2019 Northeast Symposium for Advocates of Women in Science and Medicine

Abstract Book

#1

Title: Amber ff14SB Parameters for Phosphorylated Amino Acids

Authors: **Lauren Raguette**, Kellon Belfon, Chuan Tian, Qin Wu, and Carlos Simmerling

Abstract: Phosphorylated amino acids are highly involved in many cell regulatory networks and many research groups are studying proteins containing these post-translational modifications both experimentally and computationally. However, at this time there are no force field parameters that can model these amino acids at the same level of accuracy as unmodified proteins. Current protein force fields are used to investigate a wide variety of structure and dynamics such as ligand binding , enzyme-reaction mechanisms, and protein folding events. ff14SB is the recommended protein force field for Amber, but does not contain parameters for non-standard amino acids.1 The dihedral parameters for the side chains of the most common phosphorylated amino acids will be parameterized for multiple backbone conformations using QM and MM, and tested on various systems. An application of the developed parameters will complement this work.

#2

Title: Effect of Sterol Structure on Ordered Lipid Domains in Symmetric and Asymmetric Model Membranes

Authors: **Johnna St Clair**, Erwin London

Abstract: The packing of ordered sterol-sphingolipid-rich liquid ordered domains in biomembranes is greatly impacted by sterol structure. For this reason, the dependence of biological functions upon sterol structure can be used to identify processes likely to be dependent upon ordered domain formation. In this study we compared the effect of sterol structure upon ordered domain formation in symmetric vesicles composed of a mixture of sphingomyelin, 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and cholesterol, to that in asymmetric vesicles in which sphingomyelin was introduced into only the outer leaflet of vesicles composed of DOPC and cholesterol. In most cases, sterol behavior was similar in symmetric and asymmetric vesicles, with ordered domains being most strongly stabilized by 7-dehydrocholesterol and cholesterol, to a moderate degree by lanosterol, epicholesterol and desmosterol, and very little if at all by 4-cholesten-3-one. However, we found that in asymmetric vesicles desmosterol stabilizes ordered domain almost as well as cholesterol, and stabilizes ordered domains to a much greater degree than epicholesterol. From previous studies using symmetric vesicles and a different lipid composition, we had come to the opposite conclusion: that epicholesterol stabilizes ordered domains similarly to cholesterol and to a greater degree than desmosterol. Based on behavior in asymmetric membranes, which mimic cell membranes more closely than symmetric membranes, we have re-evaluated our prior endocytosis and bacterial uptake studies and now conclude that sterol raft-forming ability may be the sole structural property of sterol that is necessary for these functions.

#3

Title: Increased Invasive Behavior of Breast Cancer Cells after Palbociclib Treatment

Authors: **K. Alexandra Larkin**, Maria Jose Gacha Garay, Battuya Bayarmagnai, Bojana Gligorijevic, David Q. Matus and Benjamin L. Martin

Abstract: One in eight women in the US will be diagnosed with breast cancer in their lifetime. Understanding this disease and its progression opens new treatment approaches and hopefully better outcomes. During the progression of metastatic cancer, certain cells break away from the primary tumor and move through the circulatory and lymphatic systems. These invasive cells can extravasate, leaving the blood vessels and entering secondary sites where they may initiate

metastatic tumors. Previous research with the model *C. elegans* suggests that anchor cell invasion into the vulval epithelium requires cell-cycle arrest in the G1/G0 state in order to obtain an invasive phenotype. To determine whether pharmacologically induced G1/G0 cell-cycle arrest acts as a causative factor in the metastatic capabilities of tumors, a series of experiments were performed using the triple-negative breast cancer cell line MDA-MB-231. These cells were fluorescently labeled with cell-cycle and cell membrane indicators, to create a distinction between proliferating and quiescent cells. They were injected into the vein of zebrafish that have fluorescently labeled vasculature at 48 hours post fertilization. Cells were treated with palbociclib, an FDA-approved, small-molecule inhibitor of CDK4/6 that results in G1 cell-cycle arrest; and evaluated for migration to the tail and its capillary beds and subsequent extravasation. The data acquired through the comparison of invasive behavior in palbociclib treated and non-treated cells suggest the possibility that single drug pharmaceutical solutions to halting proliferation may increase metastatic capabilities.

#4

Title: Shape distortion due to Tree Rings effect on LSST

Authors: **HyeYun Park**, Sergey Karpov, Andrei Nomerotski, Dmitri Tsybychev

Abstract: Tree Rings is one of the sensor effects which have to be studied for the purpose of precise measurements during LSST (Large Synoptic Survey Telescope) operation. The effect is caused by silicon wafer manufacturing process, resulting in formation of circular patterns due to silicon dopant concentration variation. We have analyzed flat field images taken at Brookhaven National Laboratory and SLAC for all the production sensors used to build LSST (both single sensor EO and raft EO), in order to measure the amplitudes and periods of the Tree Rings pattern as a function of the radius (distance from the center of the rings), the wavelength of the light source, and the back bias voltage. With the suggested back bias voltage settings, Tree Ring's amplitude and period for both ITL and E2V are considered to be negligible, but it will be studied deeper to see how crucial the effect can be for the shear measurement, using simulations. We checked size change in x, y, and xy direction, and shape change using e1 and e2 (ellipticity in + and x direction).

#5

Title: The influence of epilepsy-associated mutations in the NMDA receptor on synaptic function

Authors: **Gabrielle Moody**

Abstract: Historically, mutations that lead to disease phenotypes have been used to guide our understanding of the basic physiological mechanisms of signaling proteins and receptors. Recently, it been recognized that missense mutations in the NMDA receptor contribute to severe neurological disorders including epilepsy, schizophrenia, autism spectrum disorder, and intellectual disability/developmental delay. We have identified a set of mutations in a highly conserved amino acid in the NMDA receptor which alter channel kinetics. Using an organotypic hippocampal model we have determined that mutant channels continue to alter kinetics at the synapse. Surprisingly, these mutant NMDA receptors convey hypofunction in patients with epilepsy, a hyperfunction-associated disorder. How a single hypofunction mutation in the NMDA receptor translates into a disease phenotype is currently unknown. Understanding this translation not only contributes to our knowledge of the basic functional properties of the NMDA receptor, but also provides insights for future antiepileptic treatments.

#6

Title: Assessment of the impacts of LRRK2 on behavior and Wnt signaling during zebrafish development

Authors: **Jinelle Wint**, Alexandra DellaPena, and Howard I. Sirotkin

Abstract: Parkinson's disease (PD) is a debilitating progressive neurodegenerative disorder that affects approximately 2% of the population over the age of 65. Although the symptoms of PD stem from a degradation of dopaminergic neurons, the underlying mechanistic causes for this disease remain unknown. Approximately 5-10% of cases stem from inherited genetic mutations that provide a window to investigate the pathobiology of this disease. Leucine Rich Repeat Kinase 2 (LRRK2) is the most commonly mutated Parkinson's disease gene. The key biological processes altered by LRRK2 to produce PD are unknown, but LRRK2 is associated with autophagy, vesicular dynamics, and Wnt signaling. We are employing the CRISPR/Cas9 system to develop an allelic series of LRRK2 mutations. These include lesions in the armadillo repeats, GTPase and kinase domains. Behavioral studies were conducted to evaluate potential locomotor defects caused by LRRK2 dysfunction. We are also investigating if LRRK2 directly modulates the Wnt signaling pathway as a mechanism central to the pathogenesis of PD. Zebrafish models would not only empower mechanistic and gene interaction studies, but enable behaviorally based small molecule screens to identify compounds that alleviate Parkinson's related phenotypes.

#7

Title: Urethral Sling Trends for New York State from 2003 to 2016: FPMRS-Trained Physicians Compared to Non-Fellowship Trained Counterparts

Authors: **Alexandra Siegal**, Zhenyue Huang, Anh Nguyen, William Berg, Sina Mehraban-Far, Michael Gross, Stephen Eng, Steven Weissbart, Jason Kim

Abstract: INTRODUCTION AND OBJECTIVES: Transvaginal mesh (TVM) was first approved for stress urinary incontinence in 1996. TVM is used as a synthetic "sling" under the urethra or bladder neck to provide urethral support and help reduce urine leakage during activity. However, overtime, there has been a steady increase in adverse events reported, including mesh erosion into the vagina (causing dyspareunia, vaginal pain, bleeding, or discharge), and erosion into the bladder (causing recurrent UTIs, SUI, hematuria, dysuria, urgency, frequency, and vaginal pain). The Food and Drug Administration (FDA) issued a 2011 warning on serious complications of surgical mesh in urogynecological procedures. There is limited data on the impact of the FDA warning on urethral sling placement for stress urinary incontinence (SUI). In our study, we sought to investigate the impact of 2011 FDA warning on the usage of transvaginal mesh in SUI. We were interested in looking at its trend overtime and wanted to compare the practice patterns between differently trained providers including general gynecologists, general urologists and FPMRS trained physicians. We aimed to specifically look at differences in insertion and revision rates.

METHODS: The New York Statewide Planning and Research Cooperative System (SPARCS) is an all payer reporting system that collects physician and patient data. Data on sling implantations for SUI performed by NY physicians from 2003 to 2016 were extracted using CPT codes. Physician board certification data was collected based on NY license numbers. Pre-2011 was defined as 2006-2010 and post-2011 was defined as 2012-2016.

RESULTS: 47,303 sling insertion and 3,225 sling revision/ removal operations were identified. Total urethral sling placements decreased by 56% from 2011 to 2016. The number of sling revision somehow remained relatively stable and low in relation to the number of implantations over the study period. Interestingly, general gynecologists and general urologists historically performed majority of the sling cases; for example, in 2010, they performed 74% of all the sling implantations. However, after 2011, the proportion of slings placed by non-FPMRS physicians decreased. In recent years, the FPMRS-certified physicians have started to take up a higher proportion of sling cases (26% in 2010 vs 47% in 2016). In this time, FPMRS providers began to perform the majority of revisions (46% in 2010 v. 62% in 2016). Additionally, since the FDA warning, average time between sling implant and revision decreased for both non-FPMRS and FPMRS providers (non-FPMRS: 72 mo. to 24 mo., FPMRS: 64 mo. to 23 mo., $p<0.001$).

CONCLUSIONS: Since the FDA warning, utilization of the urethral sling by non-FPMRS physicians for SUI has greatly decreased, with an increasing proportion of procedures by FPMRS physicians. Similarly, the proportion of sling revisions by FPMRS physicians has increased. Decreased time between sling implant and revision may reflect more aggressive surveillance of patients in response to the FDA and/or patient driven concerns.

#8

Title: Exploring Protein Folding and Light Activation Using Molecular Dynamics Simulations

Authors: **SeungYoun Shin**

Abstract: A LOV2 domain, light oxygen voltage sensing domain, is a protein sensor used for plant phototropin, which is a blue light receptor that forms a cys-FMN adduct formation and leads to the enhancement of the phototropin kinase activity, glutamine rotation, as well as Jα helix unfolding. We focus on the mechanism in a LOV2 domain of the blue light photoreceptor phototropin 1 from Avena Sativa (AsLOV2). The LOV2 domain derived from the AsLOV2 binds to a flavin cofactor, flavin mononucleotide (FMN), in order to illuminate the blue light. In the dark state, the C-terminal Jα helix of the AsLOV2 tightly binds to the core domain. The Jα helix is released from the core domain of the AsLOV2 with the blue light irradiation, and we clearly observe the Jα helix unfolding in the light state. The project focuses on the mechanism of the helix unfolding in the Avena Sativa LOV2 domain using Molecular Dynamics (MD) Simulations. According to the results of the MD simulations, the dynamics of Jα-helix unfolding in N12A and N12Q mutants of the AsLOV2 are attenuated. Additionally, hydrogen bonds play an essential role in determining the structural changes of the Jα-helix. We demonstrated the conformational transitions and dynamics of the structures and side chains for the wild type and two mutants. Overall, we compared the dissociations of the Jα-helix unfolding for N12, N12A and N12Q by analyzing the RMSD plots, the hydrogen bond distance plots, the dihedral angle plots and Ramachandran plots. As a result, Asn 12 in the wild type of the AsLOV2 changes the hydrogen bonding in the LOV2 domain, which causes backbone conformation and Jα-helix unfolding. The residues in mutants, Ala 12 and Gln 12, do not show significant change in side chains and the backbone conformation, and the Jα-helix unfolding in mutants is attenuated.

#9

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backbone conformation, and the Jα-helix unfolding in mutants is attenuated.

#10

Title: Epilepsy and the Religious Experience: What Seizures Tell us about the Biology of Belief

Authors: **Christina Perri**, Stephen Post

Abstract: Epilepsy, perhaps more than any other disease, exists at the interface of neurobiology, religious history, and religious experience. Most religious traditions have complex and at times ugly relationships with epilepsy, and religion and science have battled for centuries to explain the disease. Simultaneously, speculation exists about the role that epilepsy may have played in the religious experiences of major historical figures, including saints, prophets, and apostles. Such religious experiences are typified by the writings of Fyodor Dostoevsky:

> "For a few moments before the fit, I experience a feeling of happiness such as it is quite impossible to imagine in a normal state and which other people have no idea of. I feel entirely in harmony with myself and the whole world, and this feeling is so strong and so delightful that for a few seconds of such bliss one would gladly give up ten years of one's life, if not one's whole life."

Here we explore this relationship between epilepsy and religious experience, with emphasis on historical perspectives, analysis of primary religious texts, and more recent neuroscientific studies. Religions vary in their interpretation of epilepsy, including presumed etiology and consequent treatment of people with epilepsy. Theological explanations of epilepsy appear in folk beliefs, organized religions, polytheistic religions, monotheistic religions, and across time and location. Themes emerging across multiple religious traditions include divine punishment, spiritual possession, a link to sexuality, a link to the moon, and the abnormally high (e.g. priest, shaman) or low (e.g. witch) social status of people with epilepsy. We have in literature review explored the neural correlates of religious experience, using epilepsy as a primary lens, and noted emphasis on the roles that the temporal lobes, medial prefrontal cortex, anterior insula, posterior superior parietal lobe, and the extrapersonal brain systems may play in mediating such experiences. From this emerges a philosophical question about any tendency to reduce religious experience, through epilepsy, to neurobiology. We explore the question of whether biological reductionism is defensible and its subsequent implications.

#11

Title: Exploring Protein Folding and Light Activation Using Molecular Dynamics Simulations

Authors: **Yu Wen Cheng, BA**; Michael Secko MD RDMS, Eshani Goradia, BA; Sonika Raj, MD; Henry C Thode, PhD; Lindsey Reardon, MD; Mathew Lohse, MD; Adam J Singer, MD

Abstract: Introduction: Much debate exists around the relative diagnostic accuracy of physical exam (PE) versus bedside ultrasound (US) in patients with dyspnea. We compared the accuracy of structured comprehensive PE and lung US in ED patients with dyspnea. Methods: Using a prospective, observational crossover study design, we enrolled hemodynamically stable adults who presented with dyspnea to a large academic ED. ED physicians performed both a structured PE (inspection, palpation, percussion, auscultation) and lung US (presence of A or B lines, sliding, effusion, and consolidation in 6 lung fields bilaterally) on each patient, the order of which was randomized. After each evaluation, the physician rated degree of certainty (low, moderate, high) that any of 6 diagnoses (pulmonary edema, COPD, pneumonia, pleural effusion, asthma and pneumothorax) were present. Patients also rated their confidence in PE and US, before and after evaluation. A masked adjudicator determined final diagnosis based on all clinical data. We compared the accuracies (true positive plus true negative/all) of PE and US using the adjudicated diagnosis as the criterion standard. Patients' relative confidence level with each evaluation was also assessed. Results: We enrolled 67 patients. Mean (SD) age was 63 (18), 38 (57%) were male. Patients were randomized to PE (n=37) or US (n=30) first. 20 patients had more than 1 diagnosis. Final diagnoses included pulmonary edema (n=22), COPD

(n=18), pneumonia (n=11), pleural effusion (n=7), and asthma (n=3). 34 patients had none of the six conditions. Accuracies of PE and US for the various diagnoses were pulmonary edema (72 [59-82] vs 72 [59-82]%), COPD (79 [67-88] vs 84 [72-91]%), pneumonia (79 [67-88] vs 88 [77-94]%), pleural effusion (97 [89-99] vs 87 [76-93] %), and asthma (91 [81-96] vs 94 [85-98] %); P>0.05 for all. Diagnostic accuracies did not differ based on order of evaluation. Prior to evaluation only 1 patient had more confidence in PE than US, 36 patients had more confidence in US, and 30 had equal confidence. After evaluation 3 patients had more confidence in PE, 33 had more confidence in US, and 31 considered them equal. Conclusions: PE and US have similar accuracies at diagnosing cardiopulmonary conditions in ED patients with dyspnea. Patients were more confident in US than PE.

#12

Title: Leupeptin Role Limiting Muscle Damage after Prolonged Blood Flow Occlusion

Authors: **Irene Nozal Martin**, Mikhail Gurevich, Gurtej Singh, Duc Bui, Sami Khan, David Komatsu, Alexander Dagum

Abstract: Introduction: muscle degeneration is one of the primary concerns after ischemia, or the block of oxygen supply. It is a recurrent problem in patients suffering from lower extremity artery disease (LEAD), with 150,000 new cases each year only in the US (1), and it can be a secondary effect of long-time bedridden or immobilised limbs for medical reasons. “Calpain”, a Ca2+-dependent enzyme, is mainly responsible for such damage. In our experiment, we investigate the possible effects of leupeptin, a calpain inhibitor, reducing the limb injuries in a rat model.

Materials and Methods: a tourniquet set to 300 mmHg pressure was applied for 2 hours to the left hind of 10 male Sprague-Dawley rats. Afterwards, animals were randomly split into two groups and received either saline or leupeptin injections, being the saline group used as a control. Sciatic functional index (SFI) was determined to check gait quality for two weeks. Eventually, rats were sacrificed and tissue samples including the gastrocnemii muscle were collected for histological analysis. Measuring the cross-sectional area of muscle fascicles, we expected to reveal the influence of leupeptin in trauma attenuation.

Results and Discussion: Histological images of the gastrocnemius muscle fascicle cross-sectional areas from both leupeptin and control groups’ hind limbs were imaged using a confocal microscope and analyzed using Image J software. The difference between muscle cross sectional areas of the ischemic hind limbs between these groups was found to be significant (leupeptin - 780.23 μm2 vs control - 484.40 μm2; p=0.033). These two values were notably lower as compared to their respective right muscle fascicle areas, where no tourniquet was applied (leupeptin - 1743.78 μm2 vs control -1587.14 μm2). However, differences in the SFI scores between the two cohorts were not found to be distinct (p=0.785).

Conclusion: results allow us to state the positive role of leupeptin reducing the pernicious outcome of blood occlusion. Calpain is inhibited, thus muscle fibers are preserved. Implications of these outcomes could have positive effects on patients suffering from LEAD and necrosis risks could be reduced. Still, left limb values were considerably below the “healthy” muscle area data, represented by right limbs. This indicates that further studies are required to solve the complex pathways that are triggered after ischemia.

#13

Title: Therapeutic targeting of the most aggressive subtype of pancreatic cancer

Authors: **Cindy V. Leiton**, Chun-Hao Pan, Lucia Roa-Peña, Ji Dong Bai, Alex Penson, Sruthi Babu,

Nashaat Turkman, Richard Moffitt, Markus Seeliger, David Talmage, Kenneth R. Shroyer, and Luisa F. Escobar-Hoyos

Abstract: The purpose of this study was to identify targeted therapies for the treatment of pancreatic ductal adenocarcinoma (PDAC), building on our discovery of keratin 17 (K17) as a biomarker for the most aggressive form of the disease. In vivo studies showed that animals bearing K17-expressing PDACs display early onset of death, suggesting that K17 drives tumor aggression and should be explored as a potential therapeutic target. We previously reported that K17 functions as an oncoprotein that can solubilize from cytoskeletal filaments, enter the nucleus, and target the tumor suppressor p27 for nuclear export and degradation, promoting cell proliferation and tumor growth. Here, we describe two experimental approaches to directly and indirectly target the K17 oncoprotein-nuclear export shuttle functions in PDAC. First, by protein-sequence modeling analyses and site-directed mutagenesis, we identified the active sites in K17 that bind to and promote the degradation of nuclear tumor suppressors and shift the subcellular localization of proteins that regulate gene expression. In addition, by SILAC mass spectrometry analysis of nuclear proteomes from isogenic human cells with and without K17 expression, we found that 50% of the nuclear proteome is altered by the presence of K17, and half of these proteins encode the targeting domain of K17. This suggests that the active sites of K17 may be therapeutically relevant targets to inhibit K17 oncoprotein functions and to provide the basis for understanding the biological differences in PDAC subtypes. We are currently testing small molecule and peptide inhibitors to target the K17 active sites in vitro and in vivo, as a discovery approach for small-molecule design against K17. Second, we found that K17 expression sensitized PDAC cells to small-molecule compounds that impede nuclear export, thereby repressing K17-mediated degradation of tumor suppressor p27 and other nuclear targets. Of potential translational relevance, these same compounds are currently undergoing testing in preclinical PDAC mouse models. This approach leverages existing FDA approved therapeutic agents for other cancer types, where repurposing for the treatment of K17-positive PDACs may result in enhanced expedient therapeutic efficacy. These studies may ultimately provide the basis for novel biomarker-based therapeutic approaches for 50% of PDAC cases (those that express high levels of K17) using small-molecule inhibitors that either directly target K17 active sites or the pathways impacted by this protein.

#14

Title: Therapeutic targeting of the most aggressive subtype of pancreatic cancer

Authors: **Young Sun Lee**, Ninghui Mao, Zeda Zhang, Danielle Choi, Sam Haywood, Dan Li, Cindy Lee, Yu Chen, Charles Sawyers, Brett Carver

Abstract: Introduction: Alterations in the PI3K signaling pathway have been identified in about 50% of metastatic castrate resistant prostate cancer (mCRPC), with approximately 10% of mCRPC harboring activating alterations in PIK3CA (Robinson et al. 2015). PI3K has two major isoforms of its catalytic subunit in epithelial cells, p110α (PIK3CA) and p110β (PIK3CB). Targeting PIK3CA mutations in prostate cancer has garnered interest in response to promising results of phase III clinical trial using p110α-selective inhibitor (BYL719) in PIK3CA-mutant breast cancer (Juric et al. 2018). In prostate cancer (PCa), deletion of PTEN is associated with dependency on p110β in (Wee et al. 2008). Based on this, PTEN status is used as a biomarker for p110β-selective inhibitor (AZD8186) in a phase II clinical trial (Hansen et al. 2017). However, in a PTEN-deleted PCa model, inhibition of one p110 isoform results in relief of feedback inhibition of the other isoform (Schwartz et al. 2015), emphasizing a need to further analyze isoform dependency in relation to PTEN status. Here we characterize the response of PTEN-WT and PTEN-null PCa lines to isoform-selective and pan-PI3K inhibition and investigate potential resistance mechanisms.

Methods: In vitro and in vivo experiments were conducted using the LNCaP, 22Pc-EP, and human prostate cancer organoid PCa lines. The PCa lines were obtained from Dr. Yu Chen. Protein levels were assessed by Western blot analysis, and cell viability luciferase assays were conducted using the Promega CellTiter-Glo Assay System. For xenograft experiments, 1 x 106 cells were injected into the bilateral flanks of SCID mice. When mice tumors reached around 500 mm3, mice were randomized to treatment groups.

Results: Activating mutations in PIK3CA and over-expression of wild-type PIK3CA enhanced PI3K signaling in the settings of PTEN wild type or PTEN loss prostate cancer. PTEN loss was not correlated with p110β dependency, as previously reported, and PTEN deletion or adding back PTEN did not change isoform dependency. Activating alterations in PIK3CA in the setting of wild-type PTEN promoted sensitivity to p110α inhibition. However, despite initial response to inhibition of p110α, relief of feedback inhibition promoting rebound signaling through p110β was observed. A combination of both isoforms was necessary to continuously suppress the pathway. In addition, 8 PTEN loss organoid lines demonstrated differential sensitivity to a combination of both isoform selective inhibitors. Importantly resistant lines were still dependent on downstream signaling. Increased IGF1R and INSR levels were correlated with resistance, and genetic and pharmacologic inhibition of IGF1R/INSR re-sensitized the cells to PI3K inhibition.

Conclusions: In prostate cancer, activating PIK3CA and PIK3CB mutations enhance PI3K signaling. This result validates the relevance of targeting p110 isoforms in cases with activating PIK3CA and PIK3CB mutations. Despite the fact that PTEN-null status is used as the biomarker for p110β-selective inhibitor (AZD8186) in PCa clinical trial, a panel of PTEN-WT and PTEN-null PCa lines demonstrated no correlation between PTEN-null status and p110β dependency. Due to the relief of p110 isoform feedback inhibition, a combination of both isoforms p110α and p110β inhibitors is required to effectively inhibit PI3K signaling. However, a high level of IGF1R/INSR in PTEN-null background is correlated with inherent resistance to dual inhibition of p110α and p110β. Targeting IGF1R/INSR restores sensitivity to PI3K inhibition, and this hypothesis is also being tested in vivo. The level of IGF1R/INSR can be used as a new biomarker to stratify patients that would respond to PI3K inhibition. Alternatively, IGF1R/INSR can be targeted in combination with PI3K inhibition to improve response to PI3K inhibition.

#15

Title: Real-time Prediction of Bitcoin bubbles and Crashes

Authors: **Min Shu**, Wei Zhu

Abstract: In the past decade, Bitcoin has become an emerging asset class known to most people owing to their extraordinary return potential in phases of extreme price growth as well as unpredictable massive crashes. We summarize the Bitcoin historical crashes with more than 15% sharp drop in less than 3 weeks and observe the 51 crashes just in recent seven and half years. Compared to the traditional stock market, the crash duration and the time gap between crashes of Bitcoin can be quite short. The number of short-term crashes increases as Bitcoin long-term bubble grows and a succession crashes can be triggered after the long-term bubbles mature. Based on Log Periodic Power Law Singularity (LPPLS) model, we apply the LPPLS confidence indicator as a diagnostic tool for identifying both the positive and negative bubbles using the daily data of Bitcoin price in the past two years. We find the LPPLS confidence indicator based on the daily data of Bitcoin price fails to provide effective warnings for detecting the bubbles when the Bitcoin price suffers to a large fluctuation in a short time, especially for positive bubbles. In order to diagnose the existence of bubbles and accurately predict the bubble crashes in the cryptocurrency market, this study proposes an adaptive multilevel time series detection methodology based on the LPPLS model. We adopt two levels of time series, 1 hour and 30 minutes, to demonstrate the adaptive multilevel time series detection methodology. The results show that the LPPLS confidence indicator based on the adaptive multilevel time series detection methodology have an outstanding performance to effectively detect the bubbles and accurately forecast the bubble crashes, but also monitor the development and crash of bubbles even if a bubble exists in a short time. In addition, we discover that the short-term LPPLS confidence indicator greatly affected by the extreme price fluctuations of Bitcoin price can provide the useful insights into the bubble status in a short time scale, and the long-term LPPLS confidence indicator has a stable performance and effectively monitor the bubble status in a long time scale. The adaptive multilevel time series detection methodology can provide real-time detection of bubble and timely information to warn of an

imminent crash risk not only in cryptocurrency market but also in other financial markets.

#16

Title: Ciprofloxacin Siderophore-conjugates as Theranostics for Bacterial Infections

Authors: **Apurva Pandey**, Chloé Savino and Eszter Boros

Abstract: Currently, the clinical diagnosis of bacterial infections of the bone (osteomyelitis), joints (septic arthritis) and heart valves (endocarditis) is based on assessment of several non-specific symptoms such as skin findings, fever and pain. No non-invasive tools exist to unequivocally localize and identify deep-seated, possibly lethal bacterial infections. Nuclear imaging tracers are ideally suited to detect small quantities of infected tissue in-vivo can meet the need for faster, more accurate and specific tools to diagnose bacterial infections.

Bacteria assimilate physiologically essential iron by utilizing high affinity ferric ion chelators, siderophores that an active internalization pathway through siderophore-specific bacterial transmembrane proteins. The radioisotopes 67Ga (t1/2 = 79 h, SPECT) have optimal nuclear imaging properties and a high affinity to Fe3+-siderophores. We hypothesize that 67Ga siderophores can take advantage of the active siderophore internalization pathway and accumulate in sites of infection with high specificity. The long half-life of 67Ga may enable non-invasive monitoring of the time course of bacterial infections, as treatment is employed. Furthermore, non-radioactive gallium has been hypothesized to act as an efficient Fe(III) mimic with respect to siderophore-mediated uptake but may be able to impart growth inhibition as it can not be efficiently utilized as a nutrient by bacteria.

We have successfully synthesized 2 siderophore-drug conjugates (sideromycins) based on the desferrioxamine (DFO) and desferrichrome (DFC) scaffolds. The complexation with natGa(III) and natFe(III) yielded mononuclear complexes that were characterized using MS, NMR, HPLC, ICP-OES and UV/Vis spectroscopy. Radiolabeling with 67Ga(III) was carried out with two sideromycins and their parent siderophores producing the radiochemical complexes with > 95% radiochemical yield and purity. Using the 67Ga complexes, we evaluated the kinetic inertness and in vitro stability at various time points. The in vitro stability challenge indicates that the 67Ga are suitable for short time point nuclear imaging.

Bacterial uptake under iron-sufficient and deficient conditions was evaluated in parallel with a 67Ga citrate control. To challenge active transporter-mediated uptake, 100x LDFC-Fe challenge bacterial uptake was also carried out. Minimum inhibitory concentration (MIC) assays with wt E.coli, P.aeruginosa and S.newman were performed under deficient conditions to assess the antibiotic potency of the novel metallo-sideromycins synthesized. Challenge MIC values were used to probe the siderophore specific, active transport to the bacterial cytoplasm. Biodistribution and metabolic stability experiments on naïve CBJ mice were also performed.

#17

Title: The Role of Gabrb3 in the Development of Cortical Circuits for Sensory Perception

Authors: **Rachel Babij**, Camilo Ferrer, Zhe Ran Duan, Alicia Che, Jonathan Witztum, Takumi Otsuka, Ben Huang, Conor Liston, Natalia De Marco Garcia

Abstract: Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders of diverse presentation, though sensory disturbances and altered tactile perception are a unifying feature. Understanding and treating ASD requires knowledge of the circuits involved in somatosensation, as well as the function of high-risk ASD genes, and how mutations in these genes can impact circuit development and higher-order sensory processing. A predominant hypothesis for the etiology of ASD is that the balance between inhibition and excitation is tilted toward excitation, and human postmortem studies have pointed to inhibitory neurons and neurotransmitters as relevant players in the disease process. Indeed, many of the genes implicated in human genetic studies of ASD are central to synaptic machinery and

neurotransmitter receptors, including the Beta-3 subunit of the ionotropic GABA-A receptor (GABRB3), which has repeatedly been identified in independent cohorts.

Data from our lab has shown that inhibitory interneurons strongly regulate excitatory network activity in superficial layers of the mouse developing brain. In addition, activity manipulations during development impact the maturation of efferent projections from this superficial network, though the identity of the receptors mediating this effect is unclear. To determine the identity of the relevant receptors, we conditionally eliminated the Gabrb3 subunit in cortical excitatory cells (Emx1.Gabrb3fl/fl). We found that conditional elimination of the Gabrb3 gene in excitatory cells causes an impairment in the development of GABAergic synapses. Excitatory neurons without this subunit display inhibitory synaptic currents with a shorter decay time, enhanced axonal arborization, and redistribution of projections within intracortical targets. Furthermore, network synchrony is enhanced in vivo, as measured with longitudinal cell-subtype specific calcium imaging in unanesthetized pups. These results indicate that the GABRB3 gene is fundamental for the proper development of projection neurons and the emergence of network patterns in the maturing cortex.

#18

Title: Cherenkov Radiation-Mediated In Situ Excitation of Lanthanides: A Method to Broaden the Spectrum of In Vivo Applicable Optical Imaging Probes

Authors: **Alexia Cosby**, Grace Ahn, Gregory Quevedo, and Eszter Boros

Abstract: Lanthanide-based luminescence represents an attractive alternative to conventional organic chromophores used for optical imaging applications. The unique electronic configuration of trivalent lanthanides results in sharp emission bands independent of the coordinative environment of the metal between 490-700 nm, conceptually ideal emission wavelengths for in vivo optical imaging applications. However, photophysical ramifications make the direct excitation of metal-based luminescence inefficient and require a high-energy, short-wave excitation source. Due to the incompatibility of external high-energy excitation with in vivo applications, luminescent lanthanides are not suitable for in vivo optical imaging.
We developed a system that addresses this shortcoming by in situ excitation of lanthanide complexes through Cherenkov radiation energy transfer (CRET). Cherenkov radiation (CR) is emission of short wavelength light generated by excitation of dielectric media via radioisotopes. The CR λem maximum matches with the antenna excitation energy. To utilize CR as an in situ source of short wavelength excitation, we doped aqueous lanthanide(III) complexes with radioisotopes with characteristic CR emission (18F and 89Zr) and monitored emission of lanthanide-based luminescence using a small animal fluorescence imager. With only 10 μCi of 18F, quantities as low as 5 nmol of complex are detected. In addition to our proof-of-concept studies, we evaluated the relationship between lanthanide complex quantum yield (Φ) and CRET by imaging a library of Tb(III) complexes (Φ = 0.01 – 0.65). A direct correlation allows for systematic Φ determination and selection of lanthanide complexes with ideal properties for future in vivo applications. Finally, we synthesized an intramolecular CRET probe by directly appending a CR-emitting isotope (89Zr) to the Tb(III) complex. In summary, our work shows that the CR-mediated lanthanide excitation has potential for in vivo optical imaging applications.

#19

Title: Heterogeneous adaptation of lung cancer cells to KRASG12C specific inhibition

Authors: **Jenny Xue**, Jordan Aronowitz, Yulei Zhao, Trang Mai, Alberto Vides, Besnik Qeriqi, Elisa DeStanchina, Gregory Riely, Linas Mazutis, Davide Risso, and Piro Lito

Abstract: Lanthanide-based luminescence represents an attractive alternative to conventional organic

chromophores used for optical imaging applications. The unique electronic configuration of trivalent lanthanides results in sharp emission bands independent of the coordinative environment of the metal between 490-700 nm, conceptually ideal emission wavelengths for in vivo optical imaging applications. However, photophysical ramifications make the direct excitation of metal-based luminescence inefficient and require a high-energy, short-wave excitation source. Due to the incompatibility of external high-energy excitation with in vivo applications, luminescent lanthanides are not suitable for in vivo optical imaging.
We developed a system that addresses this shortcoming by in situ excitation of lanthanide complexes through Cherenkov radiation energy transfer (CRET). Cherenkov radiation (CR) is emission of short wavelength light generated by excitation of dielectric media via radioisotopes. The CR λem maximum matches with the antenna excitation energy. To utilize CR as an in situ source of short wavelength excitation, we doped aqueous lanthanide(III) complexes with radioisotopes with characteristic CR emission (18F and 89Zr) and monitored emission of lanthanide-based luminescence using a small animal fluorescence imager. With only 10 μCi of 18F, quantities as low as 5 nmol of complex are detected. In addition to our proof-of-concept studies, we evaluated the relationship between lanthanide complex quantum yield (Φ) and CRET by imaging a library of Tb(III) complexes (Φ = 0.01 – 0.65). A direct correlation allows for systematic Φ determination and selection of lanthanide complexes with ideal properties for future in vivo applications. Finally, we synthesized an intramolecular CRET probe by directly appending a CR-emitting isotope (89Zr) to the Tb(III) complex. In summary, our work shows that the CR-mediated lanthanide excitation has potential for in vivo optical imaging applications.

#20

Title: Mass Selective UV-Vis Spectroscopy Yields Detailed Electronic Absorption Spectra of Gold Nanoclusters

Authors: **Hanna Morales Hernández**, Anthony Cirri, Christina Kmiotek, Christopher Johnson

Abstract: The growing field of nanoengineering has potential to contribute in the development of new devices for energy transfer and storage, sensing, and numerous other applications. Given that the properties of a nanomaterial are highly dependent on the nanomaterial's electronic structure, it is imperative to be able to control electronic structure in order to regulate the compound's properties. However, correlating electronic structure to chemistry and dynamics is challenging due to synthetic and experimental limitations in the field. We are addressing this challenge by conducting gas-phase, ultraviolet-visible (UV-Vis) spectroscopy on ligand-protected gold nanoclusters that are exactly mass selected from a mixture by mass spectrometry. The spectra are collected in a homogeneous, contaminant-free environment at cryogenic temperatures, providing an unprecedented level of detail that will give insight into the electronic structure of the clusters. Specifically, clusters containing different compositions and ligand types were held at 36 K and 4 K, with nitrogen and helium gas, respectively, physisorbing onto their surface and acting as solvents. Computational studies and analysis are being conducted for the definitive assignment of spectral features, as well as to determine the causes for shifts in, and splitting of, transitions. Ligand and solvent species have already demonstrated to significantly affect the electronic transitions within the core of the nanoclusters. Design rules analogous to those for organic and organometallic molecular systems will be developed by tracing the changes in electronic transitions that are caused by chemical composition and structure, which in turn will give us an understanding of how to chemically manipulate gold nanoclusters to achieve desirable electronic structures and properties.

#21

Title: A Resilience Model for Left-behind Children: The Interaction between Risk and Protective Factors

Authors: **Xiaoqing Zhang, M.S.**; Sharon Ray, ScD, OTR/L

Abstract: In China, 61 million children were left behind in villages due to their parents migrating to cities for better income opportunities (All-China Women's Federation, ACWF, 2013) since the late

1970s. They are under the supervision of their grandparents, relatives, elder siblings, or in some cases, self-supervised. Ample research has documented the adverse mental health sequelae among those children such as depression, anxiety, negative self-perception, and loneliness (e.g. Fan, Su, Gill, & Birmaher, 2010; Gao et al., 2010; Guo et al.,2012; Wen & Lin, 2012; Sun et al., 2015).

In 2013, the All-China Women's Federation (ACWF) estimated that the number of children left behind had reached 61 million—a population larger than California and New York combined. This number accounts for 38% of all rural children, and 22% of all children in China (ACWF, 2013). Although children left behind is not unique to China, the sheer magnitude of this phenomenon in China and the mental health burden borne by those children have made it a social problem and a public health issue that cannot be ignored. The left-behind children (LBC) phenomenon demands and deserves scientific study to unveil and analyze the problem, so that policies and programs can be designed to alleviate the burden borne by those children left behind. Prevention is essential because mental health problems in left-behind children have negative impacts on individuals, families, and communities in various aspects; there are high economic costs tied to mental health issues along with excessive human suffering.
For the current study, I focus on depressive symptoms as revealed by LBC's descriptions about their feelings. In addition to being one of the most studied mental health issues among LBC, depression results in a variety of health problems including diabetes, heart disease, and is associated with increased rates of substance use and a higher risk of suicide (World Health Organization, WHO).

However, not every child left behind exhibit mental health problems. Many of them are able to cope with the challenge of living separately from their parents for an extended period of time. Those children can be motivated and study even harder to go to colleges and get a better job. I call those children resilient because they prevail over the temporary adversity and they don't have mental health issues such as depressive symptoms.

Researchers had been focusing on those LBC with mental health issues and the related risk factors; what remains unknown is how some of the LBC become resilient (no depressive symptoms) and what are the contributing factors to their resiliency. Although there are risk factors that by no means affect the emotional development of LBC (e.g., living without parents), some protective factors such as parent-child cohesion and hope could mitigate the negative effects. This study discusses the risk and protective factors based on the literature, and explore how those influential factors interact with each other contributing to the resiliency in LBC. By understanding what contributes to the resiliency of LBC and how the resilience mechanisms work (the interactions between risk factors and protective factors leading to resiliency), effective policies can be designed by tapping on the protective force that disrupts risk processes and to promote the healthy development of LBC in rural China.