15th Annual VANDERBILT POSTDOCTORAL ASSOCIATION SYMPOSIUM

Program

November 1, 2021 | VU Student Life Center

Sponsored by the Office of Postdoctoral Affairs & the Office of BRET, Vanderbilt University School of Medicine
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The Vanderbilt Postdoctoral Association (VPA) was founded in 1998 as a mechanism to support the professional, personal, and scholarly success of postdocs from Vanderbilt University and Vanderbilt University Medical Center. Since then, the VPA has organized 14 annual symposia, through which the work of hundreds of previous postdoctoral scholars has been highlighted. This year marks an important milestone for the association – not only are we hosting our 15th annual symposium but it is also the association’s first in-person conference since the beginning of the COVID-19 pandemic. We are thus immensely grateful to provide you all with what has become a rare opportunity to come together and celebrate the work of fellow postdocs.

The symposium planning committee has worked to cultivate an exciting program of content that includes research from a diverse array of departments including Medicine, Earth and Environmental Sciences, Electrical and Computer Engineering, and Physics and Astronomy. The day of events is broken into two poster sessions, a single lightning talk session, a career advising session, and keynote address and lunch.

We would like to thank all of our presenters, our invited speakers Dr. Adia Harvey Wingfield and Dr. Ashley Brady, and, of course, our university sponsors, the Office of Postdoctoral Affairs and the Office of Biomedical Research Education and Training, all without whom this symposium would not be possible.

In closing, on behalf of the Vanderbilt Postdoctoral Association and the symposium planning committee, we hope this day brings opportunities for scientific discovery, collaboration, and networking!
Schedule of Events

All events are in Central Standard Time (CST)

10:00 am - 10:15 am  Welcome Remarks  
Vice Provost André Christie-Mizell  
Ballroom 1/2

10:15 am - 11:15 am  Poster Session A  
Ballroom 3

11:30 am - 12:45 pm  Keynote Address & Lunch  
Dr. Adia Harvey Wingfield  
Ballroom 1/2

1:00 pm - 1:30 pm  Career Advising Session  
Dr. Ashley Brady  
Ballroom 1/2

1:30 pm - 2:30 pm  Poster Session B  
Ballroom 3

2:45 pm - 4:15 pm  Lightning Talks  
Ballroom 1/2

4:30 pm - 5:15 pm  Awards  
Closing Remarks  
Cocktail Hour  
Board of Trust Room
REGISTRATION
Please check-in at the registration desk to get your name badge and lunch (orange), drink (yellow), reception snacks (green), and raffle (blue) tickets.

Please follow the university's COVID-19 guidelines at all times.
What happens to black professionals when work transforms? In an era of rapid technological change, shrinking protections for workers, and growing income inequality, work is no longer the secure, stable, predictable path to economic stability that it once was for some segments of the population. Instead, organizations today focus on shedding labor, cutting costs, and increasing shareholder returns. At the same time, however, many organizations also profess an interest in meeting the needs of an increasingly diverse population. How do they manage the tensions of adapting to these neoliberal ideals in a more multiracial society?

This research study focuses on black professionals in the health care industry to answer this question. Using in depth interviews, field observations, and survey data analysis, I show how work transformation fundamentally changes the labor black professionals do within and outside of organizations. This labor varies by occupational status and gender, leaving black men and black women with divergent responsibilities depending on their position in the organizational hierarchy. Ultimately, this research identifies new challenges for organizations and reveals an additional way that racial inequality gets perpetuated in the new economy.
Career Advising Session
1:00 - 1:30 PM
Ballroom 1/2

Career Development for Postdoctoral Fellows and the ASPIRE Program at Vanderbilt

What are your career plans? What should your next steps be to get you there?

If these questions overwhelm you, or you just want to be more strategic in preparing, then join Ashley Brady, PhD, as she shares ideas to help you make a plan and maximize the resources available to you, both on campus and elsewhere. Your postdoc years are an excellent time to explore career options, build skills and network to help you make the most of this important stage in your training.

Dr. Ashley Brady
Assistant Dean of Biomedical Career Engagement and Strategic Partnerships
BRET Office of Career Development ASPIRE Program
Assistant Professor of Medical Education and Administration

The Office of Biomedical Research Education & Training (BRET)
Vanderbilt University School of Medicine
Select postdocs will present their research through a brief oral presentation, which will be judged by the audience members at the symposium. Two talks with the most popular votes will receive an award at the closing event.

Dr. Shunxing Bao, Vanderbilt University
Random multi-mhannel image synthesis for multiplexed immunofluorescence imaging

Dr. Tomasz Bednarski, Vanderbilt University
The effect of LXR activation on liver metabolism and diet-induced steatohepatitis in mice

Dr. Kilian Hett, Vanderbilt University Medical Center
Parasagittal dural space increases with age and cerebrospinal fluid flow: implications for human glymphatic dysfunction in aging and neurodegeneration

Dr. Harry Barbee, Vanderbilt University
Sex in a pandemic: how gender affects our adaptations to moments of crisis

Dr. Michael Kammer, Vanderbilt University Medical Center
The tumor immune microenvironment protects against recurrence in early-stage lung adenocarcinoma

Dr. Andrew Patterson, Vanderbilt University Medical Center
Identification of metabolic underpinnings of effector CD4+ T cell development and function

Dr. Mohammad Saleem, Vanderbilt University Medical Center
Specific ablation of Jak2 from CD11c+ cells attenuates salt-sensitive hypertension through an ENaC-dependent mechanism.
Poster Sessions

Session A
10:15 - 11:14 AM

Session B
1:30 - 2:30 PM

Ballroom 3

Each poster presentation will be judged by two faculty members. Three posters with the highest scores will receive an award at the closing event.

Poster # and Session. Presenters are listed in alphabetical order.

1B Dr. Chitra Basu, Vanderbilt University Medical Center
Gene expression analysis of isolated cardiac endothelial cells at different stages of tissue repair after myocardial infarction

2A Dr. Julie Bejoy, Vanderbilt University Medical Center
An accelerated method of podocyte differentiation from human induced pluripotent stem cells for modeling diabetic nephropathy

3B Dr. Kara Eichelberger, Vanderbilt University Medical Center
A toxic relationship: Candida albicans-Staphylococcus aureus interactions during polymicrobial infection

4A Dr. Hubaida Fuseini, Vanderbilt University Medical Center
High and low leptin doses differentially effect Ki67 and IL-17A expression in CD4+ T cells from obese and lean PWH on long-term antiretroviral therapy

5B Dr. Clément Garin, Vanderbilt University
An evolutionary gap in primate default mode network organization

6A Dr. Kakali Ghoshal, Vanderbilt University Medical Center
Treatment with epoxyeicosatrienoic acid analog (EET-A) improves insulin signaling in a genetic mouse model of insulin resistance

7B Dr. Brittney Gimza, Vanderbilt University Medical Center
Investigating antibiotic failure in Staphylococcus aureus osteomyelitis

8A Dr. Benjamin Gold, Vanderbilt University Medical Center
The fMRI signal exhibits more autonomic variance in drowsiness
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<table>
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| **10B** Dr. Ann Hanna, Vanderbilt University Medical Center  
Myeloid response to immunotherapy is associated with heterogeneity in outcomes to anti-PDL1 in breast cancer | |
| **11A** Dr. Nina Hernitschek, Vanderbilt University  
Rubin Observatory Community Brokers - real-time astronomical alert processing | |
| **17B** Dr. Bhawik Kumar Jain, Vanderbilt University  
Structure and transport mechanism of neo1, a monomeric P4-ATPase lipid flippase | |
| **12A** Dr. Christopher Kalmar, Vanderbilt University Medical Center  
Cosmetic abdominoplasty vs functional panniculectomy: pulmonary embolism risk | |
| **13B** Dr. Christopher Kalmar, Vanderbilt University Medical Center  
Breast reconstruction free flap failure: does platelet count matter? | |
| **14A** Dr. Christopher Kalmar, Vanderbilt University Medical Center  
Hospital admission charges for complex midface advancement in pediatric patients | |
| **15B** Dr. Christopher Kalmar, Vanderbilt University Medical Center  
LeFort II/III midface advancement: nationwide analysis of complications | |
| **16A** Dr. Christopher Kalmar, Vanderbilt University Medical Center  
High-volume orthognathic surgery: disparities in patient populations, admission charges, and surgical complications | |
18A  Dr. Xia Lei, Vanderbilt University  
Mechanisms of orthosteric agonist and allosteric modulator cctivation of mGlu7

19B  Dr. Jimin Min, Vanderbilt University Medical Center  
Dysplastic stem cells drive dysplasia transition to gastric adenocarcinoma

Dr. Snigdha Mukerjee, Vanderbilt University

20A  Oral chemesthesis modulates perception and consumption of alcohols

Dr. Khushbu Patel, Vanderbilt University Medical Center

21B  Assessment of correlation between pretest risk of lung cancer using clinical and imaging biomarkers and radiomics derived lung adenocarcinoma aggressiveness score

Dr. Brittany Spitznagel, Vanderbilt University Medical Center

22B  Acute manganese dysregulates aspects of glutamate signaling in young APP/PSEN1 mice

Dr. Alex Steiner, Vanderbilt University Medical Center

23B  The role of glucagon-like peptide-1 positive hippocampal mossy cells in obesity related neurocognitive impairment

Dr. Georgii Vasiukov, Vanderbilt University Medical Center

24A  The aggressiveness of human lung adenocarcinoma is associated with CAFs subpopulations at early stages
25B  Dr. Lissa Ventura Antunes, Vanderbilt University Medical Center
Three-dimensional morphology of degenerative arteriolar changes in cerebral amyloid angiopathy

26A  Dr. Kelsey Voss, Vanderbilt University Medical Center
Targeting the transferring receptor normalizes T-cell function in systemic lupus erythematosus

27B  Dr. Jordyn Wilcox, Vanderbilt University Medical Center
Chronic manganese exposure induces hyperactivity and dopaminergic dysfunction in young C57Bl/6 mice
Random multi-mhannel image synthesis for multiplexed immunofluorescence imaging
Dr. Shunxing Bao

Multiplex immunofluorescence (MxIF) is an emerging imaging technique that produces the high sensitivity and specificity of single-cell mapping. With a tenet of "seeing is believing", MxIF enables iterative staining and imaging extensive antibodies, which provides comprehensive biomarkers to segment and group different cells on a single tissue section. However, considerable depletion of the scarce tissue is inevitable from extensive rounds of staining and bleaching. Moreover, the immunofluorescence imaging can occasionally fail for particular rounds ("missing stain"). It would be appealing to develop digital image synthesis approaches to restore missing stain images. Herein, we aim to develop image synthesis approaches for 11 MxIF structural molecular markers. We propose a novel multi-channel high-resolution image synthesis approach, called pixN2N-HD, to tackle possible missing stain scenarios via a high-resolution generative adversarial network (GAN). Our contribution is three-fold: (1) a deep network framework is proposed to tackle missing stain in MxIF; (2) the proposed "N-to-N" strategy reduces theoretical 4 years of computational time to 20 hours when covering up to five random missing stains and (3) this work is the first comprehensive experimental study of investigating cross-stain synthesis in MxIF. Our results elucidate a promising direction of advancing MxIF imaging with deep image synthesis.

Sex in a pandemic: how gender affects our adaptations to moments of crisis
Dr. Harry Barbee

People have adapted their sexual behaviors to the uncertain environment of the COVID-19 pandemic, but it is unclear how gender has affected those adaptations. This paper draws on a national convenience sample of LGBTQ individuals (n=1968) to examine variation in changes to sexual behaviors. We used negative binomial regression models to examine the effects of gender identity on two outcome variables: 1) the number of questions respondents asked their sexual partners and 2) the number of individual behavioral changes respondents made to avoid exposure to COVID-19. We examined outcomes across cisgender men, cisgender women, gender minority women, and gender minority men. Compared to men, women, regardless of gender minority status, asked more questions of their sex partners to avoid exposure to COVID-19. However, gender minority status is not a significant predictor of how many questions respondents ask their sex partners to avoid exposure to COVID-19-a finding that is true for both women and men. Further, gender minority women reported a higher rate of risk-avoidance changes to their individual sex behaviors compared to cisgender women. In contrast, gender minority men reported a lower rate of individual changes to their sex behaviors compared to cisgender men. Taken together, our results suggest that men, regardless of gender minority status, took a more individualistic approach to avoiding exposure to COVID-19 compared to women; however, this relationship is moderated by gender minority status. Namely, gender minority women appear to have a more individualistic approach to avoiding exposure to COVID-19 compared to gender minority men.

The effect of LXR activation on liver metabolism and diet-induced steatohepatitis in mice
Dr. Tomasz Bednarski

While non-alcoholic fatty liver disease (NAFLD) affects ~30% of the US population, there is currently no approved pharmaceutical treatment to inhibit the progression of NAFLD to its more severe stage of nonalcoholic steatohepatitis (NASH). The liver X receptors (LXRs) are key regulators of cholesterol and fatty acid homeostasis in liver. However, the effects of LXR activation on liver metabolism in NASH pathogenesis are not well understood. We hypothesize that LXR activation might reduce metabolic dysregulation in NAFLD by augmenting phospholipids and cholesterol composition of cellular membranes. To test this hypothesis, 8-week-old male wild type (WT) or obese, melanocortin-4 receptor knockout (Mc4r-/-) mice were placed on either chow or Western diet (WD) for 8 weeks. Half of the WD-fed mice were given WD supplemented with GW3965 (100mg/kg), a selective, orally active agonist for the LXRs. Animals fed GW3965-supplemented diet had increased gene expression of Abca1, regulating cholesterol metabolism, and Lpcat3, involved in PL metabolism, both transcriptional targets of LXR action. LXR activation significantly decreased body mass of both WT and Mc4r-/- mice, which was correlated with reduction of subcutaneous fat. GW3965 supplementation greatly improved the response to glucose of both in WT and Mc4r-/- that was accompanied by increased plasma insulin level. Liver damage markers, ALT and AST, where downregulated in plasma of WT and upregulated in Mc4r-/- animals fed GW3965-supplemented died compared to WD-fed groups. Taken together, these data suggest that LXR activation improves phenotype of WD-fed animals but fails to prevent liver injury in more advanced stages of NAFLD.
Parasagittal dural space increases with age and cerebrospinal fluid flow: implications for human glymphatic dysfunction in aging and neurodegeneration

Dr. Kilian Hett

Recent studies have emphasized the importance of a human glymphatic system for metabolic waste and protein clearance, whereby cerebrospinal fluid (CSF) moves from subarachnoid space to regions surrounding dural sinuses. This so-called parasagittal dural (PSD) space may be fundamental to glymphatic clearance dysfunction, however limited approaches are available for quantifying the function and structure of this space. Here, we evaluated healthy adults across the lifespan (n=62) and quantified this space from high spatial resolution T1-weighted MRI and a novel machine learning volumetric estimation in sequence with bulk CSF flux through the aqueduct, with the overall hypotheses that PSD volume increases with (i) age and (ii) bulk CSF flux. We observed a significant hypertrophy of PSD volume with increasing age (p-value < 0.001, Spearman's-$\rho$ = 0.6), CSF volume (p-value < 0.001, $\rho$ = 0.6) and CSF flux through the cerebral aqueduct (retrograde and prograde, p-values < 0.001, |Spearman's-$\rho$|=0.32-42). These findings highlight (i) feasibility of quantifying PSD volume non-invasively in vivo in humans using machine learning and MRI, (ii) that this volume increases with age, and (iii) relates to bulk CSF volume and flux. Dysfunction of this pathway may underlie proteinopathies, such as Alzheimer's disease, which have unknown etiology but for which cerebral clearance deficiencies have been implicated.

The tumor immune microenvironment protects against recurrence in early-stage lung adenocarcinoma

Dr. Michael Kammer

Lung cancer is the deadliest cancer in the US and worldwide, and lung adenocarcinoma (LUAD) is the most prevalent histological subtype in the US. LUAD exhibits a wide range of aggressiveness and risk of recurrence, but the biological underpinnings of this behavior are poorly understood. Past studies have focused on biological characteristics of the tumor itself, but the ability of the immune response to contain tumor growth represents an appealing alternative or complementary hypothesis. Emerging technologies enable us to investigate the spatial distribution of specific cell types within the tumor nest and characterize this immune infiltration. In this study, surgically resected lung adenocarcinomas from 127 patients were stained with multiplexed immunohistochemistry to study the infiltration of immune cells into the tumor nest. Patients with cancer recurrence (n=40) had a significantly lower density of mast cells and T cells within the tumor when compared with patients without recurrence (n=87, p=0.012 and p=0.016, respectively). Kaplan-Meier analysis revealed a significant difference in recurrence-free survival (RFS) based upon tumoral T-cell density (p=0.026) and Mast Cell density (p=0.005). The relation between the immune microenvironment and recurrence was strongest in stage I and II cancers. A multiple regression Cox Proportional Hazards analysis for RFS showed that in addition to tumoral T cells and mast cells, stromal proliferating B and T cells were also significantly correlated with survival (p=0.005 for ki67+ B cells, p=0.002 for ki67+ T cells). Analysis of the density of immune cells within the tumor and.

Identification of metabolic underpinnings of effector CD4+ T cell development and function

Dr. Andrew Patterson

During the past decade it has become increasingly apparent that cellular metabolism plays a critical role in the function and regulation of the immune system. Immune cell utilization of specific metabolic pathways influences immune function and can be pharmacologically targeted to alter immune outcomes. The importance of immune cell metabolism and function is further demonstrated by the development of primary immunodeficiencies in patients deficient in certain metabolic pathways. To identify novel mechanisms governing the interplay between CD4+ T cell metabolism and function, we performed a series of CRISPR screens evaluating CD4+ T cell expansion, substrate uptake, and mitochondrial function. Specifically, we evaluated genes from the Inborn Errors of Metabolism (IEM) and Immunity (IEI): genes that have been associated with defects in metabolism or immune function. Starting with these genes allows us to refine the initial gene set to those relevant to human disease - increasing the likelihood of identifying pathways that play critical roles in disease development. During these screens, I identified the transcription factor Bcl11b as a critical regulator in CD4+ effector T cell metabolism and function. I have likewise shown in screens of IEM genes that the N-linked glycosylation pathway is essential for CD4+ T cell expansion and survival. Notably, disruption of N-linked glycosylation by targeting Gfpt1 impairs CD4+ T cell expansion and pathogenicity in vitro and in mouse models of colitis. This approach offers a unique opportunity to identify novel genes and regulatory pathways critical for productive immune responses and to evaluate their effect on immunometabolism.
Specific ablation of Jak2 from CD11c+ cells attenuates salt-sensitive hypertension through an ENaC-dependent mechanism

Dr. Mohammad Saleem

Salt-sensitivity of blood pressure affects 50% of hypertensive and 25% of normotensive individuals and is an independent predictor of death due to cardiovascular disease. We recently found that gamma and alpha subunits of the epithelial sodium channel (ENaC\(\alpha \gamma\)) on dendritic cells mediate NADPH oxidase-dependent formation of immunogenic isolevuglandin (IsoLG)-protein adducts leading to inflammation and salt-sensitive hypertension. We hypothesized that expression of Jak2 specifically in antigen presenting myeloid cells contributes to salt-sensitive hypertension in an ENaC dependent mechanism. Using RNA sequencing, we found that high salt treatment upregulates genes of the Jak/STAT pathway, and their downstream regulators, the suppressor of cytokine signaling (SOCS) genes in human monocyte. Male and female mice lacking Jak2 in CD11c+ cells developed blunted hypertension (123.8±4.7) during the high salt feeding phase of the N-Nitro-L-arginine methyl ester hydrochloride (L-NAME)/high salt model of salt-sensitive hypertension compared to the wildtype littermate controls (140.5±6.5). These mice also exhibited less infiltration of monocyte/macrophages in their kidneys and less volume retention (69.55±5.8) in response to high salt-feeding when compared to the wildtype littermate controls (57.89±9.5). We also found that deletion of Jak2 in dendritic cells reduced the salt-induced expression of ENaC\(\gamma\) in CD11c+ cells. Following high salt feeding, mice lacking Jak2 in DCs exhibited less aortic infiltration of CD11c+ cells with less expression of CD86, and less production of IsoLGs and IL1-beta. These results indicate that dendritic cell Jak2 plays an important role in salt-sensitive hypertension through an ENaC-dependent mechanism.
Gene expression analysis of isolated cardiac endothelial cells at different stages of tissue repair after myocardial infarction  
Dr. Chitra Basu
Myocardial infarction (MI) induced cardiac remodeling is the major cause of ischemic heart failure. Cardiac endothelial cells (ECs) play a crucial role in cardiac repair after MI. In order to elucidate the molecular mechanisms underlying the critical roles of ECs in the cardiac tissue repair process, we performed RNAseq in ECs isolated from mouse hearts at four distinct time points before and after MI. Successful MI was confirmed by analyzing various functional and structural parameters using Echocardiography-based imaging. The RNAseq data showed that endothelial gene expression patterns change over time in a stage-specific manner, reflecting the hallmark phases of the healing process. Principal component analysis demonstrated that samples corresponding to different post-MI time-points were well separated in different clusters. RNAseq data analysis revealed the existence of a core group of MI-induced genes that remain active throughout the cardiac tissue repair process. Additionally, investigation of dynamic changes in gene expression patterns and pathway analysis uncovered many transient, stage-specific changes in cardiac ECs. The result also indicates some permanent gene expression changes that may account for endothelial dysfunction and development of heart failure. Our results also suggest that cardiac ECs activated by infarction directly contribute in fibrosis. Finally, we identified novel target genes that may play important roles in promoting angiogenesis after MI-induced injury. Taken together, our data provide comprehensive information about modulation of gene expression patterns in cardiac ECs throughout the post-MI healing process and identify novel regulators of endothelial activation, thereby offering new insights into future therapeutic targets for heart.

An accelerated method of podocyte differentiation from human induced pluripotent stem cells for modeling diabetic nephropathy  
Dr. Julie Bejoy
Podocytes are highly specialized visceral epithelial cells that maintain glomerular barrier function and play important roles during both kidney development and progression of glomerular disease. Mature podocytes extracted from mammalian kidneys are difficult to culture long-term, hindering research on podocytopathies. Establishing an alternative, inexhaustible source of podocytes would be a valuable tool for understanding podocytopathies and developing targeted therapies. The discovery of induced pluripotent stem cells (hiPSCs) led to several protocols for deriving podocytes from hiPSCs, which serve as an unlimited source of podocytes. Herein, we describe a simple and effective method to derive podocytes from hiPSCs in twelve days of culture. Our method followed a stepwise protocol in which the hiPSC were differentiated into primitive streak followed by intermediate mesoderm using activation of Activin A and Wnt signaling. The hiPSC-derived intermediate mesoderm cells were treated with FGF9 to generate nephron progenitors, followed by a cocktail of established growth factors to finally derive mature podocytes. The developed podocytes expressed podocyte markers including PODX, Synaptopodin, MAFB, Nephrin at protein levels comparable to the existing methods. We confirmed the functionality of the hiPSC-derived podocytes via permeability assay for FITC-albumin uptake. Next, we treated the cells with media containing high glucose (100mM) to generate a hiPSC-derived podocyte model of diabetic nephropathy. The podocytes showed actin rearrangement upon treatment with high glucose, with increased cytotoxicity and reduced viability. Altogether, we have discovered a faster and less expensive method of podocyte differentiation from hiPSCs, as well as a new tissue culture model of diabetic nephropathy.

A toxic relationship: Candida albicans-Staphylococcus aureus interactions during polymicrobial infection  
Dr. Kara Eichelberger
Polymicrobial infections pose a significant clinical problem, as the presence of multiple infecting organisms can alter treatment susceptibility and disease outcome. Due to overlapping niches in the human body, the fungal pathogen Candida albicans and the Gram-positive bacterium Staphylococcus aureus are commonly co-isolated from polymicrobial infections. Direct and indirect interactions between C. albicans and S. aureus contribute to greater mortality during invasive co-infection, but the mechanisms underlying these interactions remain to be fully elucidated. Osteomyelitis is a devastating invasive infection of bone that is most frequently caused by S. aureus, but over 30% of cases that develop following traumatic injury are polymicrobial. Additionally, Candida species are among the most common co-isolated microorganisms in mixed fungal-bacterial osteomyelitis. Thus, osteomyelitis serves as a model infectious niche to study mechanisms of C. albicans-S. aureus interactions during invasive disease. The goal of my project is to understand how co-culture with C. albicans alters S. aureus cytotoxicity towards bone and immune cells. Using an in vitro workflow, I determined that C. albicans enhanced S. aureus cytotoxicity towards bone cells, including osteoblasts and bone marrow macrophages (osteoclast precursors). Interestingly, C. albicans also enhanced the cytotoxicity of S. aureus mutants that are non-toxic when grown in monoculture. I further determined that C. albicans enhances S. aureus cytotoxicity in a mechanism dependent upon regulation of fungal morphogenesis, which is the switching of C. albicans growth from budding yeast to filamentous hyphae. In summary, the presence of C. albicans can change S. aureus cytotoxicity, which may impact polymicrobial osteomyelitis outcome.
High and low leptin doses differentially effect Ki67 and IL-17A expression in CD4+ T cells from obese and lean PWH on long-term antiretroviral therapy

Dr. Hubaida Fuseini

Obesity (body mass index ≥ 30 kg/m2) is associated with higher CD4+ T cell recovery in persons living with HIV (PWH) on antiretroviral therapy (ART). However, the underlying molecular mechanisms remain unclear. The adipokine leptin, is implicated in obesity and increases CD4+ T function. We investigated the effects of leptin signaling on T cell function in obese and lean PWH on ART. CD4+ T cells from obese and lean PWH, as well obese HIV negative controls were pre-treated with recombinant leptin, then activated with anti-CD3/CD28 or PMA/Ionomycin to measure Ki67 expression and cytokine production via flow cytometric analysis. In the absence of leptin, stimulated CD4+ T cells from obese PWH had decreased leptin receptor (LepR) expression compared to cells from lean PWH. LepR expression on CD4+ T cells from PWH was inversely associated with plasma leptin levels and BMI status. CD4+ T cells from obese PWH had increased Ki67 and IL-17A expression compared to cells from lean PWH. Low dose leptin treatment (10 nM) increased Ki67 expression in CD4+ T cells in both obese and lean PWH but decreased IL-17A production. In contrast, high dose leptin (50 nM) increased IL-17A production in CD4+ T cells from obese and lean PWH. Combined these studies show that in vitro, dose specific leptin signaling augments cell proliferative capacity and IL-17A effector responses of CD4+ T cells of both obese and lean PWH. Other factors potentially account for the higher CD4 reconstitution in obese PWH compared to non-obese counterparts.

An evolutionary gap in primate default mode network organization

Dr. Clément Garin

The human default mode network (DMN) is engaged at rest and in cognitive states such as self-directed thoughts. Interconnected homologous cortical areas in primates constitute a network considered as the equivalent. Here, based on a cross-species comparison of the DMN between humans and non-hominoid primates (macaques, marmosets, and mouse lemurs), we report major dissimilarities in connectivity profiles. Most importantly, the medial prefrontal cortex (mPFC) of non-hominoid primates is poorly engaged with the posterior cingulate cortex (PCC), though strong correlated activity between the human PCC and the mPFC is a key feature of the human DMN. Instead, a fronto-temporal resting-state network involving the mPFC was detected consistently across non-hominoid primate species. These common functional features shared between non-hominoid primates but not with humans, suggest a significant remodeling during the hominoid evolution of the DMN organization as well as its associated cognitive functions. We propose that reinforcing mPFC connectivity to PCC may have strengthened disengagement from external distracting events in favor of internally focused tasks, representing a hallmark of the hominoid DMN evolution.

Treatment with epoxyeicosatrienoic acid analog (EET-A) improves insulin signaling in a genetic mouse model of insulin resistance

Dr. Kakali Ghoshal

We previously showed that global deletion of the cytochrome P450 epoxygenase Cyp2c44, a major epoxyeicosatrienoic acid (EET) producing enzyme in mice, leads to impaired hepatic insulin signaling resulting in insulin resistance. This finding led us to investigate whether administration of a water soluble EET analog (EET-A) restores insulin signaling in vivo in Cyp2c44(-/-) mice and investigated the underlying mechanisms by which this effect is exerted. Cyp2c44(-/-) mice treated with the analog EET-A for 4 weeks improved fasting glucose and glucose tolerance compared to Cyp2c44(-/-) mice treated with vehicle alone. This beneficial effect was accompanied by enhanced hepatic insulin signaling, decreased expression of gluconeogenic genes and increased expression of glycogenic genes. Mechanistically, we show that insulin-stimulated phosphorylation of insulin receptor β (IRβ) is impaired in primary Cyp2c44(-/-) hepatocytes and this can be restored by cotreatment with EET-A and insulin. Plasma membrane fractionations of livers indicated that EET-A enhances the retention of IRβ in plasma membrane rich fractions, thus potentiating its activation. Altogether, EET analogs ameliorate insulin signaling in a genetic model of insulin resistance by stabilizing plasma membrane associated IRβ and potentiating insulin signaling.
Investigating antibiotic failure in Staphylococcus aureus osteomyelitis

Dr. Brittney Gimza

Staphylococcus aureus is a highly successful Gram-positive pathogen capable of causing both superficial and invasive, life-threatening diseases. Of the invasive disease manifestations, osteomyelitis or infection of bone, is one of the most prevalent, with S. aureus serving as the most common etiologic agent. Treatment of osteomyelitis is made more difficult by the widespread emergence of antimicrobial resistant strains, the capacity of staphylococci to exhibit tolerance to antibiotics despite originating from a genetically susceptible background, and the significant bone remodeling and destruction that accompanies infection. As a result, there is a need for a better understanding of the factors that lead to antibiotic failure in invasive staphylococcal infections such as osteomyelitis. To investigate non-resistance mechanisms contributing to treatment failure, we developed an in vivo model that recapitulates antibiotic failure in osteomyelitis where vancomycin recalcitrance develops within 24hrs of infection. Because abscess formation is believed to contribute to treatment failure, we hypothesized that targeting S. aureus factors that aid in survival within abscesses would improve antibiotic efficacy in vivo. To this end, we are determining the roles of staphylococcal virulence factors that interact with components of the vertebrate clotting cascade to promote formation of the staphylococcal abscess community (SAC). Additionally, we have begun visualizing the dynamic interaction of antibiotics and S. aureus in an in vitro model system that recapitulates the SAC. We believe these studies are important, as a greater understanding of the mechanisms used by S. aureus to survive antibiotic treatment is needed to improve the outcome of osteomyelitis treatment.

The fMRI signal exhibits more autonomic variance in drowsiness

Dr. Benjamin Gold

fMRI measures changes in blood oxygen levels as a proxy for neural activity but is also influenced by autonomic fluctuations such as changing heart beats or breathing rates. Separate lines of research have associated the variability of both autonomic and fMRI signals to drowsiness, suggesting that these phenomena may be linked. The present study therefore examines the extent to which the fMRI signal exhibits systemic autonomic influence across drowsiness levels, and where in the brain this effect is most pronounced. To do so, we collected simultaneous autonomic, fMRI, and EEG data (for an electrophysiological measure of drowsiness) during two 24-min conditions: a sparse auditory task (n = 12) in which participants pressed a button upon hearing rare and unpredictably spaced tones (mean interval ± S.D. = 38.84 ± 14.69 s), and rest (n = 11), i.e. no task. Dividing each session into 11 non-overlapping windows, we then evaluated the average drowsiness level and the extent of autonomic-fMRI covariance in each one. We found that drowsiness was associated with slower responses and more variable autonomic activity in task participants, but with less variable autonomic activity in resting participants. Yet in both conditions, participants evinced greater autonomic contributions to fMRI signals during drowsiness. These effects were widespread, but especially prominent in cerebrospinal fluid, the default mode network, and the salience/ventral attention network. The relationship between autonomic and fMRI activity therefore seems to vary over time, state, and space, with important implications for the distinction of local neural activity from systemic autonomic influences.

Myeloid response to immunotherapy is associated with heterogeneity in outcomes to anti-PD-L1 in breast cancer

Dr. Ann Hanna

Immune checkpoint inhibitors (ICI) have improved patient survival in some cancer types but yielded limited success in breast cancer. Clinical trials demonstrate that combining ICB with standard-of-care chemotherapy increases survival and pathologic complete response in patients. We sought to model ICI response in vivo to elucidate the mechanisms responsible for immunotherapy efficacy in breast cancer and ascertain the therapeutic benefits of different chemotherapeutic combinations with ICI. In this study, we investigated the efficacy of anti-PD-L1 as single-agent or in combination with chemotherapy in an immunocompetent orthotopic mammary tumor model. We discovered that single-agent immunotherapy was sufficiently efficacious in: 1) blunting primary tumor growth, 2) extending survival, 3) significantly enhancing the infiltration and activation of immune cells into primary mammary tumors compared to combination treatments, and 4) inducing heterogeneous responses, ranging from complete response to intrinsic resistance. Longitudinal analysis of peripheral blood from heterogeneously responding mice uncovered signatures of myeloid cell recruitment corresponding to transient responses ultimately converting to resistance. Thus, we report the immunogenic efficacy of single-agent ICB that upregulates tumoricidal immune cell infiltration into the primary tumor, thereby controlling tumor growth. Moreover, this study describes differential responses in a genetically similar host, which reflects heterogeneous patient response to ICI. Further characterization may identify systemic biomarkers and tumor antigen-specific T cell clones to accurately predict immunotherapy response in patients and uncover mechanisms for sensitizing tumors refractory to ICI. This study also has potentially significant clinical implications for re-evaluating the benefits of chemotherapy in combination with ICI in TNBC patients.
Rubin Observatory Community Brokers - real-time astronomical alert processing

Dr. Nina Hernitschek

Nowadays large-scale astronomical surveys enable us to see the universe in a much more detailed, and in particular different way than before. In the era of such large-scale surveys, methods to handle investigate these data, and especially to classify sources, become more and more important. The LSST survey, carried out by the Rubin Observatory, distribute its data in a new way: LSST will produce a nightly so-called stream of public alerts that will disseminate new information about transient, variable, and moving objects within 60 seconds of readout. Software systems called of “community brokers” will the LSST alert stream, add scientific value by such as cross-matching with archival catalogs and machine-learning based identification of objects, thus providing science users with the ability to identify targets of interest and trigger follow-up observations in a timely manner. In this talk I will give an overview of LSST community brokers in general, and specifically describe the “Point of Interest” broker developed by a small team at Vanderbilt University.

Structure and transport mechanism of neo1, a monomeric P4-ATPase lipid flippase

Dr. Bhawik Kumar Jain

The plasma membrane of a cell is characterized by an asymmetric distribution of lipid species across the exofacial and cytofacial aspects of the bilayer. Phosphatidylserine, phosphatidylinositol, and phosphatidylethanolamine are enriched in the cytofacial leaflet, whereas phosphatidylcholine and sphingolipids reside in the exofacial leaflet. P4-ATPases establish phospholipid asymmetry by transporting lipid substrate from the exofacial to the cytosolic leaflet on membranes. Most P4-ATPases are heterodimers composed of a catalytic α-subunit and accessory β-subunit, and the structures of several heterodimeric flippases in the P4A clade have been reported. The S. cerevisiae Neo1 and its orthologs represent the P4B-ATPases, which function as monomeric flippases without a β-subunit. It has been unclear whether monomeric flippases retain the architecture and transport mechanism of the dimeric flippases. Here we describe the structure of a P4B ATPase, Neo1 from Saccharomyces cerevisiae, in its E1-ATP, E2P-transition, and E2P states. The structure reveals a conserved architecture with highly similar functional intermediate states relative to dimeric flippases. We further performed structure guided mutagenesis of residues in the substrate translocation path previously defined in dimeric flippases. These mutations disrupted Neo1’s ability to establish membrane asymmetry of phosphatidylserine and phosphatidylethanolamine. These observations indicate that evolutionarily distant P4 ATPases use a structurally conserved mechanism for substrate recognition and transport.

Cosmetic abdominoplasty vs functional panniculectomy: pulmonary embolism risk

Dr. Christopher Kalmar

Background: Increased intraabdominal pressure after cosmetic abdominoplasty may decrease venous return, which we hypothesized may contribute to increased risk of DVT or PE. The purpose of this study was to investigate the relative risk of PE in patients undergoing functional panniculectomy versus cosmetic abdominoplasty. Methods: The ACS NSQIP dataset was queried for panniculectomy procedures performed between 2015 and 2019. Excision of excessive infraumbilical tissue was defined as CPT 15830. According to ASPS guidelines, cosmetic abdominoplasty was defined as cases with the ICD-10 Z41.1 or CPT 15847 modifier, while functional panniculectomy was defined as cases without these modifiers. PE occurrence within 30 postoperative days was compared between these cohorts. Results: During the study interval, 11137 patients underwent excision of excessive infraumbilical tissue, including 57.4% (n=6397) functional panniculectomy and 42.6% (n=4740) cosmetic abdominoplasty. Average age overall was 46.4±12.1 years, but those undergoing cosmetic abdominoplasty were significantly younger (p<.001, 44.9±11.5 vs 47.5±12.3). Average preoperative BMI was 31.7±8.0 kg/m2, and those undergoing functional panniculectomy had significantly higher BMI (p<.001, 33.3±8.9 vs 29.5±6.0). Patients undergoing cosmetic abdominoplasty were 2.4 times (95%CI 1.3-4.3) more likely to experience postoperative PE than patients undergoing functional panniculectomy (p=.003, 0.6% vs 0.3%). In multivariate regression, risk for postoperative PE was independently associated with cosmetic abdominoplasty (p<.001, AOR=4.1), elevated BMI (p=.001, AOR=1.3 per 5 kg/m2), and chronic renal failure on dialysis (p=.032, AOR=10.3). Conclusions: Patients undergoing cosmetic abdominoplasty are four times more likely to develop PE in the immediate postoperative period than those undergoing functional panniculectomy.
Breast reconstruction free flap failure: does platelet count matter?
Dr. Christopher Kalmar

Purpose: The purpose of this investigation was to perform a multicenter study to assess the risk of microvascular free tissue transfer (MFTT) failure based on preoperative platelet counts in the context of preexisting comorbidities. Methods: Retrospective cohort study was conducted of female patients undergoing breast reconstruction with MFTT performed in North America between 2015 and 2019 using the NSQIP database. Breast reconstruction with MFTT was defined as CPT 19364. The primary outcome was flap failure. Results: During the study interval, 7522 patients underwent MFTT breast reconstruction, and 87.1% (n=6552) patients had preoperative labs available. Average age at reconstruction was 50.9±9.5 years, and patients had an average BMI of 29.1±5.8 kg/m2. Patients with MFTT failure had significantly higher platelet counts than those with successful reconstruction (p=.001, 272±66K/mcL vs 254±61K/mcL). In multivariate regression analysis, MFTT failure was significantly higher in patients smoking cigarettes within the past year (p=.030, AOR=1.7) and dyspnea on moderate exertion or at rest (p=.025; AOR= 2.6). Each 50K/mcL elevation in platelet count was independently associated with increased odds of flap failure (p<.001; AOR=1.2). Patients experienced significantly higher rates of flap failure with platelets above 250K/mcL (p=.004, 3.2% vs 2.0%), which remained significant through progressively increasing thresholds above 450K/mcL. Conclusions: This study of the largest cohort of patients undergoing autologous free tissue breast reconstruction demonstrates that progressively higher platelet counts are significantly implicated in free flap failure. Preoperative optimization of thrombocytosis may decrease MFTT failure, especially in patients with history of tobacco use and hypertension undergoing autologous breast reconstruction.

High-volume orthognathic surgery: disparities in patient populations, admission charges, and surgical complications
Dr. Christopher Kalmar

Background: The purpose of this study is to elucidate the disparities of financial burden undergoing orthognathic surgery based on family demographics and hospital case volume. Methods: Retrospective cohort study was conducted of orthognathic procedures performed in the United States from 2010 through 2020 using the PHIS database. Admission charges and patient demographics were analyzed in context of preoperative, intraoperative, and postoperative characteristics. Results: During the study interval, 6640 patients underwent orthognathic surgery, including LF1 (59.2%, n=3928), BSSO (14.4%, n=959), and double-jaw surgery (26.4%, n=1753). Patients undergoing LF1 were billed significantly more than those undergoing BSSO (p<.001). Admission costs for orthognathic surgery have been significantly increasing over the past ten years (p<.001; $48847.1/year), more than doubling from 2010 ($41943) to 2020 ($83755). High-volume hospitals at the 80th percentile performed 252 orthognathic procedures during the ten-year study interval. Proportion of patients treated at high-volume hospitals was significantly different across regions of the country (p<.001). Patients from New England were most likely to be treated at high-volume centers (84.3%). Household income was significantly higher for patients treated at high-volume hospitals (p<.001, $52236 vs $48973). High-volume hospitals charged patients significantly less than other hospitals for orthognathic procedures (p<.001, $62983 vs $65355). High-volume hospitals were significantly more likely to perform double-jaw procedures than other hospitals (p<.001, 28.5% vs 23.0%), yet had fewer surgical complications than other hospitals (p=0.014, 4.5% vs 5.9%). Conclusions: Socioeconomic and demographic factors have an association with treatment at high-volume hospitals, which may affect surgical outcomes and cost.

LeFort II/III midface advancement: nationwide analysis of complications
Dr. Christopher Kalmar

Background: The purpose of this study was to perform a multicenter investigation of the complication profiles of complex midface procedures across the country. Methods: Retrospective cohort study was conducted of LeFort 2 (LF2), LeFort 3 (LF3), and Monobloc (MB) procedures performed in the United States from 2010 through 2020 using the PHIS database. Preoperative, intraoperative, and postoperative characteristics were analyzed with appropriate statistics. Results: During the study interval, 91 patients underwent complex midface advancement, including LF2 (22.0%, n=20), LF3 (44.0%, n=40), and MB (34.1%, n=31). Overall complication rate was 44.0% (n=40 of 91). LF2 procedures had fewer overall complications than LF3 and MB (p=.021, 20.0% vs 57.5% vs 41.9%). In multivariate regression analysis, surgical complications were significantly associated with cardiovascular (p=.024, AOR=7.8), neurologic (p=.032, AOR=5.2), and congenital comorbidities (p=.023, AOR=4.1). Overall, 63.7% (n=58 of 71) patients required blood transfusion. Patients undergoing MB were significantly more likely to require transfusion than LF3 and LF2 (p<.001). Highest-volume hospitals were significantly more likely than other hospitals to administer blood transfusions (p=.008, 67.1% vs 22.2%). This likely reflects that highest-volume hospitals were more likely to perform complex procedures, because 97.5% (n=39 of 40) LF3 and 90.3% (n=28 of 32) MB procedures were performed at the highest-volume hospitals. As such, there was no difference in transfusion rate based on hospital volume within procedure subtypes of LF2 (p=.136), LF3 (p=.168), and MB (p=.394). Conclusions: Nearly half of patients undergoing complex midface advancement experience postoperative complications, but there are significant differences in complication and need for transfusion across.
Hospital admission charges for complex midface advancement in pediatric patients
Dr. Christopher Kalmar

Background: Midface advancement require substantial surgical training and hospital resources. The purpose of this study was to perform a multicenter investigation of the financial implications of complex midface procedures. Methods: Retrospective cohort study was conducted of LeFort 2 (LF2), LeFort 3 (LF3), and Monobloc (MB) procedures performed on any pediatric patient in the United States from 2010 through 2020 using the PHIS database. Hospital admission charges and intensive care unit charges were analyzed with appropriate statistics. Results: During the study interval, 91 patients underwent complex midface advancement, including LF2 (22.0%, n=20), LF3 (44.0%, n=40), and MB (34.1%, n=31). Of the fifty hospitals indexed in this database over ten years, only 11 institutions performed these complex midface reconstructions. Admission costs for complex midface surgery have been increasing over the past ten years (p=.004, $12390.58/year). LF2 procedures had shorter hospital stays than LF3 and MB procedures (p<.001, 2.0 days vs 8.0 days vs 7.0 days). In multivariate regression, patients with cardiovascular (p=.029, B=+$107380) and gastrointestinal (p=.005, B=+$126171) comorbidities had higher admission charges after midface advancement. Patients encountered median ICU charges of $31614. LF2 had lower ICU charges than LF3 and MB (p<.001, $0 vs $45606 vs $32022). In multivariate regression, patients with history of malignancy (p<.001, B=+$157227) had higher postoperative ICU charges after midface advancement. Conclusions: Complex midface procedures are performed at only a handful of tertiary pediatric hospitals. LF2 procedures had lower admission charges and ICU charges than LF3 and MB, yet there was substantial variability based on case volume and geographic region.

Mechanisms of orthosteric agonist and allosteric modulator cctivation of mGlu7
Dr. Xia Lei

Metabotropic glutamate receptor 7 (mGlu7) is a dimeric, group III metabotropic glutamate (mGlu) receptor. It is a G protein-coupled receptor that acts to modulate neurotransmission across many brain structures. mGlu7 is most highly expressed presynaptically in neurons and is widely distributed in the central nervous system (CNS) and body. Mutations, deletions, or decreases in mGlu7 result in symptoms and phenotypes of neurodevelopmental disorders in humans and mice, including Rett syndrome. We are focused on developing new ligands that interact with mGlu7 to understand the therapeutic potential of the receptor in various CNS disorders. In vitro molecular pharmacology assays and other in vitro studies show that the orthosteric ligand, glutamate, has low affinity for mGlu7 which limits its ability to be routinely used for drug screening. An alternative agonist, L-AP4, is a synthetic compound that, while not produced naturally in vivo, activates mGlu7 with higher affinity than glutamate. Our preliminary research indicates that there are differences in the profiles of positive allosteric modulators (PAMs) when assessed using glutamate versus L-AP4. This difference creates a challenge for the development of mGlu7-selective PAMs, and the focus of our current studies is to understand the difference between these two agonists in activating the mGlu7 receptor. In here, we hypothesize that glutamate and L-AP4 activate mGlu7 either via a different number of agonist binding sites or a different number of effector (G-protein) binding sites. Our current studies are designed to differentiate between these two possibilities.

Dysplastic stem cells drive dysplasia transition to gastric adenocarcinoma
Dr. Jimin Min

Intestinal-type gastric cancer develops within a cascade of pre-cancerous metaplasia to dysplasia and adenocarcinoma. Gastric dysplasia is especially a key transition state between pre-cancer and cancer with the greatest risk of developing adenocarcinoma. Cancer stem cells (CSCs) are a key population leading to cancer initiation or progression. However, the presence of stem cells, which are responsible for the maintenance and progression of dysplastic cells, is unclear. We previously identified two putative dysplastic stem cell (DSC) populations, CD44v6-CD133+CD166+ (DP) and CD44v6+CD133+CD166+ (TP), which highly express CSC markers. To investigate whether the DSCs are responsible for maintaining dysplastic cell lineages and evolution of dysplasia to adenocarcinoma, DP- and TP-DSCs were isolated from dysplastic organoids established from active Kras-induced mouse stomachs. Transcriptome profiles of the two DSC populations displayed high similarity of molecular characteristics as CSCs, but DP-DSCs showed more dynamic differentiation capacity than TP-DSCs. DP-DSCs evolved to heterogeneous types of tumors including high-grade invasive adenocarcinoma in immunodeficient mice, and additional genetic mutations related to human gastric cancers were acquired during the tumor formation. Growth and survival of dysplastic organoids were controlled by Pyrvinium targeting CK1α, a downstream intermediate of Wnt pathway. We confirmed the presence of DSCs in human dysplasia and the effect of Pyrvinium in human dysplastic organoid survival. Therefore, DSCs are de novo CSCs driving dysplasia evolution to gastric cancer and can be targeted by CK1α inhibition. This study will provide important insights to guide the future therapeutic strategies by targeting DSCs as cancer-initiating cells in patients with gastric dysplasia.
Oral chemesthesia modulates perception and consumption of alcohols

Dr. Snigdha Mukerjee

Trigeminal chemesthesia is the sensitivity to irritant, or burning sensations produced by compounds like chili pepper (capsaicin) via TRPV1 channels. Evolutionarily, taste and chemesthetic innervation in the mouth exists to prevent ingestion of toxic, or spoiled food for improved survival. n-alcohols are known to become more toxic as number of carbons added to the chain increases. It’s unknown, how the chemesthetic perception changes in mammals. We hypothesize that the trigeminal innervation to the tongue controls palatability and consumption of alcohols. Functionally relevant brain regions that respond to acute 50% ethanol (irritant range) exposure on the tongue was identified by visualizing cFos labelling-marker for neuronal activation. The regions that responded significantly to ethanol compared to water were the trigeminal nucleus [Δ: 16.08 ± 5.786, p<0.05], nucleus tractus solitarius [Δ: 122.1 ± 43.9, p<0.05], area postrema [Δ: 73.0 ± 7.5, p<0.0001], lateral parabrachial nucleus [Δ: 70.63 ± 13.13, p<0.0001]. In contrast, other taste/chemesthetic reactivity associated regions that did not respond to treatment were the medial parabrachial nucleus [Δ: 5.462 ± 2.547, p=0.05] and insular cortex [Δ: 12.07 ± 6.823, p>0.05] [unpaired t-test, n=5]. A dose-response curve obtained by a brief access lickometer test, indicated that mice lacking the TRPV1-trigeminal neurons tend to prefer ethanol (0-60%) over water [Δ AUC: 40.58 ± 20.81, n=4-5, p<0.05]. This proved that the trigeminal innervation is vital for chemesthetic perception of alcohol. Calcium dynamics of the trigeminal ganglion in response to n-alcohols will direct our search towards receptors that are our vital for palatability of n-alcohols.

Assessment of correlation between pretest risk of lung cancer using clinical and imaging biomarkers and radiomics derived lung adenocarcinoma aggressiveness score

Dr. Khushbu Patel

Lung adenocarcinoma has a broad spectrum of biological behavior, ranging from indolent to aggressive. Many of the screen-detected lung cancers are indolent and, these overdiagnosed nodules expose patients to unnecessary morbidity and mortality. Non-invasive risk stratification of lung ADC using computed tomography (CT)-based quantitative imaging features would aid in individualized management strategies for patients diagnosed with lung ADCs. Objectives: 1. To correlate malignancy-risk score derived using the Combined biomarker model (CBM) and score indicative of lesion aggression (SILA) derived from a radiomic software - CANARY (Computer-Aided Nodule Assessment and Risk Yield) 2. To correlate specific radiomic features from CBM with SILA Methods:The pretest probability of cancer was calculated for 91 nodules using CBM, a pre-trained and externally validated model that includes clinical variables and radiomic signature developed using CT images. SILA was derived for the same subset of 91 nodules in CANARY. Malignancy risk and aggressiveness scores were correlated using a scatter plot. Specific radiomic features such as median, intensity, skewness, energy, density of solid regions, coefficient of variance were then correlated with SILA using Spearman's correlation coefficient. Results and Conclusion: There was a good correlation between the malignancy-risk score of the CBM and aggressiveness by SILA. Nodules with a high pretest malignancy score had high SILA. Correlation between specific radiomic features and SILA also showed a high correlation with a correlation coefficient of 0.8.

Acute manganese dysregulates aspects of glutamate signaling in young APP/PSEN1 mouse

Dr. Brittany Spitznagel

Manganese (Mn) is an essential metal that serves as a cofactor for metalloenzymes important in moderating oxidative stress and the glutamate/glutamine cycle. Typically, sufficient Mn is acquired through the diet. In contrast, Mn toxicity can arise through the drinking of contaminated water or inhalation of Mn-containing industrial byproducts. Recent data suggest that excess Mn may also contribute to development of Alzheimer's disease (AD) neuropathology. We hypothesized that Mn toxicity would result in dysregulation of astrocytic glutamatergic transport and exacerbate aberrant epileptiform activity. 3-month-old APPswe/PSEN1dE9 mice, a mouse model of AD, were exposed to 50mg/kg MnCl2·4H2O subcutaneously 3 times over the course of a week as an acute high dose exposure of Mn. We then determined changes in glutamate signaling proteins, synaptic plasticity, and epileptiform activity in AD in response to Mn exposure. Mn exposure decreased cortical expression of glutamate reuptake transporters and increased sensitivity to kainic acid as indexed by faster onset of seizure activity. Additionally, Mn exposed APPswe/PSEN1dE9 mice show enhanced long-term potentiation in later phases compared to saline treated AD mice and wild-type mice in either treatment group. Together these findings are consistent with glutamatergic changes contributing to excitotoxicity and support the hypothesis that Mn acutely dysregulates aspects of glutamate signaling resembling phenotypes associated with early onset AD. Further, APPswe/PSEN1dE9 were more sensitive to Mn exposure than wild-type littermates even at an early age prior to significant beta-amyloid accumulation suggesting a genotype x environment interaction and a role for Mn exposure in accelerated development of disease pathology.
The role of glucagon-like peptide-1 positive hippocampal mossy cells in obesity related neurocognitive impairment

Dr. Alex Steiner

Observed neurocognitive deficits are seen in obese individuals. Bariatric surgery is shown to improve cognition regardless of weight loss. While poorly understood, a dramatic rise in fasting and postprandial levels of Glucagon-like Peptide-1 (GLP-1), a hormone produced in the small intestine and the brain, is seen following bariatric surgery. GLP-1 and its receptor are important to hippocampal dependent learning and memory, although the specific cellular circuitry is unknown. Our lab and others have previously shown that Mossy cells (MC) of the hippocampal dentate gyrus are necessary for spatial memory. We examined publicly available datasets and found that GLP-1Rs are strongly and selectively expressed in MCs, and GLP-1R+ MCs were activated in food containing contexts. We found that bath application of the GLP-1R agonist exendin-4 (200 nM) strongly increased MC firing in DG slices. Based on these results, we hypothesize that GLP-1R positive MCs are critical for GLP-1 hippocampal-dependent learning and memory. Additionally, we hypothesize that recovery of GLP-1R MC signaling in obese mice will improve spatial memory. Through a series of experiments, we quantify GLP-1R MC neuroanatomy and characterize the signal cascades downstream of MC GLP-1R activation in obese and lean mice. Secondly, we will test the necessity of MC GLP-1R for spatial memory. Lastly, we will test if overexpression of GLP-1R reverses memory impairment seen in obese mice when compared to lean mice. The current experiments will yield a greater insight to the specific involvement of MC GLP-1Rs in hippocampal-dependent memory in clinical obesity and treatments.

The aggressiveness of human lung adenocarcinoma is associated with CAFs subpopulations at early stages

Dr. Georgii Vasiukov

Human lung adenocarcinoma (ADC) is characterized by a wide range of behavior that can be aggressive or indolent. Our preliminary data showed that at the early stages indolent and aggressive ADC are characterized by different deposition of extracellular matrix and fibroblasts play the lead role in that process. In this research work, we aimed to decipher the role of cancer associated fibroblasts in the determination of indolent or aggressive behavior of human lung ADC at early stages. Using image analysis platform CANARY we analyzed ADC patients’ CT scans and calculated SILA score which has been used for the prediction of lung ADC behavior. Single-cell RNA sequencing (scRNAseq) has been used to analyze cancer associated fibroblast’s (CAF) population in patients’ tumor samples. Aggressive group was characterized by the increased proportion of CAFs population. The differential gene expression analysis revealed enhanced expression of COL1, COL3, COL6, and COL11 by CAFs in aggressive group. In addition, CAFs from aggressive ADC demonstrated increased expression of CXCL12. The expression analysis of genes involved in basic cancer associated pathways demonstrated enhanced activity of JAK-STAT, PI3K, and TNFa. Cluster analysis identified 3 subpopulations of CAFs: aSMAhigh, PDGFRbhigh, and COLIlow - myoCAFs; COLIhigh, PDGFRbhigh, and aSMAlow - eCAFs; FSP-1high, CXCL12high, and aSMAlow - iCAFs. Aggressive ADC showed an increased proportion of eCAFs and decreased iCAFs. We assume that aggressiveness of ADC is associated with different mechanisms of CAFs activation at early stages that lead to disproportion in their subpopulations and involvement in pro- or antitumorigenic processes.

Three-dimensional morphology of degenerative arteriolar changes in cerebral amyloid angiopathy

Dr. Lissa Ventura Antunes

The accumulation of β-amyloid plaques and tangles in the brain tissue are hallmarks of Alzheimer’s disease, but vascular deposition of β-amyloid, cerebral amyloid angiopathy (CAA), is a common finding. CAA is a vasculopathy produced when the β-amyloid forms toxic deposits on cerebral arterioles and capillaries. β-amyloid accumulation is associated with stiffening of blood vessels and increased thickness of vessel walls, reducing blood flow and energy supply for the subserved tissue. This process leads to microvascular hemorrhagic and ischemic changes that independently contribute to cognitive decline and stroke. The mechanisms by which CAA causes changes in the structural integrity of the vasculature remain unclear. We used the CLARITY method to preserve the integrity of the vascular network while rendering blocks of human brain tissue optically transparent for lightsheet microscopy. We analyzed tissue samples from patients with CAA, focusing on changes in vessel morphology associated with vascular degeneration and rupture. We stained the blood vessels with Isolectin and β-amyloid with Thiazine red. We used three-dimensional microscopy and coupled to volume surface reconstruction to understand the morphological features of vascular degeneration and establish the relationship between vascular degeneration and β-amyloid deposition. Remarkably, β-amyloid deposits in arterioles in human brain tissue have an organized ring-shape. These rings present, but often shattered, at sites of arteriolar degeneration or rupture along with circumferential dilation of the arteriole and depletion of vascular smooth muscle, suggesting a close association between β-amyloid and vascular degeneration.
Targeting the transferring receptor normalizes T-cell function in systemic lupus erythematosus

Dr. Kelsey Voss

Systemic lupus erythematosus (SLE) is a complex, heterogenous autoimmune disease that impacts millions worldwide. Lupus patients exhibit an assortment of T cell dysfunctions, including impaired mitochondrial function, reduced regulatory T cell (Treg) suppressive capacity, high metabolic activity, oxidative stress, and expansion of pathogenic Th1-like Th17 cells. Therefore, some goals for improved therapeutic options for lupus include restoring homeostasis to T cell subsets, restoring mitochondrial health, normalizing T cell metabolism, and boosting Treg function. While metabolic targeting of T cells shows promise, previous studies using standard metabolic pathway inhibitors have failed to rescue both mitochondrial dysfunction and T cell subset homeostasis. Micronutrients such as iron, however, have not been well explored. T cells upregulate the transferrin iron receptor, CD71, during activation, but lupus-prone mice and SLE patient CD4 T cells have elevated CD71 expression and intracellular iron levels compared to healthy controls. We hypothesized that increased iron accumulation contributes to mitochondrial dysfunction and oxidative stress in SLE T cells. CD71 blockade during T cell activation in SLE mice restored mitochondrial proton leak, oxidative stress, and mitochondrial mass. Importantly, targeting CD71 was detrimental to pathogenic Th1 cells, but facilitated induced regulatory T cell (iTreg) cultures and increased their FoxP3 expression. SLE mice treated with CD71 blocking antibody showed reduced liver and renal pathology, accompanied by a reduction in CD4 T cells and increased IL-10. Finally, we describe an association between disease severity and elevated CD71 expression on SLE patient T cells and provide a rationale for CD71 blockade in patient T cells.

Chronic manganese exposure induces hyperactivity and dopaminergic dysfunction in young C57Bl/6 mice

Dr. Jordan Wilcox

Manganese (Mn) is a ubiquitous required mineral but is neurotoxic in excess. Male and female C57Bl/6 mice were chronically exposed to Mn via a control (70 ppm) or high Mn (2400 ppm) diet from weaning through 12 weeks of age, or acutely exposed via subcutaneous injection (3x/week; 50 mg/kg MnCl2-tetrahydrate) at 6-8 weeks of age. Behavioral testing was conducted to measure changes in exploratory locomotor activity in a novel environment. Brain Mn levels were confirmed by mass spectrometry and key proteins in striatal dopaminergic function were assayed by Western blot. Chronic dietary Mn caused hyperactivity in female mice exclusively whereas acute systemic dosing decreased activity in females and attenuated the activity-inducing effect of scopolamine, again in females only. In both cases Mn exposures caused altered expression of the dopamine transporter (DAT), Tyrosine hydroxylase (TH) and phosphorylated tyrosine hydroxylase (pTH) in females with a different pattern of changes observed in male mice suggesting sex-specific dysregulation of dopaminergic function. Excess Mn via two distinct exposure routes led to dysregulation of dopaminergic function and clear behavioral differences in mice that were more prominent in female mice than males. The data highlight the potential for environmental exposure to redox-sensitive metals such as Mn to directly impact adolescent brain health and development with clear adverse behavioral outcomes. The data also clearly highlight the need for developmental and toxicological studies to be conducted in both male and female animals, and the importance of considering route and duration of administration when studying toxicological effects in animals.
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