, NC) was used for data cleaning and analysis.

Results: Similar to previous studies socio-demographic differences exist in hypertensive adults by sex. Almost 20% (n=3,221) of women have ever been told they have high blood pressure. Women are only slightly more likely to use antihypertensive medications than their male counterparts, but are significantly less likely to have their blood pressure under control (37% to 29%, respectively). Notably, there are significant race differences in control of hypertension as well. Non-Hispanic white women are less likely to have controlled blood pressure than non-Hispanic white men, while non-Hispanic Black women are more likely to have controlled blood pressure than non-Hispanic Black men.

Conclusions: A previous study using data from 1999-2004 found that women with hypertension were less likely to have their blood pressure under control, despite being more likely to take medication(s) for hypertension. Using more recent data, 2007-2012, we find some similar patterns, but also some additional factors in this area of complex patient care. Why are white women less likely to have controlled hypertensive compared to white men, while we see an opposite pattern for Black men and women. These sex and racial disparities in hypertensive patients remain and require additional study and intervention to offer better strategies for reducing patient risk.

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Lynch Syndrome Survivors and Preivors as Educators in Their Health Care Provider Relationships

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Background: Lynch Syndrome (LS), a hereditary cancer syndrome, predisposes individuals to several early onset cancers, including endometrial and colorectal cancer (CRC). Patients with LS are advised to follow a complex medical management regimen to decrease incidence of cancer and increase rates of survival. However, prior research has shown a lack of LS-specific knowledge in some providers, which has been associated with lower levels of health care provider (HCP) satisfaction and adherence to screening and surveillance recommendations.

Methods: Multiple domains of the patient-provider relationship, including care transitions, health care utilization, interpersonal skills, and perceived HCP knowledge of the patient and LS, were assessed using a mixed methods approach (online survey followed by a semi-structured, in-depth telephone interview). This study focuses on findings from the interview data.

Results: LS survivors and preivors (n=55) participated in a telephone interview which examined current HCP relationships as well as factors that impact these relationships. Participants were asked if they had ever educated a provider on LS. For those who reported that they had educated a provider, follow-up questions assessing details of the interaction as well as outcomes were asked. Participants were predominantly female (75%) and white (95%) with a mean age of 44 years (range 21-68). The sample included 23 (42%) preivors and 32 (58%) survivors. Sixty-seven percent (67%; n=37) reported that they had educated a provider on LS. Among those patients, internet resources were the most commonly used material to educate providers (90%), followed by paperwork they received from genetic counselors (11%). Patients used these materials to educate providers about LS as well as on appropriate screening and surveillance guidelines. The provider specialty that participants reported educating most were primary care physicians, followed by gastroenterologists then obstetrics/gynecologists. Patients reported that providers whom they educated learned more about LS, became more aware of the screening and surveillance guidelines, and became more invested in the patient's care. Additionally, patients reported higher levels of satisfaction with providers who responded positively to these interactions.

Conclusions: The results suggest that LS survivors and preivors utilize materials that they receive from the internet and their genetic counselors to educate their providers on LS. Patients also report positive impacts on their relationships with their HCPs as a result of these educational interactions. Further research should focus on the development of materials that all LS patients can use to educate their providers, the empowerment of patients to take, when needed, on the role of provider educator, and understanding the providers' experience during these interactions.

Evaluation of an Adjusted Body Weight Based Vancomycin Dosing Guideline

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Purpose:

Although vancomycin has been used for decades, discrepancies exist regarding optimal dosing, given that dosing is weight-based and dependent on kidney function. Dosing nomograms can help guide appropriate dosing to achieve target concentrations. In July 2015, a St. Peters Hospital (SPH) pharmacy-use only nomogram using adjusted body weight and renal function was developed and distributed. Being that the nomogram has been in use for the past year, the objective of this study is to assess and validate the effectiveness of the vancomycin dosing guideline to achieve target trough concentrations of 15-20 mcg/ml for serious infections and 10-15 mcg/ml for less serious infections.

Methods:

The study will involve retrospective medical chart review of patients admitted to SPH. Data will be collected from July 2015 – October 2016, following IRB approval. Patients will be included upon meeting the following criteria: 1) adult (age > 18 years), 2) receipt of ≥ 2 doses of vancomycin dosed in a manner consistent with pharmacy guideline dosing recommendations, 3) documented trough concentration within 1 hour prior to the next vancomycin dose. Patients will be excluded if any of the following apply: pregnancy, requirement of peritoneal dialysis (PD), vancomycin for perioperative prophylaxis, and patients with acute kidney injury or with a CrCl < 15 ml/min. The primary outcome will be attainment of therapeutic trough levels of 15-20 mcg/ml for infections such as bacteremia, pneumonia, diabetic foot infection, intra-abdominal infection, endocarditis, meningitis, osteomyelitis, septic joint, febrile neutropenia, documented MRSA infection, and clinical instability (if empiric use). Secondary outcomes include 1) attainment of therapeutic trough levels of 10-15 mcg/ml for less serious infections like skin/soft tissue infection, cellulitis, and urinary tract infection, and 2) patient variables associated with lack of goal trough attainment (e.g. age, weight, renal function, and treatment in the ICU). Data to be collected include age, gender, co-morbidities, height and weight, serum creatinine, vancomycin regimen, indication per medical record documentation and presence of culture data, trough serum concentrations, and location of treatment

Assessment of Institutional Fluoroquinolone Use for Uncomplicated Infections

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PURPOSE: In May of 2016 the Food and Drug Administration (FDA) issued drug safety communications warning of risk-benefit concerns with fluoroquinolones for treatment of uncomplicated infections. Infections of interest are acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, and uncomplicated urinary tract infections in adults. Considering fluoroquinolone usage for these infections is now discouraged due to safety concerns, the purpose of this study is to characterize fluoroquinolone prescribing for the aforementioned uncomplicated infections at our community hospital. Findings will be used to identify interventions to improve institutional prescribing practices and promote patient safety.

METHODS: Fluoroquinolone usage in both the emergency department and inpatient for treatment of uncomplicated infections will be retrospectively assessed between July 2015 and June 2016. This study has been approved by our institutional review board. Patients will be included if at least 18 years of age and prescribed a fluoroquinolone (levofloxacin, ciprofloxacin, moxifloxacin, gemifloxacin) for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or uncomplicated urinary tract infections. Data to be collected include age, gender, ethnicity, comorbidities, antibiotic allergies, baseline renal function, evidence of sepsis, cultures, admission or discharge after prescription, prescriber type, presentation from a healthcare facility or home, documented antibiotic use within 3 months, and readmission within 30 days with evidence for toxicity potentially due to fluoroquinolone use. Adequate sample size permitting, univariate and multivariate regression analyses will be conducted to determine patient characteristics that are associated with fluoroquinolone prescription for the infection of interest.

PRELIMINARY FINDINGS: Of the infections of interest, AECB-COPD appears to be the most common indication for fluoroquinolone use, of which levofloxacin has been the most frequent FQ prescribed in these patients. Currently, we have found that few patients who present to the ED, or who are admitted to the hospital, and are treated with a fluoroquinolone qualify for a diagnosis of uUTI or ABS. In the future these findings will be used to identify opportunities for prescriber education and to potentially create institution-specific treatment/management algorithms

Modeling the Genetic Basis for the Development of Antimicrobial Resistance

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Staphylococcus aureus is a major human pathogen and a model bacterium that has demonstrated rapid emergence of resistance against novel antibiotics shortly after their introduction. Daptomycin is one of the few available intravenous antibiotics used to treat serious bloodstream infections including endocarditis secondary to methicillin-resistant *S. aureus* (MRSA). Emergence of daptomycin resistance during therapy of MRSA-endocarditis has been documented with this high organism load infection. Daptomycin systemic exposures within a “*mutation selection window*” have been postulated to contribute to this emergence of daptomycin resistant *S. aureus* (DRSA) but the underlying mechanisms that drive this phenomenon have not been fully elucidated. Understanding the antibiotic exposure-mutation selection relationship is necessary to define novel strategies to change the existing paradigm. Our hypothesis is that **“antimicrobial exposure contributes to stepwise acquisition of antimicrobial drug resistance and mapping of exposure profiles will facilitate an understanding of the genetic mechanisms of antimicrobial drug resistance”**. The objectives of our ongoing work is to: 1) identify and validate daptomycin exposure profiles that contribute to the emergence and suppression of DRSA using an *in vitro* bioreactor infection model and innovative mathematical pharmacokinetic /pharmacodynamic (PK/PD) systems analyses; and 2) to compare genetic mutations of DRSA clinical isolates to those generated *in vitro* using whole genome sequence analysis and comprehensive variant analysis using advanced bioinformatics tools. It is our expectation that this study will unravel unique molecular mechanisms responsible for the emergence of daptomycin resistance and the results of this work will be directly applicable to antimicrobial drug development.

Characterization of the Role of Transcriptional Regulator AraC of *Francisella tularensis*

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Francisella tularensis is the causative agent of a deadly human disease tularemia. *F. tularensis* has been used in bioweapon programs in the past and now it is feared to be used as a potential biothreat agent. The CDC has classified *Francisella* as Category A Select Agent. *Francisella* possesses very few transcription regulators. A majority of these have been shown to regulate genes involved in virulence and cellular functions. *Francisella* also possesses a transcriptional regulator known as AraC. In several Gram-negative bacteria, AraC is transcribed divergently from, and control *araBAD* operon involved in arabinose utilization. In contrast, in *F. tularensis* *araC* is transcribed divergently from an operon encoding EmrA multidrug efflux pump and is not required for arabinose utilization, indicating a unique role for AraC. This study is characterizing the role of AraC as a transcriptional regulator of *F. tularensis*. A deletion mutant of *FTL_689* gene encoding AraC (Δ *araC*) of *F. tularensis* LVS and its transcomplemented strain were generated. The Δ *araC* mutant was characterized for the role in of AraC in carbohydrate utilization, resistance to oxidants, antibiotics, intramacrophage survival and virulence in mice, and its role as a transcriptional regulator. The results demonstrate that the Δ *araC* mutant grows similar to wild type *F. tularensis* LVS in the presence of arabinose, indicating that AraC does not regulate arabinose utilization genes of *F. tularensis*. The Δ *araC* mutant exhibits enhanced sensitivity towards oxidants such as Cumene hydroperoxide, Tert-butyl hydroperoxide and Paraquat. The Δ *araC* mutant does not exhibit enhanced sensitivity towards tetracycline, nalidixic acid, chloramphenicol and streptomycin and is attenuated for intramacrophage growth and virulence in mice as compared to the wild type *F. tularensis* LVS. Deep RNA sequencing revealed differential expression of several genes involved in general stress resistance and transport functions in the Δ *araC* mutant. To conclude, this study demonstrates that AraC of *F. tularensis* is required for resistance against oxidative stress but not for arabinose utilization. Moreover, AraC plays an important role as a transcriptional regulator of genes involved in general stress response. Further studies elucidating the role of AraC in gene regulation are currently underway.

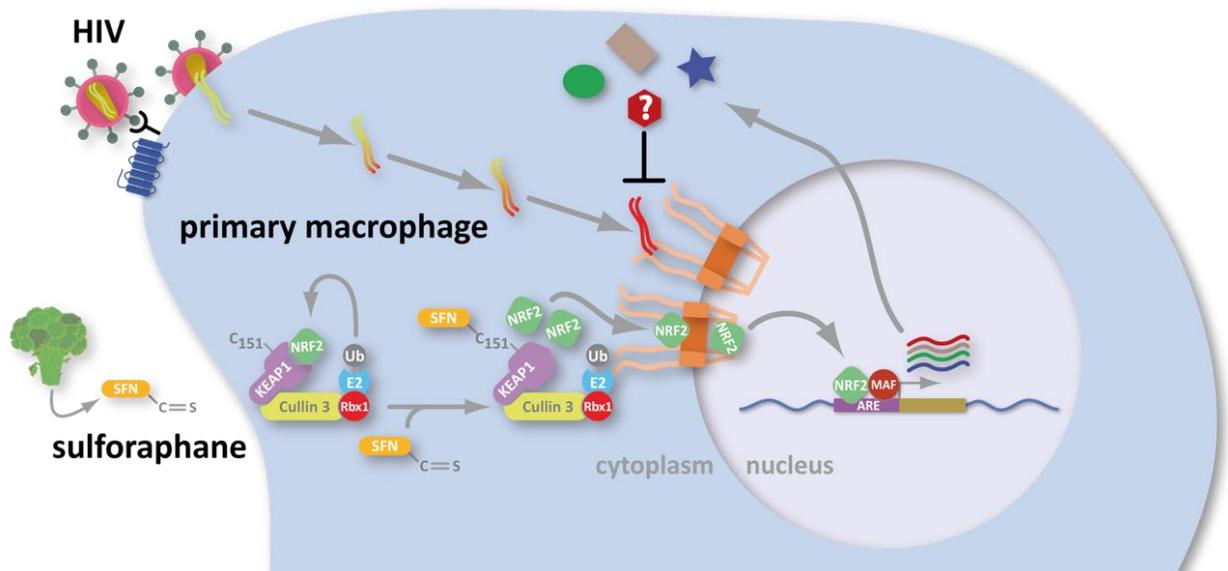
xCT as a Novel Restriction Factor of HIV Replication

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The human immunodeficiency virus (HIV) primarily infects CD4+ T-cells and macrophages. We have recently shown that sulforaphane (SFN), a natural product found in cruciferous vegetables, inhibits HIV infection of primary human macrophages, but not CD4+ T-cells, by upregulating the cellular transcription factor Nrf2. We therefore hypothesized that Nrf2 initiates the transcription of one or more genes that antagonize HIV replication in macrophages. Microarray analysis revealed that the Nrf2 responsive gene, xCT, is markedly upregulated in macrophages upon SFN treatment, but not in CD4+ T-cells. Further experimentation demonstrates an inverse relationship between Nrf2 or xCT protein levels and HIV infection wherein higher Nrf2 or xCT levels is associated with lower HIV infection. These findings suggest that xCT may be a previously unrecognized cellular restriction factor that acts to defend against viral infection.



The Suppression of HIV Early Replication by Tumor Suppressor p53

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It is well known that p53 tumor suppressor is essential for maintaining host cell genome integrity. Antiretroviral roles of p53 have previously been suggested in virus late stage replication, mainly in the regulation at HIV-1 transcription level. In this study the function of p53 in HIV early replication was identified and studied. VSV-G pseudotyped HIV-1 and HIV-2 viruses with GFP or luciferase reporters were used to infect paired p53^{+/+} and its isogenic knockout cells p53^{-/-} cells. The infection of HIV-1 were significantly blocked in HCT116 p53^{+/+} cells and MEF p53^{+/+} cells compared to their isogenic knockout HCT116 p53^{-/-} and MEF p53^{-/-} cells, especially when non-cycling cells cultured in serum depletion were used in experiment. Further analysis showed that HIV-1 reverse transcription were significantly reduced in these p53^{+/+} cells. HIV-2 infection was also found significantly blocked in non-cycling HCT 116 p53^{+/+} cells compared to HCT116 p53^{-/-} cells. The amount of infection difference between non-cycling HCT116 p53^{+/+} and HCT116 p53^{-/-} cells did not change even when cellular dNTPs levels were reduced after the hydroxyurea treatment. Analysis also showed that the levels of SAMHD1 at both transcription and protein were very similar between HCT116p53^{+/+} and HCT116 p53^{-/-}, which highly suggests that the observed block in HIV reverse transcription was likely independent of SAMHD1. Furthermore, knock down p53 by siRNA in both HCT116 p53^{+/+} cells and primary human macrophage significantly reduced HIV-1 infection. The host restriction to HIV-1 infection mediated by p53 has not been well understood. The block of HIV-1 reverse transcription by p53 will not only provide information on the virus-host interaction during infection, but also enhance our understanding on HIV pathogenesis such as the immune cell death caused by pyroptosis.

Molecular Regulation of Host Inflammation during Influenza A Virus Infection

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Influenza A virus is a negative-sense RNA virus that causes respiratory infection. It is important to study influenza viruses because it is a public health problem due to the high morbidity and mortality worldwide. Annual flu epidemics result in approximately three to five million cases of severe illness and about 250,000 to 500,000 deaths worldwide annually. The host innate immune system is critical for containing the spread of the virus early during infection and for the induction of a protective adaptive immune response. Innate immune cells express a collection of molecular “sensors” that allow them to detect the presence of the virus, including the cytoplasmic NLRP3 inflammasome complex, which promotes the maturation and secretion of the pro-inflammatory cytokines IL-1 β and IL-18. Also, the NF- κ B signaling pathway plays an important role in this immune response through transcribing the mRNA for the inactive forms of these cytokines. Virus-induced NLRP3 inflammasome activation serves a protective role, although excessive NLRP3 inflammasome activity, especially during infection by a highly pathogenic or pandemic strain of influenza virus can result in excess inflammation that is detrimental to the host. Recent studies have identified a small molecule known as pyrin-only protein 2 (POP2) that blocks the formation and activation of inflammasome complexes in humans and inhibits the NF- κ B signaling pathway. Because of these findings, we hypothesize that POP2 functions to modulate the robust NLRP3 and NF- κ B dependent IL-1 β responses elicited during influenza virus infection. Data from our initial studies suggest that seasonal and pandemic strains of influenza virus differ in their ability to induce POP2 gene expression in human monocytes. Additionally, our data suggest that POP2 may play a dual role during flu infection to regulate both NF- κ B- and NLRP3-dependent inflammatory responses. These findings suggest that POP2 may represent a critical factor in promoting a controlled, “protective” pulmonary inflammatory response during human influenza virus infection. Similarly, POP2 dysfunction may be implicated in flu infected individuals where extensive pro-inflammatory cytokine production results in increased morbidity and death.

Identification and Characterization of Unknown Antioxidant Defense Mechanisms of *Francisella tularensis*

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Francisella tularensis (*Ft*), an intracellular gram negative bacterium, is the causative agent of tularemia. It is classified as Category A select agent by the Centers for Disease Control (CDC) for being the deadliest agent of biological warfare and bioterrorism. *Ft* has been shown to possess a robust antioxidant defense system and surprisingly, the loss of one or more of these antioxidant genes of *Ft* does not exhibit an oxidant-sensitive phenotype which suggests that additional factors provide compensatory mechanisms. This study is aimed at identifying additional unknown antioxidant mechanisms that act independently or in concert with the known classical antioxidants to render robust oxidant resistance to *Ft*. In order to identify additional unknown antioxidants, by screening a transposon insertion library of *Ft* live vaccine strain (LVS) in the presence of hydrogen peroxide we have identified oxidant sensitive mutants with transposon insertions in the *FTL_0283* (*aromatic acid transporter*) and between *FTL_0283* and *FTL_0284* (*hypothetical protein*) genes. Further characterization of the transposon insertion locus indicated that these genes along with *FTL_0285* (*GTP Pyrophosphokinase*) constitute an operon. The *FTL_0283* and *FTL_0283/284* mutants do not exhibit compromised structural integrity. However, both the mutants are highly sensitive to H₂O₂, organic peroxides and superoxide generating compounds. Both *FTL_0283* and *FTL_0283/284* mutants are attenuated for intramacrophage survival as compared to the wild type *Ft* LVS. Collectively, these results demonstrate that *FTL_0283-285* locus plays an essential role in resisting oxidative stress. Elucidation of the exact mechanisms through which the *FTL_0283-285* gene products contribute to oxidant resistance, intramacrophage survival and virulence of *Ft* are currently underway.

Impact of Host Glycosphingolipid Biosynthesis on Influenza Virus Infectivity

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Respiratory infection by influenza viruses are a significant cause of morbidity and mortality worldwide. Despite the existence of effective vaccines and anti-viral drugs, their effectiveness are limited by antigenic drift and the appearance of drug resistance strains of virus. Influenza viruses interact with several host membrane and cytoplasmic constituents during the various stages of its life cycle. Accordingly, some of these host factors may represent novel targets for future antiviral drugs. Experimental findings that manipulation of host cell membrane lipid composition adversely impacts of replication of many enveloped viruses, including influenza, has revealed the importance of host lipid biosynthesis and specific lipid molecules on the production of infectious viral particles. 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 involved in influenza virus entry, protein glycosylation, and viral budding. Lipidomics has revealed that influenza virus particles are markedly enriched in glycosphingolipids, likely acquired from the plasma membrane during egress. Despite these findings, the exact roles of glycosphingolipids in the influenza virus life cycle are not well understood. Data from our studies suggest that influenza virus co-opts several cellular glycosphingolipid biosynthetic proteins to facilitate virion assembly and particle release, with GCS playing a critical role. Thus interference with glycosphingolipid biosynthesis may represent a novel therapy to combat infection by influenza viruses as well as other enveloped human viruses.

Anti-CD24 Nano-targeted Delivery of Docetaxel for the Treatment of Prostate Cancer

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Nanoparticle (NP)-mediated, noninvasively targeted and image-guided therapies have potential to improve efficacy and safety of cancer therapeutics. We report synthesis and use of poly(lactide-co-glycolide)-polyethylene glycol (PLGA-PEG) NPs for targeted delivery of docetaxel. We synthesized docetaxel encapsulated NPs conjugated to anti-CD24 (for targeting) and/or an optical probe (for tracking) and evaluated efficacy in a prostate cancer mouse model. We observed preferential accumulation of anti-CD24 conjugated NPs (encapsulating docetaxel) compared to the non-conjugated NPs 24 hours after a single injection into luciferase-expressing PC3M prostate cancer tumor in mice. In the same mouse model, we found significant ($P < 0.01$) accumulation of docetaxel (~10-fold higher) in tumor after treatment with PLGA-PEG NPs encapsulating docetaxel and conjugated to anti-CD24 compared to non-conjugated NPs. Enhanced accumulation was associated with reduced tumor mass and tumor viability. These data support the potential impact of nano-targeted delivery of chemotherapy in enhancing the differential tumor delivery and anticancer efficacy in prostate cancer.

Self-assembly of Green Tea Catechin Derivatives Nanoparticles for Oral Lycopene Delivery

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Lycopene is a natural antioxidant that has a lot of health benefits. However, high instability and extremely low bioavailability limits its further clinical development. Here we selected a green tea catechin derivative, oligomerized (-)-epigallocatechin-3-*O*-gallate (OEGCG) as the natural carrier for oral lycopene delivery. Lycopene-loaded OEGCG nanoparticles were prepared by a nanoprecipitation method, followed by coating with chitosan to form a shell. This method not only can easily control the size of the nanoparticle to be below 200 nm to improve its bioavailability, but also effectively protects the lycopene against degradation due to EGCG's antioxidant property. *N*-trimethyl chitosan TMC-chitosan coated OEGCG/lycopene nanoparticle had a diameter of 150 ± 30 nm and a ζ -potential of 50.4 ± 3.8 mv. The loading capacity of lycopene was 20% and encapsulation efficiency was 89%. X-ray diffraction analysis revealed the amorphous nature of the encapsulated lycopene in OEGCG nanoparticles. Freeze drying of this nanoparticle was also evaluated as a means to improve shelf life. Dynamic light scattering data showed that no aggregation occurred, and the size of the nanoparticle increased 1.2 times (S_f/S_i ratio) in the presence of 10% sucrose after freeze-drying. The *in vitro* release study showed slow release of lycopene in simulated gastric juice at acidic pH and faster release in simulated intestinal fluid. In an *in vivo* study in mice, lycopene pharmacokinetic parameters were improved by lycopene/OEGCG/chitosan NPs, but not improved by lycopene/PLGA/chitosan NPs. The self-assembled nanostructure of OEGCG combined with lycopene may be a promising application in oral drug delivery.

Targeted Delivery of Paclitaxel and Doxorubicin to Cancer Xenografts via the Nanoparticle of Nano-diamino-tetrac

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The tetrac component of Nano-diamino-tetrac (NDAT) is chemically bonded via a linker to a poly(lactic-co-glycolic acid) nanoparticle that can encapsulate anticancer drugs. Tetrac targets the plasma membrane of cancer cells at a receptor on the extracellular domain of integrin $\alpha v \beta 3$. We evaluate here the efficiency of NDAT delivery of paclitaxel and doxorubicin to, respectively, pancreatic and breast cancer orthotopic nude mouse xenografts. Intra-tumoral drug concentrations were 5-fold higher (paclitaxel) ($P < 0.001$) and 2.3-fold (doxorubicin) ($P < 0.01$) than with conventional systemic drug administration. Tumor volume reductions reflected enhanced xenograft drug uptake. Cell viability was estimated by bioluminescent signaling in pancreatic tumors and confirmed an increased paclitaxel effect with drug delivery by NDAT. NDAT delivery of chemotherapy increases drug delivery to cancers and increases drug efficacy.

Targeted Delivery of Cisplatin to Tumor Xenografts via the Nanoparticle Component of Nano-diamino-tetrac

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Aims: Nano-diamino-tetrac (NDAT) targets a receptor on integrin $\alpha v \beta 3$; $\alpha v \beta 3$ is generously expressed by cancer cells and dividing endothelial cells and to a small extent by nonmalignant cells. The tetrac (tetraiodothyroacetic acid) of NDAT is covalently bound to a poly(lactic-co-glycolic acid) nanoparticle that encapsulates anticancer drugs. We report NDAT delivery efficiency of cisplatin to agent-susceptible urinary bladder cancer xenografts.

Materials & Methods: Cisplatin-loaded NDAT (NDAT-cisplatin) was administered to xenograft-bearing nude mice. Tumor size response and drug content were measured.

Results: Intra-tumoral drug concentration was up to 5-fold higher ($P < 0.001$) in NDAT-cisplatin-exposed lesions than with conventional systemic administration. Tumor volume reduction achieved was NDAT-cisplatin > NDAT without cisplatin > cisplatin alone.

Conclusions: NDAT markedly enhances cisplatin delivery to urinary bladder cancer xenografts and increases drug efficacy.

Nanoparticulate Tetrac (Nano-diamino-tetrac, NDAT) Inhibits Growth and Vascularity of Glioma Xenografts

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Thyroid hormone as L-thyroxine (T₄) stimulates proliferation of glioma cells in vitro and medical induction of hypothyroidism slows clinical growth of glioblastoma multiforme (GBM). The proliferative action of T₄ on glioma cells is initiated at a cell surface receptor for thyroid hormone on the extracellular domain of integrin $\alpha\beta 3$. Tetraiodothyroacetic acid (tetrac) is a thyroid hormone derivative that blocks T₄ action at $\alpha\beta 3$ and has anticancer and anti-angiogenic activity. Tetrac has been covalently bonded via a linker to a nanoparticle (Nanotetrac, Nano-diamino-tetrac, NDAT) that increases the potency of tetrac and broadens the anticancer properties of the drug. In the present studies of human GBM xenografts in immunodeficient mice, NDAT administered daily for 10 days subcutaneously as 1 mg tetrac equivalent/kg reduced tumor xenograft weight at animal sacrifice by 50%, compared to untreated control lesions ($p < 0.01$). Histopathological analysis of tumors revealed a 95% loss of the vascularity of treated tumors compared to controls at 10 days ($p < 0.001$), without intratumoral hemorrhage. Up to 80% of tumor cells were necrotic in various microscopic fields ($p < 0.001$ vs. control tumors), an effect attributable to devascularization. There was substantial evidence of apoptosis in other fields ($p < 0.001$ vs. control tumors). Induction of apoptosis in cancer cells is a well-described quality of NDAT. In summary, systemic NDAT has been shown to be effective by multiple mechanisms in treatment of GBM xenografts.

Development of Bioanalytical Method for Pharmacokinetics and Biodistribution of Novel Targeted Anticancer Drugs

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Targeted anticancer drugs have been developed based on multiple chemical scaffolds, including conjugates of nanoparticles and active drugs. β -C-TAT is a newly developed targeted anticancer drug, which is a conjugate of β -cyclodextrin and a derivative of tetraiodothyroacetic acid (tetrac). We developed a bioanalytical liquid chromatography-mass spectrometry (LC-MS) method for the novel drug and applied to bioanalytical quantification in mouse plasma. A LC-MS method in selected ion monitoring mode was used in ESI negative mode; and γ -C-TAT, a conjugate of γ -cyclodextrin and tetrac, was used for internal standard. Solid-phase extraction using OASIS HLB columns with 50 % acetonitrile in water showed higher recovery efficiency than liquid-liquid extraction with methanol. The overall recovery efficiency was 60% with a matrix effect of -31 %. The limit of quantification was estimated to be 1 ng/ μ L. The developed method is robust and applicable to study of pharmacokinetics and biodistribution of β -C-TAT.

Improved Efficacy of Temozolomide (Temodar) Against Glioma by Nanotargeting Using Tetraiodothyroacetic Acid (Tetrac)

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Malignant gliomas [glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA)] have a combined incidence of 5-8/100,000 people and represent the most common primary central nervous system tumors. The treatment outcomes, even with aggressive approaches, are poor. More recently, the alkylating agent temozolamide (TMZ), sold as Temodar, has been approved as the drug of choice for treating these forms of glioma. Gliomas are characterized by the increased expression of $\alpha\beta3$ integrin receptors, an adhesion molecule that promotes angiogenesis and tumor proliferation. This receptor has been shown to be effectively blocked by tetraiodothyroacetic acid (tetrac) and nano-diamino-tetrac (nDAT), *in vitro* and *in vivo*, in several tumor cell lines and tumor types, thereby preventing proliferation and angiogenesis. Based on this, we hypothesize that these tetrac-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) could be used to improve the targeting of TMZ to glioma cells with the added benefit of inhibiting proliferation, while improving delivery and cell killing. Following synthesis of PLGANPs, with and without encapsulated TMZ, the hypothesis will be tested *in vitro* in U87MG glioma cells using the quantification of cytotoxicity in glioma in response to non-NP TMZ alone, nDAT alone, nDAT with free TMZ and nDAT with encapsulated TMZ using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

The Effect of GANT61 on Mouse Mammary Tumor Stem Cells

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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. Elucidation of the proteins and signaling pathways that are altered in tumor stem cells will lead to strategies to specifically target tumor stem cells. This project focused on characterization of Hh signaling in tumor stem 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 (MMMTV-PyMT). A cell line (419II cells obtained from the Sell lab) exhibiting properties of tumor stem cells was isolated from these tumors using specific stem cell markers (CD44⁺CD24⁺CD49f⁺). The research hypothesis was that these 419II tumor stem cells exhibit an active Hh signaling pathway that contributes to regulation of growth and differentiation of these mouse mammary tumor stem cells. The effects of exposure to Hh antagonists or a differentiating agent, bromodeoxyuridine (BrdU), on the growth of 419II cells and on the expression of Hh target genes was investigated. The effect of the Hh antagonists GANT61 (10 μ M) and cyclopamine (10 μ M) on the growth of 419II cells was determined by an MTT assay. Following 96 hours of treatment, both GANT61 and cyclopamine significantly inhibited the growth of 419II cells. The effect of GANT61 treatment on the expression of Gli1 and VDUP-1 mRNA was investigated by qPCR analysis of Gli1 and VDUP-1 mRNA expression. GANT61 treatment for 72 hours resulted in a significant decrease in both Gli1 and VDUP-1 mRNA. Gli1 is the transcription factor whose expression is increased as a result of activation of Hh signaling and VDUP-1 is a tumor suppressor gene whose expression has been shown to be down-regulated by Hh signaling in MDA-231 cells. These results suggest that GANT61 is inhibiting the growth of 419II cells by inhibiting Hh signaling in these cells. 419II cells were grown in the presence of 10 μ M BrdU for two weeks to induce differentiation. Cell growth assays demonstrated a significant reduction in growth after the two week treatment. The treated cells appeared to be larger with a more flattened morphology. BrdU treatment dramatically reduced the expression of smooth muscle actin and cytokeratin -14, both of which are markers of mouse mammary myoepithelial cells. Overall the data suggest that drugs which target Hh signaling may reduce the growth potential of mouse mammary stem cells, thereby providing an effective approach to targeting cancer stem cells.

Nano-Diamino Propane Tetrac in the Management of Glioblastoma Multiforme

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Glioblastoma multiforme is an aggressive and fatal form of brain cancer with an incidence rate of about 3 in every 100,000 adults per year. Due to a lack of understanding of the disease, average life expectancy is about 14 months from the time of diagnosis. Current treatments are very invasive, and minimally effective. A new drug, nano-diamino propane tetrac (NDAT), is revolutionary in the fact that it targets the glioblastoma replication site exclusively. This drug is designed to bind to an extracellular site on the integrin $\alpha v \beta 3$, which is known to become mutated in glioblastoma cases. This drug is designed to target only one area on the integrin responsible for the mutation, and not affect the remaining function of the receptor meaning there will be essentially no side effects associated with treatment. NDAT is minimally invasive, dosed subcutaneously once daily, and is expected to extend the survival of patients up to two years past their expected survival time without treatment. Studies have shown decreases in tumor volume and weight after just 10 days of treatment in mice, showing promise for success. Once clinical studies and clinical trials have been approved and conducted, the drug will be available on the market for patients in need. Some side effects that can be expected with dosing include nausea, vomiting, anorexia, and potentially constipation. The drug is expected to be dispensed in a hospital setting, more specifically cancer treatment centers, and will be available via AmerisourceBergen suppliers as a wholesaler so it can be available to any hospital in need of the treatment. Due to the specificity, design, and patient base of NDAT, costs will be higher than other treatments for the disease. Insurance companies are expected to cover a portion of treatment cost, but at a cost of \$90,000-\$120,000 per 10 day treatment, patients are still expected to pay out of pocket for a large sum. Due to the specificity of this treatment to glioblastoma alone, treatment is promising and patients are likely to pay the extra charge for an extended life expectancy.

Hicu-Gone: A Prospective Anti-Hiccup Medication

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Purpose of the study: We reflected and estimated the feasibility of newly developed drug Hicu-Gone created by FeasiblePharma. Hicu-Gone was developed to aid in symptom control of short and long term episodes of hiccups in adults. The brand contains the active ingredient Antisingultus.

Methods: The active ingredient of Hicu-Gone, Antisingultus was discovered after lead testing and lead optimization to narrow down the prospective compounds to try for this indication. After about 600 compounds were identified, preclinical testing started with multiple instances of in vitro testing for the pharmacodynamic properties of the compounds. Pre-clinical trials then proceeded to toxicology studies in rats.

Results: The final compound Antisingultus was selected because of its pharmacokinetic and pharmacodynamic profile. The ingredient is a reversible acetylcholinesterase inhibitor designed to work specifically on the vagus nerve stimulating it to “reset” the diaphragm that was causing the spasms. Other medications in this class can have strong sedating or adverse systemic effects, so special care was used to select a compound that can be released, and reaches peak effectiveness in an average of five minutes. Ten minutes after administration, a majority of the medication is bound to serum albumin, causing it to be inactivated in the body. This results in a medication that can work quickly on the vagus nerve and then rapidly be inactivated by the body, thus reducing negative systemic effects.

Conclusion: Hicu-Gone, active ingredient “Antisingultus” is a safe, effective, novel treatment of both short and long term episodes of hiccups in many adults, from many walks of life.

Diabest: The Revolutionary Antidiabetic Agent Combining a GLP-1 RA and a DPP-IV Inhibitor

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Diabetes Mellitus type 2 is a very prominent disease in the United States, with 9.3% of the population diagnosed and over 8.1 million people undiagnosed. In 2011, there were 282,000 emergency room visits caused by hypoglycemia.

Objective. The target selection for our product was glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase IV inhibitors (DPP-4i). This combination is, hypothetically, selected to drastically reduce the risk of hypoglycemia in patients treated for diabetes while maintaining efficacy and safety and improving the HbA(1c) levels.

Rationale. GLP-1 agonists are naturally released by the body when food is consumed and stimulate the release of insulin. DPP-4 is an enzyme that degrades the GLP-1 agonists, therefore limiting the effect of GLP-1 from stimulating the release of insulin. Combining a GLP-1 RA and DPP-4i would increase the stimulation of insulin. However, both being glucose-dependant would reduce their effect as blood glucose decreases, thus reducing the risk of hypoglycemia in patients being treated with this medication as monotherapy.

Research and Development. During the clinical trials of this medication, a total of 3156 individuals were tested. Diabest was able to reduce the HbA(1c) levels by 2% from baseline compared to the current therapies such as liraglutide at 1.5% and sitagliptin at 0.9%. During the clinical trials, blood glucose of patients was at target level and the risk of hypoglycemia was found to be 0.05%.

Transitional Medicine. Diabest is an injectable product with a subcutaneous bioavailability of 60% and it is renally excreted. Dosing is once daily in the morning before meals, and three different dose formulations are available. Dose adjustment is required for patients who have decreased renal function.

Regulatory. The regulatory department is the liaison between the FDA and the rest of the company with the goal of obtaining both the IND and NDA. Numerous meetings will take place in order to ensure the approval of the company's product in order to reach patients at a high volume to reduce the risk of hypoglycemia for patients with diabetes.

Marketing and Sales. As the product is launched, the marketing and sales teams will educate on the disease and provide clinical information including outcome data comparing Diabest to other competitors. Both selling and caution points will be shared. Diabest has a predicted formulary access of 55% throughout insurance plans and will be sold at \$367 per package (includes 4 pre-filled dosage adjusted pens).

Ethical Decision Making. The ethics department collaborated with all the departments in order to be compliant with the laws while maintaining the ethics during those decisions.

Efficacy of Nano-formulated Temozolomide in Glioblastoma Multiforme Treatment

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Nano-formulated medications are becoming increasingly popular in the medical world as unique and novel methods to more effectively treat disease states. As treatments are becoming more personalized to the patient, nanotechnology is starting to appear as the way of the future in regards to healthcare treatment options. We propose that Nano-formulated Temozolomide (Neuropozyme) will provide more efficacious and cost-effective treatment to patients suffering from Glioblastoma Multiforme.

Temozolomide (TMZ) is currently the first line treatment for Glioblastoma Multiforme. The nanotechnology we utilized to formulate nano-TMZ is as follows: Poly Lactic-co-Glycolic Acid (PLGA) was solubilized in acetonitrile and a dose of TMZ was then added to the solution and solubilized. The solution was then emulsified with 0.5% poloxamer 188, and this solution was poured into another solution of pre-chilled 0.5% poloxamer 188 and stirred. The solution was then allowed to diffuse and create homogenized nanoparticles. PLGA was selected because of its biodegradability.

Our comparative study found that Neuropozyme increased overall survivability in patients by 2 years compared to non nano-formulations while also decreasing TMZ-related symptoms in 80% of patients. Thus, this novel nano-formulation was shown to markedly increase drug specificity, effectiveness, and safety.

Renerva: Potential Huntington's Disease Treatment

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Purpose: We conducted trials for feasibility and effectiveness of a newly developed drug Renerva (rexicuzimab) designed and synthesized by RevLife pharmaceuticals. Renerva was developed to help control and alleviate symptoms of Huntington's disease and delay progression of disease.

Methods: The drug was discovered from analyzing the HD gene. Silencing certain segments of the gene would cause it to become inactive. The active component of Renerva, rexicuzimab, was identified after lead testing and narrowing the index from 800 compounds. Preclinical testing was then initiated to test the mechanism of action. Phase 1 clinical testing then proceeded with healthy volunteers to determine pharmacokinetics of the drug. Phase 2 followed with studies for interactions with other drugs.

Results: The drug Renerva has been shown to prolong life span by 68%. It results in the silencing of the C-A-G codons in HD genes, resulting in decreased buildup of Htt aggregates, leading to decreased symptoms. Renerva duration of action is 36 hours with optimal dosage at 5-10 mg per day. It is 75% hepatically cleared, with the added benefit of no dose adjusting for renally impaired patients.

Conclusion: Renerva (rexicuzimab) is a safe, effective treatment for controlling and delaying progression of Huntington's Disease.

Development of Lipaxa® (gavicaserin) a More Specific Serotonergic Weight Loss Medication Also Indicated in Younger Populations



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The purpose was to develop a medication for weight loss that targets and agonizes the 5-HT_{2c} receptor more selectively than currently available medications. To that end, we screened several thousand 5-HT_{2c} receptor analogue molecules and discovered compound LNG-1769 (gavicaserin). This molecule was found to have safe and predictable therapeutic concentrations in murine and canine models. Phase one and two clinical trials proceeded and determined effective dosages between 5 and 10 mg once daily. Phase three clinical trials further confirmed safety and efficacy findings. A comparative study was carried out with lorcaserin (Belviq®) and gavicaserin was found to have greater efficacy and reduced side effects. Additional pediatric (8-13 years) and adolescent (13-18 years) dose studies were approved and found to be safe and effective. Additional dietician and fitness coaching resources were developed to increase patient success with this drug. Minor side effects included: nausea, headache, upper respiratory tract infections, dizziness, and fatigue. Serious but rare side effects may include depression or mood disorders. Precaution should be taken in patients with mental disorders. Gavicaserin is contraindicated with concomitant SSRI therapy. No reports of valvular myopathy or pulmonary hypertension were reported with gavicaserin.

Snoozeon: A Summary of a Blockbuster Insomnia Medication

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Objective. Our Company's goal over the past decades has been to make a safe and effective treatment for insomnia. The marketplace is saturated with hypnotics that are controlled substances. Schlaf's mission statement has always been improve health care and don't be evil. A large portion of our funding went into improving insomnia therapy and making the safest treatment option available. **Rationale.** Approximately 30% of the US population has reported a symptom of insomnia. Most therapies for insomnia vary only in duration of action and retain the common oral formulation. Schlaf challenged the status quo and developed a new formulation with a similar onset and six hour duration of action. The tireless work of our research team led to the discovery of the SMART transdermal patch. The patch provided different pharmacokinetics compared to our oral formulation, in terms of metabolism and absorption route, but achieved similar pharmacodynamic results. **Research, Clinical, and Development.** Development started with the testing of thousands of compounds that bind to the BNZ receptors of the central nervous system. The goal of research was to create the safest and most effective benzodiazepine in the market using existing literature of molecules and a well-defined target receptor. The trials started in toxicity in subgroups and general populations that eventually led to massive phase III trials. **Regulatory.** Schlaf faced some limitations in the making of Snoozeon. Some progress was hindered due to FDA regulations when it was found that the PO tablet formulation caused major GI symptoms, which included diarrhea, vomiting, and nausea. After several meetings and trials, the formulation was changed to a much lower dose which was effective transdermally, delivered through a SMART transdermal patch system. The doses of 0.25-0.5 mcg were found to be extremely effective. **Marketing and Sales.** The marketing and sales team came up with a strategy that gave adults 18 years and older and pregnant women in any trimester the possibility of a trial at a reduced or no-cost option, requiring a thorough medical evaluation. **Post-Market.** A post-market study was funded by Schlaf to prove its efficacy in substance abusers. It was shown that not only did it help this specific population improve their insomnia, but it also promoted anxiolytic effects. The study, named the ANX-TRIAL, showed that with continuous administration, Snoozeon improved the overall sleep latency and maintenance and showed added benefits with other co-morbid conditions, mainly anxiety.

Complevir: a Long-Term Solution to the Global Pandemic of HIV

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Rationale. Human immunodeficiency virus (HIV) is a global pandemic of the 20th century, with over 1.2 million people in the US alone living with this disease and 1 in 8 individuals being unaware of their status. Acquisition often leads to acquired immunodeficiency disease (AIDS). Currently there is no effective cure, however progression is often controlled with proper treatment and medical care. Highly active antiretroviral therapy is the best FDA approved treatment, however this option is not convenient and practical for populations who are in dire need of treatment. By 2025, the World Health Organization (WHO) wants 90% of all individuals living with HIV to: (1) know their HIV status, (2) receive antiretroviral therapy, and, (3) have viral suppression. The proposed therapy is an injectable HAART, Complevir, a unique therapy option that targets various aspects of the HIV life cycle with nanotechnology. **Research, Clinical, and Development.** Development focused on interdepartmental collaboration, based on need, plausibility, reproducibility, marketability and profitability. An injectable route of administration was chosen due to benefits seen for low adherence patients and patients in remote areas who cannot access oral medications consistently. Nanotechnology was incorporated for improved pharmacokinetics and pharmacodynamics and to have targeted delivery with minimal side effects. Cost and production time would be greatly decreased because of the already existing HAART therapies on the market. **Regulatory.** In order to make Complevir available to at risk populations, it is important to be compliant with regulations set by the FDA as well as regulatory agencies in other countries. A common technical document was created as per the requirement for marketing overseas, and a biologic license was obtained prior to marketing our product. **Marketing and Sales.** Complevir is a revolutionary product in terms of antiretroviral therapies currently on the market. It is the first injectable antiretroviral combination medication that offers an increased survival rate (from 65% to 85%) for patients who develop opportunistic infections. Unlike the current regimens, this product offers once-a-month dosing with fewer side effects and medication interactions. With no stringent storage requirements, it is easily transported and has a better shelf life. Above all, Complevir offers an annual patient cost of \$15,000, a drastic decrease in comparison to current HAART therapies on the market. **Medical Affairs.** Collaboration with a variety of medical leadership positions was done to aid in the creation and design of Complevir. In order to optimize medical treatment of HIV, tangible value was provided compared to other oral-based HIV medications on the market. **Ethical Decision Making.** Several parameters within each department and phase of the product lifecycle were maintained to ensure privacy and avoid potential conflict of interest. The end goal aligned with the WHO, prolonging longevity to millions across the globe.

eyeMAC for Macular Degeneration

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Background. Macular degeneration is a major cause of irreversible vision loss in people over the age of 60 years, and the prevalence worldwide is very significant. There are two types of this disease including wet and dry macular degeneration. The dry form includes an accumulation of lipid deposits beneath the macula and the wet form includes the abnormal growth of blood vessels toward the macula that often leak and cause the macula to lift. The newly discovered eyeMAC ointment is focused on the treatment of the wet form of macular degeneration. Current therapies include intravitreal injections of Lucentis, Eylea, and Macugen, which are much more invasive. eyeMAC is a Fab fragment that selectively antagonizes VEGF, which causes the formation of abnormal blood vessels. The main goal of this study is to develop a less invasive as well as effective treatment for wet macular degeneration.

Conclusion. The goal of the study was to assess the treatment of eyeMAC ophthalmic ointment vs intravitreal injections used to treat wet macular degeneration and to determine the optimal and most tolerable dose for a patient using eyeMAC. The results showed that the most optimal dose with the most tolerable side effects was 1.4 mg. Maximum tolerable dose was 3 mg, which resulted in irritation and red eye. eyeMAC proved to be the less invasive of the available treatments for wet macular degeneration. In comparison to Lucentis, eyeMAC showed evidence of therapeutic efficacy in 6 months vs Lucentis' 12 months. Benefits included higher affinity antagonism for VEGF; eyeMAC's Fab fragment target, requirement of no renal elimination, and less invasive administration. In conclusion, eyeMAC proved to be an effective form of treatment for wet macular degeneration as an ointment when compared to its competitors.

ResuClick: A Reloadable, Reusable Epinephrine Auto Injector as an Answer to the Current Epinephrine Market Monopoly

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Pharmaceutical Industry and the Pharmacist's Role Project
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Rationale. Between 2008 and 2015, the price of EpiPen® (Mylan Pharmaceuticals), a drug that is used to treat anaphylaxis from allergen exposure, jumped from \$100 to over \$600 in cost to the patient. Due to the increase in cost, both patients and healthcare providers are being left without the device or turning to purchasing epinephrine multi-dose vials and syringes instead of purchasing the autoinjector pen. While there have been many similar devices that have been developed (such as Auvi-Q® by Kaleo Pharmaceuticals) and generic epinephrine products that have entered and been taken off the market, there is a lack of an epinephrine autoinjector that aims to reduce negative patient outcomes by reducing burden and cost to the patient. ResuClick, an epinephrine autoinjector designed around this idea, aims to become the solution to this long-standing health issue. **Research, Clinical, and Development.** The development of this device would require outsourcing development engineering with numerous companies due to needing to redesign the available technology to be suitable for the goals of the ResuClick device. Cost and production time would be greatly decreased because of the technologies that are already available for similar devices such as insulin pens and syringes. **Regulatory.** The purpose of Regulatory Affairs during the development and launch of ResuClick is to ensure that the product follows necessary regulations and procedures in place by the Food and Drug Administration. A 501(K) application submission would need to be filed with the Center for Devices and Radiological Health to ensure the device follows medical device regulations. In addition, an Abbreviated New Drug Application would need to be filed with the Food and Drug Administration to allow for accelerated review of the drug to be placed on the market. **Marketing and Sales.** ResuClick would be marketed towards outpatient settings and community pharmacies and primary care physicians, where promotional focus would be on the ease of the device, the reduced cost burden to both patients and healthcare providers, as well as demonstrating that ResuClick is a breakthrough within the epinephrine autoinjector market by allowing choice for all individuals. **Medical Affairs.** The Medical Affairs team would provide independent medical education to both healthcare providers and patients for the correct assembly and usage of the device through publication, research, call centers, Frequently Asked Questions sheets, and formulary dossier. **Ethical Decision Making.** The purpose of this department is to collaborate with other departments and various professionals to make sure that all parts and individuals that are involved with the development, launch, and product lifecycle of ResuClick follow moral and ethical standards. This would include oversight of all departments involved with ResuClick as well as current and future patients who may use ResuClick.