



The National Institutes of Health's Medical Research Scholars Program

2016-2017 Scholars & Abstracts



About the NIH Medical Research Scholars Program

“Medical discoveries of tomorrow depend on the students we train today.”

-NIH Director Francis S. Collins, M.D., Ph.D.

This publication lists the 2016-2017 Scholars of the National Institutes of Health’s (NIH) Medical Research Scholars Program (MRSP), and outlines their research studies in their year-long participation in the program.

The MRSP, built on decades of NIH experience in training clinician-scientists, provides outstanding U.S. medical, dental and veterinary students with advanced training in laboratory, clinical and translational research. Its one-year intensive training program enables the most promising clinicians to understand the biological underpinnings of disease and translate basic science into health care interventions.

Launched by the NIH in 2012, the MRSP combines and re-envisioned two highly successful NIH training initiatives: the Clinical Research Training Program (CRTP) that operated from 1997 to 2012 and the HHMI-NIH Research Scholars Program that operated from 1985 to 2012. The MRSP is designed for students who have completed their initial clinical rotations and are primarily between their third and fourth years of professional school.

The MRSP recruitment process begins with an NIH press release issued in August and announcements posted on the websites of the NIH, the NIH Clinical Center and the NIH Office of Clinical Research Training and Medical Education. Promotional information is sent to all U.S. accredited medical, osteopathic, dental and veterinary medicine schools and shared at a variety of national meetings and with past and present CRTP/MRSP participants.

Applications are submitted between October 1 and January 15, and applicants are reviewed and selected by the MRSP’s Board of Advisors, Executive Advisory Committee and staff. The Board of Advisors consists of more than 70 highly successful NIH intramural basic, translational and clinical scientists. These individuals play a key role in interviewing and selecting Scholars and serve as Mentors and Advisors for the program. The Executive Advisory Committee is a subgroup of the Board of Advisors, consisting of approximately 20 individuals who serve as an Advisory Board to the MRSP Director. They are instrumental in selecting the final MRSP participants.

In the course of their year at the NIH, the MRSP Scholars work with an Advisor, who provides research support and career guidance, and a Mentor, who helps them to develop a year-long laboratory, clinical or translational research project that aligns with their clinical interests and career goals. Based on the nature of their project, Scholars conduct research at one of the 27 Institutes or Centers within the NIH intramural program.

The MRSP is distinguished from other training programs by the Scholars’ unique access to the full range of NIH resources. These include laboratories and clinical research facilities that are among the most extensive and highly regarded in the world; access to the NIH’s 27 intramural Institutes and Centers; NIH lectures and tutorials on seminal research and new clinical discoveries; and teaching rounds at the NIH Clinical Center, America’s Research Hospital. Scholars spend the majority of their time on their research but they also participate in a complementary program of professional development, enrichment, scholarship and leadership opportunities.

Recognizing that successful biomedical research depends on the talent and dedication of the scientific workforce, the NIH supports innovative training programs like the MRSP that foster scientific creativity and exploration. The NIH’s goal is to strengthen our nation’s research capacity, broaden our research base and inspire a passion for science in current and future generations of researchers.

For more information about the MRSP or to learn about opportunities to support the program, please contact the Development Office at Development@nih.org.

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“The future promises remarkable advances in biomedical research. To attain that goal, we need broad, transformative training for clinician scientists. It is time to invest boldly in new ways of learning so that the next generation of innovative thinkers can open new frontiers in knowledge and transform medicine.”

NIH Director Francis S. Collins, M.D., Ph.D.



Marib Akanda

School: SUNY Downstate Medical Center

Mentor: H. Nida Sen, M.D., M.H.S., Director, Uveitis and Ocular Immunology Fellowship Program

Institute: National Eye Institute (NEI)

Research: Development of an Automated Methodology for Quantitative Analysis of Optical Coherence Tomography Angiography (OCTA) Images: Standardization, Artifact Removal, and Quantitative Analysis of Retinal and Choroidal Vasculature

Optical coherence tomography angiography (OCTA) is a non-invasive modality that provides high-resolution images of the retinal vasculature. Three issues complicate its use in studying retinal and choroidal diseases: 1) image quality varies; 2) large superficial retinal vessels project shadow-like artifacts onto the choriocapillaris; 3) quantitative measures are absent from current OCTA software. We developed a technique using ImageJ, an open source Java-based image processing program developed at NIH, to standardize OCTA images. We also removed artifacts and created a quantitative algorithm to analyze OCTA images.

OCTA images of 3x3 mm² and 6x6 mm² were acquired from patients using Zeiss Cirrus-HD OCT AngioPlex Angiography. The software generated images of the superficial retinal plexus (SCP), deep capillary plexus (DCP), avascular layer, and choriocapillaris. These images were standardized in ImageJ. Projection artifacts were removed and SCP/DCP images were binarized for quantitative measurement. A customized ImageJ macro applied contrast stretching to each image based on the central 50% region.

For choriocapillaris, projection artifacts were removed by overlaying a binarized image of the major superficial vessels obtained by subtracting two SCP and choriocapillaris layers. Each patient's images across different visits were aligned in ImageJ and cropped to compare the same region. Quantitative analysis of non-perfusion was performed by thresholding to the average pixel intensity value of the avascular OCTA layer that represented no flow. For the SCP/DCP, the standardized images were binarized by Otsu thresholding to black and white images. A custom macro calculated the total area represented by vasculature and the area of the foveal avascular zone (FAZ) from a drawn outline.

Our methods generated standardized images, diminished projection artifacts, and provided quantitative measures that enable inter-visit comparison studies using OCTA. The repeatable methods employed use publicly available software. These methods facilitate further analysis and improve the utility of OCTA in both understanding retinal and choroidal diseases, and monitoring the response to therapy.

Full Length Publications:

- **Akanda M**, Gangaputra S, Kodati S, Melamud A, Sen HN. Multimodal imaging in dengue fever-associated maculopathy. *Ocul Immunol Inflamm*. [Under review]
- Knickelbein J, Tucker W, Kodati S, **Akanda M**, Sen HN. Non-invasive method of monitoring retinal vasculitis in patients with birdshot chorioretinopathy using optical coherence tomography. *Brit J Ophthalmol*. [Under review]

Abstract Publications:

- **Akanda M**, Kodati S, Gangaputra S, Sen HN. Standardization of OCT angiography images and removal of superficial retinal vessel projections on deeper layers. ARVO Imaging, Baltimore, MD; May 6, 2017.
- **Akanda M**, Kodati S, Gangaputra S, Sen HN. Retinoschisis in intermediate uveitis: clinical characteristics and outcomes. ARVO Imaging, Baltimore, MD; May 8, 2017.

Travel to Professional Meetings:

- American Academy of Ophthalmology Annual Meeting, Chicago, IL; Oct. 15-18, 2017.
- Association for Research in Vision and Ophthalmology Imaging Conference, Baltimore, MD; May 6, 2017.
- Association for Research in Vision and Ophthalmology Annual Conference, Baltimore, MD; May 7-11, 2017.



Yajie "Julie" An

School: Northeast Ohio Medical University

Mentor: Bradford J. Wood, M.D., Director, Center for Interventional Oncology; Chief, Interventional Radiology, NIH Clinical Center

Institute: Clinical Center (CC)

Research: Does a Negative Prostate mpMRI Rule-Out Clinically Significant Cancer?

Prostate multiparametric MRI (mpMRI) has significantly changed the paradigm of prostate cancer evaluation. However, the utility of systematic prostate biopsy in the presence of a negative mpMRI is still uncertain. In a retrospective database analysis, we evaluated the histopathologic results from systematic 12-core biopsies performed in patients with a negative prostate mpMRI.

Under an IRB-approved protocol, we queried our prostate mpMRI database for men who underwent systematic 12-core biopsy within a year of a negative prostate mpMRI. Clinicopathologic features were analyzed and stratified by biopsy history. Negative predictive

value (NPV) was calculated for detection of any cancer (Gleason Score ≥ 6) and clinically significant cancer (Gleason Score ≥ 7). Regression analysis was performed to identify outcome predictors.

Overall, 114 men met the inclusion criteria. Median age and PSA in this cohort were 61 (IQR 57-67) years and 5.5 (IQR 3.6-8.7) ng/ml, respectively. The NPV of mpMRI for clinically significant cancer was 96.5% (95%CI 93.1 to 99.9%) overall. NPV for significant cancer in biopsy naïve (n=20), prior negative biopsy (n=53), and prior positive biopsy (n=41) cohorts was 100%, 100%, and 90%, respectively. No significant predictors were identified for detection of prostate cancer in this cohort.

Negative prostate mpMRI has an excellent NPV for clinically significant cancer and serves as a useful modality for stratifying risk in patients with suspicion of prostate cancer. Patients with negative mpMRI can avoid unnecessary prostate biopsy, thereby decreasing the detection of clinically insignificant cancer and avoiding morbidity due to overtreatment.

Full Length Publications:

- DiBianco JM, **An JY**, Tanakchi S, Stanik Z, McGowan A, Maruf M, Sidana A, Jain AL, Muthigi A, George AK, Bayne C, Linehan WM, Boyle SL, Metwalli AR. Managing renal cell carcinoma associated paraneoplastic syndrome with nephron-sparing surgery in a patient with von Hippel-Lindau. *Urol Case Rep.* 2017 Apr 27;13:101-103.
- McGowan A, **An JY**, Tanakchi S, Maruf M, Muthigi A, George A, Su D, Merino MJ, Linehan WM, Boyle SL, Metwalli AR. Multiple recurrent paraganglioma in a pediatric patient with germline SDH-B mutation. *Urol Case Rep.* 2017 Apr 27;13:107-109.
- **An JY**, Sidana A, Choyke PL, Wood BJ, Pinto PA, Turkbey B. Multiparametric magnetic resonance imaging for active surveillance of prostate cancer. *Balkan Medical Journal.* [Under review]
- **An JY**, Sidana A, Holzman SA, Biaccio JA, Choyke PL, Wood BJ, Turkbey B, Pinto PA. Does a negative prostate mpMRI rule-out clinically significant cancer? [Under review]

Abstract Publications:

- Boyle SL, **An JY**, Krishnasamy VP, Metwalli AR, Wood BJ. Multiple radiofrequency ablation zones on renal function. Poster presentation at American Urological Association Annual Meeting, Boston, MA; May 2017.
- Boyle SL, **An JY**, Krishnasamy VP, Metwalli AR, Wood BJ. Accelerated growth rate of ipsilateral renal tumors after radiofrequency ablation in multifocal hereditary renal cell carcinoma. Podium presentation at Society of Interventional Radiology Annual Meeting, Washington, DC; Mar. 2017.

- **An JY**, Chen AW, Xu S, Wood BJ. Compensation for internal organ motion using a tracked anchoring needle: a feasibility study. Poster presentation at Society of Interventional Radiology Annual Meeting, Washington, DC; Mar. 2017.
- Boyle SL, Fascelli M, **An JY**, Kim D, Cristomo-Wynne T, Linehan WM, Metwalli AR. Renal failure and surgery: How low is too low? Partial nephrectomy in hereditary renal cancer population with impaired renal function. Poster presentation at Society of Urologic Oncology Annual Meeting, San Antonio, TX; Nov. 2016.
- Crisostomo-Wynne T, Boyle SL, **An JY**, Kim D, Fascelli M, Linehan WM, Metwalli AR. Perioperative outcomes for robotic and open multiplex partial nephrectomy in the management of multifocal renal cell carcinoma. Poster Presentation at Society of Urologic Oncology Annual Meeting, San Antonio, TX; Nov. 2016.

Travel to Professional Meetings:

- American Urological Association Annual Meeting, Boston, MA; May 2017.
- Society of Interventional Radiology Annual Meeting, Washington, DC; Mar. 2017.
- Society of Urologic Oncology Annual Meeting, San Antonio, TX; Nov. 2016.



Joseph Baiocco

School: Sidney Kimmel Medical College at Thomas Jefferson University

Mentor: Leonard M. Neckers, Ph.D., Head, Tumor Cell Biology Section, Urological Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Novel Therapies Targeting Androgen Receptor Variants in an *In Vitro* Model of Castrate Resistant Prostate Cancer

Heat shock proteins (Hsp) are molecular chaperones required for stabilization/activation of androgen receptor (AR). Although targeting the AR ligand-binding domain (LBD) initially improves patient survival, CRPC invariably develops. CRPC is frequently characterized by expression of AR splice variants (ARv). Because they lack an LBD, ARvs can maintain the AR transcriptional program. While full-length AR (FL-AR) activity depends on Hsp90 and LBD interaction, we believe that ARv, particularly ARv7, retains dependence on Hsp40/Hsp70 interaction with the N-terminal domain. Using 22Rv1 CRPC-derived cells (which express FL-AR and Arv7), we tested whether targeting these chaperones with specific inhibitors would

lead to FL-AR and ARv7 destabilization, causing decreased cell viability. We then asked whether our Hsp inhibitors could be used with VT464, a CYP17A1 inhibitor that prevents AR synthesis. Because VT464 is in trials as a single agent therapy for CRPC, we investigated whether its effect on cell viability would be enhanced in combination with inhibition of Hsp40/Hsp70. Additionally, ARv7 leads to changes in metabolism such that cells are more dependent on glutaminolysis and fatty acid synthesis. Therefore, we also hypothesized that inhibition of glutaminase (Gls) and/or fatty acid synthase (FASn), would act in concert with VT464 for efficacy in CRPC. We analyzed the effects of VT464, C86 (Hsp40-inhibitor), JG98 (Hsp70-inhibitor), CB839 (Gls-inhibitor), and 3V-3166 (FASn-inhibitor) on cell viability as single agents and in combination *in vitro*. Changes in expression of FL-AR and ARv7 on Western blot analysis was correlated to the respective cell viability data. VT464 caused a dose-dependent decrease in cell viability, as did C86, JG98, CB839, and 3V-3166. Combination of these with VT464 showed additive toxicity. Importantly, C86 and JG98 decreased FL-AR and ARv7 protein expression, which may explain these combinatorial effects. Because of their unique mechanism of action, these therapies may be of use in CRPC. Further mechanistic and *in vivo* assays are warranted.

Full Length Publications:

- **Baiocco JA**, Metwalli AR. What is the optimal management strategy for multifocal and hereditary kidney cancer? *J Renal Med*, 2017 Apr.; 1(1).
- An JY, **Baiocco JA**, Rais-Bahrami S. Trends in the authorship of peer-reviewed publications in the urology literature. *Urol Pract*. [In press]
- Chelluri R, George AK, Baiocco JA, Turkbey B, Pinto PA. The role and methodology of multiparametric MRI and fusion-guided biopsy in the management of prostate cancer patients. *Smith's Textbook of Endourology*, Chapter 130. [In press]

Abstract Publications:

- **Baiocco JA**, Moses M, Watson MJ, Chelluri R, Gestwicki J, Trepel J, Neckers L. Novel therapies targeting androgen receptor variants in an *in vitro* model of castrate resistant prostate cancer. American Urological Association Annual Meeting, Boston, MA; May 12-16, 2017, Poster MP57-04.
- **Baiocco JA**, Sidana A, Chelluri R, Yim K, George AK, Valera V, Kongnyuy M, Muthigi A, Watson MJ, Maruf M, Merino MJ, Turkbey B, Choyke PL, Wood BJ, Pinto PA. MRI use alters prostate cancer management patterns: Treatment trends in the image-guided biopsy era. American Urological Association Annual Meeting, Boston, MA; May, 12-16, 2017, Poster MP47-10.

Travel to Professional Meetings:

- American Urological Association annual meeting, Boston, MA; May 12-16, 2017.
- Society of Urologic Oncology annual meeting, San Antonio, TX; Nov. 30-Dec. 2, 2016.



Jason Berglund

School: Tufts University School of Dental Medicine

Mentor: Michael T. Collins, M.D., Chief, Section on Skeletal Disorders and Mineral Homeostasis

Institute: National Institute of Dental and Craniofacial Research (NIDCR)

Research: Insights into the Molecular and Cellular Etiology of the Tumors Responsible for Tumor-Induced Osteomalacia

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic condition associated with hypophosphatemia, muscle weakness, bone pain, and pathological fracture. It is caused by secretion of FGF23 by phosphaturic mesenchymal tumors (PMTs) with histological features reminiscent of osteogenic cells. The molecular and cellular origins of these tumors have yet to be clearly elucidated, but the recent identification of a fibronectin-fibroblast growth factor receptor 1 (FN1/FGFR1) translocation in a subset of these tumors suggests FGFR1 signaling as a potential tumorigenic driver.

26 tumors clinically proven to cause TIO were assessed. Analyses included translocation testing with FN1/FGFR1-specific FISH, immunohistochemical and/or immunofluorescent testing of markers of FGF23 and FGFR1 pathway signaling, and osteogenic cell markers. A comparison was made *in vitro* of the response in FGF23 production to FGFR and/or mTOR blockade by BGJ398 and rapamycin, respectively, in separate FN1/FGFR1 translocation positive and negative tumors.

14/26 (54%) tumors were successfully assessed by FISH (tumors arising in bone were generally unanalyzable). Of the 14 samples, 4/14 (29%) were positive for a FN1/FGFR1 translocation. All tumors were FGF23 positive. Tumors were positive for various early and late osteogenic lineage markers (including DMP1, which showed a high level of co-expression with FGF23), the FGF23 UDP-GalNAc transferase, GALNT3, and the FGF23 co-receptor KLOTHO. *In vitro*, addition of the FGFR inhibitor BGJ398, with and without presence of the synergistic mTOR inhibitor rapamycin, decreased FGF23 production by 80% in a FN1/FGFR1 translocation positive tumor, but had a negligible effect on a tumor lacking the translocation.

PMTs express osteogenic cell markers consistent with having differentiated from an inducible skeletal stem cell. Significant proportions of PMTs harbor a FN1/FGFR1 translocation, and may be responsive to FGFR pathway blockade. These data suggest a role for FGFR1 signaling in tumorigenesis and FGF23 production, and identify the FGFR1 pathway as a potential target for treatment.

Full Length Publications:

- **Berglund JA**, Gafni RI, Wodojo F, Cowen EW, El-Maouche D, Chang R, Chen, CC, Guthrie LC, Molinolo AA, Collins MT. Tumor-induced osteomalacia in association with PTEN-negative Cowden Syndrome. *Osteoporosis International*. [Under review]

Travel to Professional Meetings:

- Endocrine Society, 99th Annual Meeting, Orlando, FL; Apr. 1-4, 2017.
- 8th International Conference on Children's Bone Health. Würzburg, Germany; Jun. 10-13, 2017.

Abstract Publications:

- **Berglund JA**, Gafni RI, Forsberg JA, Molinolo, AA, Fernandez de Castro L, Ten Hagen KG, Tian E, Metwally T, Overjero Crespo D, Chong W, Collins MT. Insight into the molecular and cellular etiology of the tumors responsible for tumor-induced osteomalacia. 99th Annual Meeting of the Endocrine Society. Orlando, FL; Apr. 2017. [Oral presentation]
- **Berglund JA**, Tella S, Kim L, Stanton R, Collins MT, Boyce AM. Scoliosis in fibrous dysplasia/McCune-Albright Syndrome. 8th International Conference on Children's Bone Health. Würzburg, Germany; June 2017. [Oral presentation]



Thomas Bolig

School: Wayne State University School of Medicine

Mentor: Anthony Suffredini, M.D., Deputy Chief, Critical Care Medicine Department

Institute: Clinical Center (CC)

Research: A Genoproteomic Approach to *Burkholderia cepacia* Complex Species Identification

Burkholderia species are clinically important pathogens and molecular methods define at least 20 distinct species within the *Burkholderia cepacia* complex (Bcc). Definitive identification of Bcc species is important given different pathogenicity as suggested by patient outcomes. However, identification of species within the Bcc is challenging due to the phenotypic similarity and intraspecies diversity. My lab developed a rapid, culture-independent method to identify bacterial pathogens using genoproteomics. It combines theoretical peptidome analysis (from *in silico* translation and digestion of bacterial whole genome sequences) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) with multiple reaction monitoring (MRM) to detect unique peptides following rapid trypsin digestion of bacteria. We applied this

approach to discover unique peptide markers that distinguish Bcc isolates to the species level.

Three Bcc species (*B. cepacia*, *B. cenocepacia*, *B. multivorans*) and *B. gladioli* (an outgroup) were chosen for analysis, and their core tryptic peptidomes were constructed *in silico*. Lowest common ancestor analysis was performed on theoretical core peptidomes to generate a list of potential markers that are unique to each species. Peptide identification by LC-MS/MS was performed to experimentally identify unique peptides. After candidate peptide markers were identified, a rapid, MRM assay was developed and optimized for peptide markers on a triple quadrupole LC/MS System using type-strains of both positive and negative controls from the Bcc.

Eight unique peptides were selected for analysis and were verified experimentally to be specific only for their respective species and not detected in the other Bcc strains. Thus, the genoproteomic approach to identify unique peptide markers for gram-negative respiratory pathogens is applicable to the Bcc. These experimentally identified peptide markers may be useful candidates for a clinical LC-MS/MS assay to rapidly and reliably identify Bcc species where traditional laboratory diagnostic techniques are currently unreliable or time intensive.

Full Length Publications:

- Curran, CS; Bolig, TC; Torabi-Parizi, P. Mechanisms and targeted therapies for *Pseudomonas aeruginosa* lung infection. *Am J Resp Crit Care*. [Under review]

Travel to Professional Meetings:

- American Thoracic Society International Conference, Washington, DC; May 23, 2017.

Abstract Publications:

- Bolig TC, Wang H, Drake SK, Yong C, Gucek M, Lyes MA, Rosenberg AZ, Soderblom E, Dekker JP, Suffredini AF. A genoproteomic approach to identify species-specific peptide markers for *Burkholderia cepacia* complex species. American Thoracic Society International Conference, Washington, DC; May 23, 2017. [Poster presentation]



Alejandro Bugarini

School: San Juan Bautista School of Medicine

Mentor: Prashant Chittiboyna, M.D., M.P.H., Assistant Clinical Investigator, Surgical Neurology Branch

Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research: Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid (SAHA) is a Novel, Promising Treatment for Cushing's Disease

Recurrence (or remission failure) following transsphenoidal surgery in Cushing's disease (CD) due to pituitary corticotroph tumors (CtT) is a challenging clinical problem. Definitive therapy for recurrent/unremitting CD is limited to radiation and medical/surgical adrenalectomy, however, these therapies come with a significant burden of adverse effects. Suberoylanilide hydroxamic acid (SAHA) is an FDA-approved histone deacetylase inhibitor (HDACi) which has been shown to induce growth arrest and cell death in pituitary adenoma-derived cells. The effects of SAHA on adrenocorticotropin hormone (ACTH)-secreting adenomas and the potential for biochemical remission have not been unexplored.

ACTH secretion, apoptosis, and gene expression profile were examined in AtT-20 cells with or without SAHA (0–4 μ M). In-vivo efficacy of SAHA was examined in a mouse AtT-20 xenograft model. SAHA's efficacy against human-derived CtT (hCtT) was also assessed.

SAHA (1 μ M) reduced AtT-20 viability to 75% at 24h and 43% at 48h ($p=0.002$). Apoptosis was confirmed with elevated BAX/Bcl2 ratio and FACS. Xenografted nude-mice tumor involution ($p=0.0005$) was observed with 5-day intraperitoneal SAHA, with reversal of elevated ACTH ($p<0.0001$). SAHA did not affect serum ACTH in non-tumor mice. Subsequently, we confirmed that SAHA (1 μ M/24h) decreased hCtT survival (78.92%, $p=0.0007$) and ACTH secretion (83.64%, $p=0.03$). Intriguingly, independent of apoptosis-mediated cytotoxicity, we detected an early reduction in AtT20 ACTH secretion *in vitro* (70%, $p<0.0001$) and *in-vivo* (76%). Further, diminished proopiomelanocortin (POMC) transcription (39%, $p=0.0001$) and POMC promoter activation were detected. Microarray revealed a direct association between liver X receptor alpha (LXR α) and POMC. Accordingly, SAHA reduced LXR α in AtT-20 but not in normal corticotrophs. Finally, LXR α transcriptional augmentation with CRISPR/dCas9 system rescued AtT-20 cells from SAHA-mediated (1-4 μ M/3h) POMC downregulation and ACTH secretion suppression.

Our study demonstrates SAHA's efficacy in reducing survival and ACTH secretion in AtT-20 and hCtT cells. These novel findings support the potential use of SAHA in the management of recurrent/unremitting CD.

Full Length Publications:

- Lu J, **Bugarini A**, Chatain G, Wang X, Maric D, Walbridge S, Zhengping Z, Chittiboyna P. Histone deacetylase inhibitor SAHA is a promising treatment of Cushing disease. *J Clin Endocrinol Metab*. [In press]
- Lu J, **Bugarini A**, Chatain G, Zhang Q, Wang X, Edwards NA, Ray-Chaudhury A, Merrill MJ, Lonser RR, Chittiboyna P. Corticotropin releasing hormone can selectively stimulate glucose uptake in corticotropinoma via glucose transporter 1. *Mol Cell Endocrinol*. [In review]

Abstract Publications:

- **Bugarini A**, Chatain G, Lu J, Wang X, Maric D, Walbridge S, Zhengping Z, Chittiboyna P. SAHA suppresses ACTH production from corticotropinomas causing Cushing's disease: normal corticotroph escape mechanism and the role of liver X receptor alpha. National Institute of Neurological Disorders and Stroke (NINDS) Intramural Scientific Retreat, Potomac, MD; June 1-2, 2017.
- Shepard M, **Bugarini A**, Zhang Q, Zhuang Z, Chittiboyna P. Repurposing propranolol as a novel anti-tumor agent for glioblastoma. National Institute of Neurological Disorders and Stroke (NINDS) Intramural Scientific Retreat, Potomac, MD; June 1-2, 2017.

Travel to Professional Meetings:

- National Institute of Neurological Disorders and Stroke (NINDS) Intramural Scientific Retreat, Potomac, MD; June 1-2, 2017.



Steven B. Cai

School: Chicago Medical School at Rosalind Franklin University

Mentor: Jack Yanovski, M.D., Ph.D., Chief, Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics

Institute: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Research: Melanocortin 3 Receptor Regulates Autophagy and Lipid Metabolism in Liver

Melanocortin 3 Receptor (MC3R) is known to modulate metabolic homeostasis in humans and mice. We previously reported that humans with *MC3R* hypoactive mutations have altered nutrient partitioning, with accumulation of triglycerides in adipose tissue and liver, developing obesity. However, the cellular processes by which MC3R modulates metabolic homeostasis remain unclear. Based on evidence for an essential role of autophagy in metabolic regulation in liver, we hypothesized that the MC3R modulates hepatic autophagy and lipid metabolism in obesity.

We used homozygous knock-in mouse models replacing murine MC3R with wild type human *MC3R* (*MC3R^{hWT/hWT}*) and “double mutant” human *MC3R* (*MC3R^{hDM/hDM}*, expressing the sequence variants C17A and G241A that are associated with human obesity) as well as *MC3R^{-/-}* mice. Liver tissues were collected from fed and 24-hour fasted animals to study mRNA and protein expression.

MC3R^{hDM/hDM} mice and *MC3R^{-/-}* mice had significantly greater body weight and fat mass but less fat-free mass and increased hepatic triglycerides compared to *MC3R^{hWT/hWT}*. Liver from *MC3R^{hDM/hDM}* and *MC3R^{-/-}* mice failed to show induced autophagy after 24-hour fasting. Also, lipogenic genes including *FAS* and *PPAR γ* were up-regulated with no change in beta-oxidative genes such as *PPAR α* and *CPT1 α* in the liver of *MC3R^{hDM/hDM}* and *MC3R^{-/-}* mice compared to *MC3R^{hWT/hWT}* or BL6 mice. We also found that *MC3R^{hDM/hDM}* and *MC3R^{-/-}* mice had upregulation of basal LC3-II in the fed state and poor induction of LC3-II in the fasting state. Chloroquine treatment and serum starvation in primary hepatocytes also demonstrated impaired autophagy flux in both *MC3R^{hDM/hDM}* and *MC3R^{-/-}* mice cells.

MC3R^{hDM/hDM} and *MC3R^{-/-}* mice exhibit an obese phenotype with increased hepatic lipid content that may be in part due to defective autophagy induction and increased lipogenesis in liver.

Abstract Publications:

- Cai S, Yanovski J. Melanocortin 3 receptor regulates autophagy and lipid metabolism in liver. American Diabetes Association 76th Annual Scientific Sessions, New Orleans, LA; June 2017. [Poster presentation]

Travel to Professional Meetings:

- American Diabetes Association 77th Annual Scientific Sessions, New Orleans, LA; June 9-13, 2017.



Brian Calio

School: Sidney Kimmel Medical College at Thomas Jefferson University

Mentor: Peter A. Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Utility of Multiparametric MRI and Fusion Biopsy on Patient Selection for Focal Therapy in Intermediate Risk Prostate Cancer Patients

Patients with intermediate risk prostate cancer (IRPCa) often receive whole gland therapy, potentially exposing them to overtreatment and side effects associated with treatment. Focal therapy (FT) minimizes these risks while treating all clinically significant cancer. We aimed to determine the accuracy of multiparametric MRI (mpMRI) and fusion biopsy (Fbx) in selecting candidates for FT. Clinical and pathology data were prospectively collected from IRPCa patients who underwent prostate MpMRI prior to radical prostatectomy (RP) (2010-16). Patients were analyzed in two cohorts: those who received mpMRI with systematic 12-core biopsy (Sbx) alone and those who received Fbx in addition to Sbx (Fbx/Sbx). Patients were considered suitable for FT if they had IRPCa in only one lobe of the prostate with a corresponding mpMRI

visible lesion on the same side. Poor candidates were patients found to have high risk cancer (Gleason 8-10), IRPCa bilaterally, or PCa lesions that crossed the midline. Good candidates were confirmed with whole mount pathology analysis. 190 patients with IRPCa were included in the study. 131 had MRI and combination Fbx/Sbx. 80 patients were considered good FT candidates based on preoperative MpMRI and biopsy findings. A higher proportion of candidates suitable for FT was determined by mpMRI and Fbx/Sbx and confirmed on whole mount than FT candidates determined by mpMRI and Sbx alone (54% vs 20%; $p=0.02$). Failure on whole mount was due to Gleason upgrade in 25% of patients and due to presence of bilateral IRPCa in the rest. On regression analysis, low PSA was the sole predictor of confirmed FT candidates on final pathology ($p=0.021$). MpMRI Fbx/Sbx is a more accurate tool than mpMRI with Sbx alone for predicting FT candidates. However, the application of mpMRI and Fbx/Sbx criteria to predict FT candidates may result in undertreatment of approximately one quarter of the patients with significant cancer. More accurate predictive capability is needed before FT can be offered to all patients with IRPCa.

Full Length Publications:

- **Calio B**, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Changes in prostate cancer detection rate of fusion vs systematic biopsy over time: evidence of a learning curve. *Prostate Cancer Prostatic Dis*. [In press]
- **Calio B**, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Eliminating risk of upgrade from MRI-TRUS fusion biopsy to radical prostatectomy: could saturation biopsy of the index tumor be the solution? *J Urol*. [Under review]

Abstract Publications:

- **Calio B**, Sidana A, Sugano D, Stanik Z, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. MRI-TRUS fusion biopsy at NCI: Changes in prostate cancer detection rate of fusion vs systematic biopsy over 10 years. Society of Urologic Oncology Annual Meeting, San Antonio, TX; Dec. 2016. [Poster presentation]
- **Calio B**, Sidana A, Valera V, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. A model for predicting focal ablation candidates in patients with prostate cancer based on MRI and biopsy criteria. ASCO Genitourinary Cancers Symposium, Orlando, FL; Feb. 2017. [Poster presentation]
- Sugano D, Sidana A, **Calio B**, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood, BJ, Pinto P. Can index lesion tumor volume on T2 weighted MRI predict biochemical recurrence following radical prostatectomy? ASCO Genitourinary Cancers Symposium, Orlando, FL; Feb. 2017. [Poster presentation]
- Sugano D, Sidana A, **Calio B**, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood, BJ, Pinto P. Index lesion tumor volume on MRI to predict adverse pathologic outcomes following radical prostatectomy. ASCO Genitourinary Cancers Symposium, Orlando, FL; Feb. 2017. [Poster presentation]
- **Calio B**, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Eliminating risk of upgrade from MRI-TRUS fusion biopsy to radical prostatectomy: Could Saturation biopsy of the index tumor be the solution? American Urological Association Annual Meeting, Boston, MA; May 2017. [Podium presentation]

- **Calio B**, Sidana A, Valera V, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Utility of multiparametric MRI on patient selection for focal therapy in intermediate risk prostate cancer. American Urological Association Annual Meeting, Boston, MA; May 2017. [Poster presentation]
- **Calio B**, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Changes in prostate cancer detection rate of fusion vs systematic biopsy over time: a single center experience. American Urological Association Annual Meeting, Boston, MA; May 2017. [Poster presentation]
- Sugano D, Sidana A, Wright C, **Calio B**, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto, P. Technique and case series of MRI guided in-bore biopsy for patients without rectum. American Urological Association Annual Meeting, Boston, MA; May 2017, [Poster presentation]
- Sugano D, Sidana A, **Calio B**, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood, BJ, Pinto P. Effect of hypogonadism on prostate imaging and cancer detection. American Urological Association Annual Meeting, Boston, MA; May 2017. [Poster presentation]

Travel to Professional Meetings:

- Society of Urologic Oncology Annual Meeting, San Antonio, TX; Nov. 30-Dec. 2, 2016.
- American Society for Clinical Oncology - Genitourinary Cancers Section, Orlando, FL; Feb. 14-16, 2017.
- American Urologic Association Annual meeting, Boston, MA; May 12-16, 2017.

Awards:

- Best Poster, American Urologic Association, Prostate Cancer Detection & Screening Session, May 12, 2017.



Angela Wei Chen

School: University of Pittsburgh School of Medicine

Mentor: Bradford Wood, M.D., Director, Center for Interventional Oncology, Chief of Interventional Radiology Section

Institute: Clinical Center (CC)

Research: Tremelimumab combined with subtotal locoregional therapy induces systemic tumor response in patients with unresectable multifocal hepatocellular carcinoma

Tremelimumab, a monoclonal antibody against T lymphocyte surface receptor CTLA-4, inhibits B7-CTLA-4-mediated downregulation of T-cell activation. Ablation has been shown to induce a peripheral immune response to enhance the effect of anti-CTLA4 treatment in patients with advanced HCC. The purpose of this study was to describe changes in the radiographic appearance of hepatocellular carcinoma treated with tremelimumab in combination with limited ablation.

A retrospective review of imaging was conducted for seven consecutive patients (age 70.8 ± 4.2 , all male) with multifocal discrete HCC (Childs Pugh A/B7; BCLC B/C; ECOG 0/1; post-sorafenib) treated on clinical trial with tremelimumab (10 mg/kg/IV q4 weekly x6 doses) followed by cryoablation (n=4), microwave (MWA) (n=1) or radiofrequency ablation (RFA) (n=2) of a single lesion on day 36. Changes in size, density, and enhancement pattern of lesions were summarized.

Mean cross-sectional imaging follow-up was 160 days. Of the seven ablated tumors, four increased in size, two decreased, and one remained unchanged. Four showed increased enhancement, one showed decreased enhancement, and two remained unchanged. 18/42 (43%) of the ablation-naive remote tumors demonstrated growth at the first post-ablation imaging interval. At subsequent imaging of 15/18 lesions, 7 regressed in size while 6 progressed and 2 remained stable. The majority of remote tumors (67%) showed increased enhancement, compared to 15% with decreased enhancement, and 18% with unchanged enhancement.

In a subset of patients receiving immune checkpoint inhibition therapy with supplemental limited ablation, a majority of ablation-naive tumors showed initial growth, followed by subsequent shrinkage. This imaging response may initially be misclassified according to RECIST criteria. Although speculative, initial increased enhancement could be a consequence of immunocyte infiltration which has been previously documented in a subset of responding patients who underwent repeat biopsy.

Abstract Publications:

- **Chen AW**, Greten T, Duffy A, Anderson V, Krishnasamy V, Levy EB, Wood BJ. Imaging response of distant un-ablated hepatocellular carcinoma following limited hepatic thermal ablation combined with tremelimumab, a monoclonal antibody against CTLA4. *J Vasc Interv Radiol* 2017; 28(2): S60-S61. *Society of Interventional Radiology*, Washington, DC; Mar. 2017.

Travel to Professional Meetings:

- Society of Interventional Radiology, Washington, DC; Mar. 2017.

Awards:

- Medical Student Travel Scholarship for Outstanding Abstract, Society of Interventional Radiology, Washington, DC; Mar. 2017.



Xenia Chepa-Lotrea

School: Georgetown University School of Medicine

Mentor: William A. Gahl, M.D., Ph.D., Research Institute Clinical Director, NHGRI; Head, Undiagnosed Diseases Program; Head, Human Biochemical Genetics Section; Senior Investigator, Medical Genetics Branch

Institute: National Human Genome Research Institute (NHGRI)

Research: Compound Heterozygosity for Loss-of-Function Glycyl-tRNA Synthetase (GARS) Mutations Results in a Multi-System Developmental Syndrome that Includes Severe Growth Retardation

Aminoacyl-tRNA synthetases (ARSs) are ubiquitously expressed enzymes that ligate amino acids onto tRNA molecules. Genes encoding ARSs have been implicated in myriad dominant and recessive disease phenotypes. Glycyl-tRNA synthetase (GARS) is a bi-functional ARS that charges tRNA^{Gly} in the cytoplasm and mitochondria. GARS mutations have been associated with dominant Charcot-Marie-Tooth disease but have not been implicated in recessive phenotypes. Here we describe a patient from the NIH Undiagnosed Diseases Program with a

multi-system, developmental phenotype.

The patient was a Caucasian female of non-consanguineous northern European ancestry with microcephaly, extreme growth retardation, and multiple organ involvement. On initial NIH evaluation at 3 yrs, the child's features included a triangular face with broad forehead, prominent epicanthal folds, hypotelorism, smooth philtrum, and high-arched palate. She was non-ambulatory and had spasticity of upper and lower extremities but normal range of motion and hypermobility of her ankles. Her verbal skills included 20 single words with poor intelligibility. Whole-exome sequence analysis revealed that the patient was compound heterozygous for one frameshift (p.Glu831Ilefs*6) and one missense (p.Arg310Gln) GARS mutation. Using in vitro and in vivo functional studies, we demonstrated that both GARS mutations cause a loss-of-function effect: the frameshift mutation results in depleted protein levels and the missense mutation reduces GARS tRNA charging activity. In support of GARS mutation pathogenicity, our patient showed striking phenotypic overlap with other patients having ARS-related recessive diseases, including features associated with mutations in both cytoplasmic and mitochondrial ARSs. This observation is consistent with the essential function of GARS in the cytoplasm and mitochondria.

In summary, our clinical, genetic, and functional analyses expand the phenotypic spectrum associated with GARS mutations.

Full Length Publications:

- Oprescu SN, **Chepa-Lotrea X**, Takase R, Golas G, Markello TC, Adams DR, Toro C, Hou Y, Malicdan MCV, Gahl WA, Tiffit CJ, and Antonellis A. Compound heterozygosity for loss-of-function GARS mutations results in a multi-system developmental syndrome that includes severe growth retardation. *Hum Mutat*. [Under review]

Abstract Publications:

- **Chepa-Lotrea X**, Roney J, Bodine S, Dorward H, Guo J, Gunay-Aygun M, Krakow D, Gahl WA, Malicdan MCV. Mutations in WDR91 result in the dysfunction of endosomal pathways and manifest in human disease. American College of Medical Genetics Annual Clinical Genetics Meeting. Phoenix, AZ; Mar. 2017.
- Morimoto M, **Chepa-Lotrea X**, Sincan M, Draper D, Boerkoel CF, Golas G, Adams DR, Gahl WA, Malicdan MCV. A novel genetic disorder characterized by severe developmental delay and dysmorphism, recurrent pancreatitis, and organomegaly. American Society for Human Genetics. Orlando, FL; Oct. 2017.

- Behnam B, Chin JJ, Davids M, Sharma P, Wang C, **Chepa-Lotrea X**, Zein W, Golas GA, Toro C, Adams DR, Tiffit CJ, Gahl WA, Malicdan MCV. Novel mutations in CLN6 cause late-infantile neuronal ceroid lipofuscinosis in two unrelated patients. American Society for Human Genetics. Orlando, FL; Oct. 2017.
- **Chepa-Lotrea X**, Urban A, Peterson J, Darnell D, Stratton P and Freeman AF. Obstetric and gynecological outcomes in STAT3-deficient Hyper-Immunoglobulin E Syndrome. American College of Obstetricians and Gynecologists. Austin, TX; Apr. 2018.

Travel to Professional Meetings:

- American College of Medical Genetics Annual Clinical Genetics Meeting. Phoenix, AZ; Mar. 21-25, 2017.



Ashley E. Chorath

School: Sidney Kimmel Medical College at Thomas Jefferson University

Mentor: David A. Bluemke, M.D., Ph.D., F.A.H.A., F.A.C.R., Director, Radiology and Imaging Sciences; Senior Investigator, National Institute of Biomedical Imaging and Bioengineering Institute: Clinical Center (CC)

Research: Coronary CT Angiography and Carotid MRI Improve Phenotyping of Disease Extent Compared to ACC/AHA Risk Score Alone

Novel anti-atherosclerotic therapies can markedly reduce low density lipoprotein (LDL) levels, but therapy costs are high, suggesting the need for precise identification of at-risk patients. The purpose of this study was to determine the relationship between 2013 American College of Cardiology/American Heart Association (ACC/AHA) risk score and actual plaque phenotype assessed directly using computed tomographic angiography (CTA) and magnetic resonance imaging (MRI) in the coronary and carotid arteries.

Asymptomatic subjects eligible for statin therapy underwent coronary artery calcium scoring (CAC), coronary CTA and MRI of the carotid artery. Quartiles were calculated for non-calcified plaque (NCP), CAC, average carotid wall volume and were compared to ACC/AHA risk quartiles. Characteristics of patients with a risk score misclassification of ≥ 2 quartiles were compared.

203 subjects were enrolled (60% men, mean age 65). There were weak correlations between carotid wall volume (Kendall's tau= 0.29), NCP (tau= 0.16), and CAC (tau= 0.33, all $p < 0.01$). ACC/AHA risk alone misclassified plaque extent compared to measurement by carotid wall volume, CAC, and NCP in 22.1%, 23.8% and 29.6% of subjects, respectively. On average, 13% of the subjects were under-classified and 12.5% over-classified. Subjects who were under-classified in all methods were younger and over-classified patients were older ($p < 0.001$). Correlation between carotid wall volume and CAC was low (tau=0.15, $p = 0.004$). When predicting carotid plaque extent based on risk, there was no significant improvement when adding CAC to the model, while the addition of NCP led to significant improvement (Area Under the Curve of 0.75 and 0.79, respectively, NRI 0.52, $p = 0.001$).

Approximately 25% of patients had large discrepancies between ACC/AHA clinical risk and actual plaque burden measured with imaging. These results suggest that treatment based on risk score models alone may result in substantial over- and under-treatment of at-risk individuals, which should be considered when prescribing anti-atherosclerotic therapies with high treatment costs.

Travel to Professional Meetings:

- Society of Interventional Radiology, Washington, DC; Mar. 2017.
- American Academy of Neurology, Boston, MA; Apr. 2017.
- American Roentgen Ray Society, New Orleans, LA; Apr. 2017.
- American College of Radiology, Washington, DC; May 2017.



Jonathan H. Chung

School: SUNY Downstate Medical Center

Mentor: Nehal N. Mehta, M.D., M.S.C.E., F.A.H.A., Lasker Clinical Research Scholar, Section of Inflammation and Cardiometabolic Diseases

Institute: National Heart, Lung, Blood Institute (NHLBI)

Research: Treatment of Skin Inflammation is Associated With a Reduction in High Risk Coronary Plaque Progression at One-Year Follow-Up

Psoriasis is a chronic inflammatory skin disease associated with increased vascular inflammation, accelerated coronary heart disease, and an elevated relative risk of cardiovascular events, beyond traditional risk factors. As such, the disease serves as an ideal clinical human model to study of the role of inflammation in atherosclerosis.

Coronary computed tomography angiography (CCTA)-identified low-attenuation and/or positive remodeling are characteristics of rupture-prone, or “high-risk” coronary plaques (HRP). Numerous studies suggest that HRP are predictive of prospective cardiovascular events. Psoriasis patients have been shown to have an increased prevalence of HRP compared to healthy controls of the same age; furthermore, when compared to a decade older statin-eligible patients, psoriasis patients have a similar prevalence of HRP. However, no study has attempted to characterize the longitudinal effect of change in psoriasis severity on HRP morphology.

We hypothesized that improvement in skin inflammation would associate with improvement in HRP morphology. To examine this question, psoriasis patients (N=72) underwent CCTA at baseline and one-year. The cohort was middle-aged, had a low Framingham risk score and had moderate to severe psoriasis. When stratified by change in skin disease severity, 47 patients worsened their skin disease by 50% ($p < 0.001$) while 25 patients had a reduction by 77% ($p < 0.001$). Those who improved their skin disease had a 68% decrease in HRP score (mean \pm SD: 0.19 ± 0.45 vs 0.06 ± 0.25 , $p = 0.02$), while those who worsened had a 50% increase in HRP score (mean \pm SD: 0.24 ± 0.52 vs 0.48 ± 0.82 , $p = 0.07$). Finally, change in skin disease associated with change in HRP score, a finding which persisted beyond cardiovascular risk factors ($\beta = 0.61$, $p = 0.04$).

Improvement in skin inflammation was associated with reduction in HRP score potentially suggesting that reducing *in vivo* inflammation may have remote benefits on high risk coronary plaque in psoriasis.

Full Length Publications:

- Lerman JB, Joshi AA, Chaturvedi A, Aberra TM, Dey AK, Rodante JA, Salahuddin T, **Chung JH**, Rana A, Teague HL, Wu JJ, Playford MP, Lockshin BN, Chen MY, Sandfort V, Bluemke DA, Mehta NN. Coronary Plaque Characterization in Psoriasis Reveals High Risk Features Which Improve Following Treatment in a Prospective Observational Study. *Circulation*. 2017 May 8. doi: 10.1161/circulationaha.116.026859. [Epub ahead of print]
- Dey AK, Joshi AA, Chaturvedi A, Lerman JB, Aberra TM, Rodante JA, Teague HL, Harrington CL, Rivers JP, **Chung JH**, Kabbany MT, Natarajan B, Silverman JI, Ng Q, Sanda GE, Sorokin AV, Baumer Y, Gerson E, Prussick RB, Ehrlich A, Green LJ, Lockshin BN, Ahlman MA, Playford MP, Gelfand JM, Mehta NN. Association between skin and aortic vascular inflammation in patients with psoriasis: a case-cohort study using positron emission tomography/computed tomography. *JAMA Cardiol*. 2017 May 31. doi: 10.1001/jamacardio.2017.1213. [Epub ahead of print]

Abstract Publications — Podium (Oral) Presentations:

- Chung JH**, Dey AK, Lerman JB, Joshi AA, Rivers JP, Rana A, Rodante JA, Playford MP, Chen MY, Mehta NN. High Risk Coronary Plaque Characteristics Directly Associate with Psoriasis Severity over a 1-Year Period of Time. European Academy of Dermatology and Venereology Congress. Geneva, Switzerland; Sept. 2017.
- Dey AK, **Chung JH**, Rivers JP, Sajja A, Kabbany MT, Natarajan B, Lerman JB, Joshi AA, Shukla P, Rodante JA, Teague HL, Harrington CL, Playford MP, Chen MY, Bluemke DA, Mehta NN. Small Dense Low-density Lipoprotein Particle Number Relates to Coronary Plaque Burden Independent of Traditional Cardiovascular Risk Factors in Psoriatic arthritis group. Rheumatism Society of the District of Columbia, Fellows Forum. Washington, DC; May 2017.
- Chung JH**, Playford MP, Dey AK, Chaturvedi A, Rivers JP, Lerman JB, Harrington CL, Gordon SM, Remaley AT, Chen MY, Bluemke DA, Mehta NN. Lipid rich plaque by coronary CT angiography associates with cholesterol efflux capacity independent of traditional cardiovascular risk factors in

those at risk for myocardial infarction. American Federation for Medical Research - Eastern Regional Meeting. Washington, DC; Apr. 2017.

- Chaturvedi A, Lerman JB, Sandfort V, **Chung JH**, Dey AK, Rivers JP, Joshi AA, Rana A, Rodante JA, Teague HL, Silverman JI, Ng Q, Sanda GE, Harrington CL, Sorokin AV, Baumer Y, Gelfand JM, Playford MP, Ahlman MA, Bluemke DA, Mehta NN, Chen MY. Aortic vascular inflammation by 18-FDG PET/CT associates with high-risk coronary plaques in young psoriasis patients. American Federation for Medical Research - Eastern Regional Meeting. Washington, DC; Apr. 2017.
- Rivers JP, Dey AK, Chaturvedi A, **Chung JH**, Kabbany MT, Harrington CL, Ahlman MA, Rodante JA, Joshi AA, Yao J, Powell-Wiley TM, Playford MP, Mehta NN. Visceral but not subcutaneous adipose tissue associates with vascular inflammation by 18-FDG PET/CT in psoriasis. American Federation for Medical Research - Eastern Regional Meeting. Washington, DC; Apr. 2017.
- Dey AK, Joshi AA, Rivers JP, Chaturvedi A, **Chung JH**, Lerman JB, Aberra TM, Kabbany MT, Shukla P, Rana A, Rodante JA, Teague HL, Silverman JI, Harrington CL, Ng Q, Sanda GE, Sorokin AV, Baumer Y, Gelfand JM, Playford MP, Mehta NN. Improvement in cholesterol efflux capacity is associated with improvement in vascular inflammation by 18-FDG PET/CT in psoriasis. American Federation for Medical Research - Eastern Regional Meeting. Washington, DC; Apr. 2017.

Abstract Publications — Poster Presentations:

- Chung JH**, Dey AK, Lerman JB, Joshi AA, Rivers JP, Rana A, Rodante JA, Playford MP, Chen MY, Mehta NN. High Risk Coronary Plaque Characteristics Directly Associate with Psoriasis Severity over a 1-Year Period of Time. European Academy of Dermatology and Venereology Congress. Geneva, Switzerland; Sept. 2017.

Continued on the Next Page

- Rivers JP, Dey AK, **Chung JH**, Rana A, Chaturvedi A, Rodante JA, Lerman JB, Playford MP, Yao J, Chen MY, Bluemke DA, Powell-Wiley TM, Mehta NN. Visceral Adipose Tissue Associates with Coronary Plaque Burdens beyond Cardiovascular Risk Factors in Psoriasis. Arteriosclerosis, Thrombosis and Vascular Biology/Peripheral Vascular Disease. Minneapolis, MN; May 2017.
 - Dey AK, Rivers JP, **Chung JH**, Lerman JB, Joshi AA, Chaturvedi A, Kabbany MT, Rana A, Rodante JA, Teague HL, Harrington CL, Playford MP, Chen MY, Sandfort V, Bluemke DA, Mehta NN. Increased Vascular Inflammation Relates to Increased Prevalence of High Risk Coronary Plaque in Psoriasis. Translational and Molecular Imaging Institute Symposium. New York, NY; Apr. 2017.
 - **Chung JH**, Dey AK, Chaturvedi A, Rivers JP, Lerman JB, Harrington CL, Playford MP, Gordon SM, Remaley AT, Chen MY, Bluemke DA, Mehta NN. Lipid rich plaque by coronary CT angiography associates with cholesterol efflux capacity independent of traditional cardiovascular risk factors in those at risk for myocardial infarction. American Heart Association (AHA) EPI Lifestyle Scientific Session. Portland, OR; Mar. 2017.
 - Rivers JP, Dey AK, Chaturvedi A, **Chung JH**, Kabbany MT, Ahlman MA, Rodante JA, Joshi AA, Harrington CL, Playford MP, Yao J, Powell-Wiley TM, Mehta NN. Visceral adipose tissue but not subcutaneous adipose tissue associates with cholesterol efflux capacity in psoriasis. American Heart Association (AHA) EPI Lifestyle Scientific Session. Portland, OR; Mar. 2017.
 - Natarajan B, Chaturvedi A, Dey AK, **Chung JH**, Rivers JP, Rana A, Rodante JA, Teague HL, Silverman JI, Sanda GE, Sorokin AV, Baumer Y, Harrington CL, Lerman JB, Joshi AA, Playford MP, Mehta NN. Small dense low density lipoprotein particle number relates to coronary plaque burden independent of traditional cardiovascular risk factors in psoriasis. American College of Cardiology Scientific Session. Washington, DC; Mar. 2017.
 - Chaturvedi A, Lerman JB, Sandfort V, **Chung JH**, Dey AK, Rivers JP, Joshi AA, Rana A, Rodante JA, Teague HL, Silverman JI, Ng Q, Sanda GE, Harrington CL, Sorokin AV, Baumer Y, Gelfand JM, Playford MP, Ahlman MA, Bluemke DA, Mehta NN. Aortic vascular inflammation by 18-FDG PET/CT associates with high-risk coronary plaques in young psoriasis patients. American College of Cardiology Scientific Session. Washington, DC; Mar. 2017.
 - Rivers JP, Dey AK, Chaturvedi A, **Chung JH**, Kabbany MT, Ahlman MA, Rodante JA, Joshi AA, Harrington CL, Playford MP, Yao J, Powell-Wiley TM, Mehta NN. Visceral but not subcutaneous adipose tissue associates with vascular inflammation by 18-FDG PET/CT in psoriasis. American College of Cardiology Scientific Session. Washington, DC; Mar. 2017.
 - Joshi AA, Dey AK, Chaturvedi A, **Chung JH**, Rivers JP, Kabbany MT, Ahlman MA, Playford MP, Mehta NN. Improvement in cholesterol efflux capacity is associated with improvement in vascular inflammation by 18- FDG PET/CT in psoriasis. American College of Cardiology Scientific Session. Washington, DC; Mar. 2017.
 - Kabbany MT, Dey AK, Shukla P, Chaturvedi A, Rana A, Rivers JP, **Chung JH**, Joshi AA, Lerman JB, Aberra TM, Rodante JA, Teague HL, Silverman JI, Ng Q, Ahlman MA, Playford MP, Mehta NN. Improvement in cholesterol efflux capacity is associated with a reduction in aortic wall thickness by MRI independent of traditional CV risk factors. American College of Cardiology Scientific Session. Washington, DC; Mar. 2017.
 - Dey AK, Rivers JP, Chaturvedi A, **Chung JH**, Joshi AA, Lerman JB, Aberra TM, Kabbany MT, Rodante JA, Teague HL, Silverman JI, Sanda GE, Harrington CL, Sorokin AV, Baumer Y, Rana A, Gelfand JM, Playford MP, Mehta NN. Improvement In Vascular Inflammation By 18-FDG PET/CT Is Associated With Reduction In GlycA Levels At 1-Year In Psoriasis. Unraveling Vascular Inflammation: from Immunology to Imaging Symposium. Bethesda, MD; Oct. 2016.
 - Chaturvedi A, **Chung JH**, Dey AK, Rivers JP, Rana A, Playford MP, Gelfand JM, Herschovitch P, Ahlman MA, Mehta NN. Determinants of Vascular Inflammation Using [18F]-Fluorodeoxyglucose PET/CT: Findings from the Psoriasis, Atherosclerosis and Cardiometabolic Disease Initiative (PACI). Unraveling Vascular Inflammation: from Immunology to Imaging Symposium, Bethesda, MD; Oct. 2016.
- Travel to Professional Meetings:**
- Unraveling Vascular Inflammation: from Immunology to Imaging Symposium. Bethesda, MD; Oct. 2016.
 - American Heart Association (AHA) EPI Lifestyle Scientific Session; Portland, OR; Mar. 7-10, 2017.
 - American College of Cardiology Scientific Session, Washington, DC; Mar. 17-19, 2017.
 - American Federation for Medical Research, Eastern Regional Meeting Washington, DC; Apr. 18, 2017.
 - Arteriosclerosis, Thrombosis and Vascular Biology - Peripheral Vascular Disease, Minneapolis, MN; May 2017.
- Awards:**
- American Federation for Medical Research (AFMR) Scholar Award 2017.



Hannah M. Conn

School: Georgetown University School of Medicine

Mentor: Mark Hallett, M.D., Chief, Human Motor Control Section, Medical Neurology Branch

Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research: Exploring the Neurophysiology of Impaired Cortical Inhibition Relevant to Focal Hand Dystonia and Parkinson's Disease

The electroencephalography (EEG) response to transcranial magnetic stimulation (TMS) can be used to assess cortical physiology in human subjects. Motor surround inhibition (mSI) is a cortical phenomenon involved in fine motor tasks. Together with excitatory outputs from the primary motor cortex (M1), mSI actively inhibits neighboring areas of M1 that control adjacent muscles. This helps to produce precise movements. Short-interval intracortical inhibition (SICI) is a TMS measure of GABA-A receptor mediated cortical inhibition. A decrease in these inhibitory phenomena is implicated in patients with Parkinson's disease (PD) and focal hand dystonia (FHD) who have difficulty making precise movements.

The purpose of our study was to improve understanding of the underlying mechanisms of mSI and SICI as they apply to the neurophysiology of the cortical inhibitory circuits that are impaired in PD and FHD.

We investigated mSI and SICI in healthy volunteers using TMS applied over M1. We recorded TMS-evoked potentials (TEP) with EEG and measured the amplitudes of components at different latencies. A three-way ANOVA found a significant interaction between EEG region of interest (ROI) and TEP component ($p < 0.001$), as well as between condition (mSI, SICI) and TEP component ($p < 0.001$). Post-hoc analysis showed changes in the TEP curve at a time latency of 100 ms after the TMS pulse delivery in both mSI and SICI conditions. These preliminary results of TEP changes with movement suggest that GABA-B receptor mediated cortical inhibition is decreased at movement onset when surround inhibition is known to be greatest; similar changes are seen during SICI. We will be investigating a correlation between the magnitude of TEP components with the amount of mSI.

These results will help to further profile the mechanisms underlying these cortical phenomena which then can be applied to the study of movement abnormalities in PD and FHD.

Travel to Professional Meetings:

- American Academy of Neurology 2017 Annual Meeting, Boston, MA.



Sonia S. Gaur

School: Sidney Kimmel Medical College at Thomas Jefferson University

Mentor: Peter L. Choyke, M.D., Program Director, Molecular Imaging Program; Head, Imaging Section

Institute: National Cancer Institute (NCI)

Research: A Global Multi-Reader Investigation of Computer-Aided Diagnosis for Prostate Cancer Detection on Multiparametric Magnetic Resonance Imaging

Prostate cancer diagnosis has evolved with the advent of multiparametric MRI (mpMRI), which combines anatomical and functional data for optimal visualization of disease. Use of mpMRI and subsequent targeted biopsy has led to more accurate diagnosis of high-grade cancer, and less over-diagnosis of low-grade disease. Unfortunately, mpMRI suffers from limited standardized image acquisition (e.g. use of endorectal coil), a steep learning curve for interpretation, and inter-rater variability; in addition, 25% of high-grade index lesions are still missed on imaging. One potential solution is the use of computer-aided diagnosis (CAD) as an assist system to optimize reader performance. A CAD system for non-endorectal coil

prostate mpMRI was recently developed by our group.

The purpose of this study was to test broad application of this CAD system for prostate cancer diagnosis. Five institutions representing four countries provided a total of 216 patients (144 cases, 72 controls), imaged by mpMRI at three tesla, without endorectal coil. Images were distributed to nine readers representing six countries for interpretation in two read-out sessions. Images were first read in an mpMRI-only arm, and then after a four-week hiatus, a “first-reader design” was implemented in which readers identified suspicious lesions on each CAD map, and then could accept or reject these based on the corresponding mpMRI. To facilitate application of the CAD system to a multi-institutional setting, a series of pilot studies were performed to validate CAD performance.

Based on cross-validation with a non-endorectal coil training population, the CAD readings had an area under the curve (AUC) of 88%. The first pilot study showed 79% sensitivity on mpMRI alone, versus 65% sensitivity with CAD assistance ($p=0.18$). A subsequent pilot study showed 83% sensitivity with mpMRI alone, versus 87% sensitivity with CAD assistance. These results suggest reasonable detection of prostate cancer by CAD on non-endorectal coil images; the findings are being validated by an analysis of the multi-institutional data.

Full Length Publications:

- Mehralivand S, Bednarova S, Shih J, Mertan FV, **Gaur S**, Merino MJ, Wood BJ, Pinto PA, Choyke PL, Turkbey B. Prospective evaluation of prostate imaging-reporting and data system version 2 (PI-RADSv2) using the International Society of Urological Pathology (ISUP) prostate cancer grade group system. *J Urol*. 2017 Mar 31. doi: 10.1016/j.juro.2017.03.131. [Epub ahead of print]
- **Gaur S**, Turkbey B, Choyke PL. Hereditary renal tumor syndromes: Update on diagnosis and management. *Semin Ultrasound CT*. Oct. 2016. PMID: 28237281
- **Gaur S**, Turkbey B. Prostate MRI for post-treatment evaluation and recurrence. *Radiol Clin N Amer*. [In press]
- **Gaur S**, Mehralivand S, Choyke PL, Turkbey B. Role of magnetic resonance imaging in prostate cancer assessment. In: *Imaging and Focal Therapy of Early Prostate Cancer*, 2nd Edition, Polascik TJ (ed). Springer Publishing, Mar. 2017.
- **Gaur S**, Turkbey B, Choyke PL. Prostatic magnetic imaging principles. In: *Smith's Textbook of Endourology*, 4th Edition, Smith AD (ed). Wiley Publishing. Chapter 139. [In press]
- Calio B, Sidana A, Sugano D, **Gaur S**, Jain A, Maruf M, Xu S, Kruecker J, Merino MJ, Choyke PL, Turkbey B, Wood BJ, Pinto PA. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: evidence of a learning curve. *Prostate Cancer Prostatic Dis*. [In press]

Abstract Publications:

- **Gaur S**, Mehralivand S, Bednarova S, Calio BP, Sugano D, Mertan FV, Merino MJ, Choyke PL, Wood BJ, Pinto PA, Turkbey B. Comparison of PIRADSv2 and in-house system in detection of prostate cancer for subsequent MR/US fusion biopsy. Society of Interventional Radiology (SIR) - Interventional Oncology: Biopsy Scientific Session. Washington, DC; 2017. [Poster presentation]

- **Gaur S**, Lay N, Mertan FV, Merino MJ, Wood BJ, Pinto PA, Choyke PL, Summers RM, Turkbey B. Computer-aided diagnosis for bi-parametric non-ERC prostate MRI: Preliminary results of a multi-institutional study. Society of Abdominal Radiology - Genitourinary Scientific Session. Hollywood, FL; 2017. [Podium presentation]
- **Gaur S**, Mehralivand S, Bednarova S, Calio BP, Sugano D, Mertan FV, Merino MJ, Choyke PL, Wood BJ, Pinto PA, Turkbey B. Prospective comparison of PIRADSv2 and in-house system in detection of prostate cancer. Society of Abdominal Radiology - Genitourinary Scientific Session. Hollywood, FL; 2017. [Poster presentation]
- **Gaur S**, Lay N, Harmon S, Mehralivand S, Merino MJ, Wood BJ, Pinto PA, Choyke PL, Summers RM, Turkbey B. Computer-aided diagnosis for prostate cancer detection on non-endorectal coil prostate MRI: Pilot results of a multi-institutional study. Frontiers Conference of Biomedical Imaging Science. Nashville, TN; 2017. [Podium presentation]

Travel to Professional Meetings:

- Radiologic Society of North America, Chicago, IL; Nov. 27- Dec. 2, 2016.
- Society of Interventional Radiology, Washington, DC; Mar. 6-9, 2017.
- Society of Abdominal Radiology, Hollywood, FL; Mar. 26-31, 2017.
- Frontiers Conference of Biomedical Imaging Science, Nashville, TN; May 16-19, 2017.

Awards:

- Society of Abdominal Radiology Trainee Travel Award - Top Abstract Submitted.
- Frontiers Conference of Biomedical Imaging Science - Best Oral Presentation Award.



Vissagan Gopalakrishnan

School: Rush Medical College of Rush University Medical Center

Mentor: Joel Moss, M.D., Ph.D., Deputy Branch Chief, Laboratory of Translational Research and Senior Investigator, Cardiovascular and Pulmonary Branch

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Computer Tomographic-based Detection of Lung Parenchymal Changes Surrounding Cysts in Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a multisystem disease characterized by cystic lung destruction that primarily affects women. Treatment with sirolimus decreases the rate of decline in lung function and slows changes in lung volume occupied by cysts. There are limited longitudinal data on the effect of sirolimus on the degradation of lung parenchyma surrounding cysts. Thus, we determined whether computational analysis of high resolution CTs (HRCT) is capable of quantifying lung parenchymal changes in LAM.

Texture properties are established mathematical calculations used to quantify the distribution and intensity of pixels. A computer-aided diagnostic system reports 26 different values (texture properties), falling under three broader categories (histogram, co-occurrence matrix, and run length measures), that highlight different aspects of pixel arrangement and signal strength.

Thirty-five patients with LAM were evaluated in a longitudinal study to determine the effect of sirolimus treatment on changes in texture around cysts over time. Two hundred seventy-four HRCTs were collected both prior to and during treatment. Of 26 texture properties, the rate of change in 9 properties was significantly different ($p < 0.05$) after starting treatment, and demonstrated a $97 \pm 4.4\%$ decrease in rate of change after treatment was initiated. Lower FEV1 and DLCO findings were associated with greater degradation of texture around cysts ($p < 0.0001$) in all 9 texture properties. Notably, none of the 9 texture properties identified were histogram measures. Histogram measures are the only set of texture properties calculated exclusively based on pixel intensity, without incorporation of spatial information. We conclude that the use of spatial information in calculating texture is essential to computing values that reflect lung changes.

Overall, our findings show that certain texture properties are sensitive to changes in lung parenchyma surrounding cysts in LAM and correlate with pulmonary function. Clinically, these texture properties could serve as additional markers of disease status.



Daniel J. Gromer

School: The Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania

Mentor: Warren J. Leonard, M.D., NIH Distinguished Investigator; Chief, Laboratory of Molecular Immunology

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Divergent Roles of Interleukin-2 and Interleukin-21 in CD8⁺ T Cell Metabolism

CD8⁺ T cells defend the host against viral infections and cancers via multiple mechanisms, including cytolytic killing and the release of soluble mediators. Mounting evidence indicates a crucial role for cell metabolism in the control of inflammation and the performance of these functions. Interleukin-2 (IL2), a therapeutically important, pleiotropic type I cytokine that drives T cell proliferation and promotes regulatory T cell differentiation, is known to profoundly alter T cell metabolism. In contrast, the metabolic role of interleukin-21 (IL21), a related cytokine shown to contribute to follicular helper T cell differentiation and improve anti-tumor defense by CD8⁺ T cells, remains unexplored.

Here, we investigated the comparative effects of IL2 and IL21 on mouse splenic CD8⁺ T cell metabolism. When T cell receptor pre-activated CD8⁺ T cells were stimulated with IL21 instead of IL2, we found by RNA sequencing that IL21 induced lesser expression of genes related to hypoxia and glycolysis. Stimulation with IL2 or IL21 resulted in major differences in mitochondrial structure, as revealed by electron microscopy. IL21-treated cells, which we showed to be metabolically relatively quiescent using extracellular flux analysis, displayed an increase in spare respiratory capacity after blockade of fatty acid oxidation (FAO). The novel response to FAO inhibition could be abrogated or recapitulated with the addition of drugs that alter pyruvate and lactate transport, respectively, indicating that this phenomenon depends on the fate of pyruvate.

These data suggest that IL2 and IL21 differentially regulate the metabolic outcomes of glycolysis, and that manipulating pyruvate flux may impact the therapeutic efficacy of CD8⁺ T cells.

Travel to Professional Meetings:

- Association of American Physicians/American Society for Clinical Investigation/American Physician Scientist Association Joint Meeting. Chicago, IL; Apr. 21-23, 2017.
- Fundamental Immunology and Its Therapeutic Potential. Cold Spring Harbor Laboratory, NY; Apr. 25-29, 2017.
- Immunology 2017, American Association of Immunologists Annual Meeting. Washington, DC; May 12-16, 2017.



Alex F. Grubb

School: Cleveland Clinic Lerner College of Medicine at Case Western Reserve University

Mentor: Manfred Boehm, M.D., Division of Cardiovascular Sciences, Laboratory of Cardiovascular and Regenerative Medicine

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: The Role of CD73 in Monocytes and Macrophages and Functional Consequences of Deficiency

Arterial calcification due to CD73 deficiency (ACDC) is an inherited disorder resulting from mutations in the *NT5E* gene encoding the CD73 5' nucleosidase, which converts adenosine-monophosphate (AMP) to adenosine. Patients develop severe obstructive peripheral arterial disease due to significant medial calcification of the arteries. Little is known about the role of CD73 in human macrophages and the cellular consequences of its deficiency.

Primary human monocytes were isolated from whole blood in 5 healthy controls and 5 ACDC patients, and the cells were allowed to differentiate into macrophages *in vitro*. Cells were analyzed for mRNA, protein expression, 5' nucleosidase activity, and cytokine secretion using qPCR, flow cytometry, liquid chromatography mass spectrometry, and Luminex cytokine array.

CD73 is expressed in low levels on macrophages (6.5% \pm 4.5) and neither expression nor activity is significantly changed with polarization to the M1 or M2 phenotype. When challenged with exogenous AMP, ACDC macrophages retain the same ability to metabolize AMP to adenosine compared to controls ($p=.75$). Addition of a CD73 inhibitor has little effect on ACDC macrophage 5' nucleosidase activity ($p=.3768$), while significantly inhibiting control macrophage activity ($p=.0137$). Addition of levamisole, an inhibitor of tissue non-specific alkaline phosphatase (TNAP), eliminates adenosine generation after AMP addition in ACDC macrophages ($p=.0012$) but not in control cells ($p=0.121$). Correspondingly, there is increased TNAP mRNA expression in ACDC macrophages. There was little difference in cytokine secretion profiles of ACDC and control macrophages after polarization to M1 or M2. When simulating the resolution of an inflammatory response, ACDC cells demonstrated sustained and increased secretion of pro-inflammatory cytokines such as IFN γ , IL1 β , and MIP1 β .

These data indicate that CD73 plays a minor role in the extracellular AMP metabolism of monocytes and macrophages. There is little difference in the activation and polarization of CD73-deficient macrophages. ACDC cells lacking CD73 can compensate for its loss, likely through the upregulation of TNAP.

Abstract Publications:

- **Grubb A**, Dmitrieva NI, Walts A, Chen G, Zhang X, Wang X, Freeman AF, Holland SM, Boehm, M. Hypoxia inducible factor 1 α stabilization in autosomal dominant Hyper IgE Syndrome fibroblasts rescues impaired ability to support angiogenesis. Atherosclerosis Thrombosis and Vascular Biology. Minneapolis, MN; May 4-6, 2017.
- Dmitrieva NI, Walts A, Chen G, **Grubb A**, Zhang X, Wang X, Freeman AF, Holland SM, Boehm, M. Studies of mechanisms involved in autosomal dominant Hyper-IgE Syndrome: hypoxia inducible factor 1 α stabilization as a possible therapy option for impaired ability to support angiogenesis. 4th Translational Medicine Conference on Pathogenesis and Therapy of Immune-Mediated Diseases. Palermo, Italy; Mar. 27-29, 2017.

Travel to Professional Meetings:

- Atherosclerosis Thrombosis and Vascular Biology, Minneapolis, MN; May 4-6, 2017.
- Immune Regulation in Cancer and Autoimmunity, Keystone Symposia. Whistler, BC, Canada; Mar. 26-30, 2017.



Kathryn O. Harris

School: Meharry Medical College

Mentor: Michael N. Sack, M.D., Ph.D., Senior Investigator, Laboratory of Mitochondrial Biology and Metabolism

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: A Randomized Controlled Trial to Evaluate the Effects of Nicotinamide Riboside on Immunity in Healthy Human Subjects

Atherosclerosis and type 2 diabetes are associated with sterile inflammation that exacerbates vascular injury and insulin resistance. Upon activation of the immune system with damage-associated molecular patterns (DAMPs), NOD-like receptor family pyrin domain containing 3 (NLRP3) increases the production and release of pro-inflammatory cytokines in the interleukin 1 family, including IL1 β and IL18 from macrophages and other myeloid cell lines. The link between metabolic diseases and the immune system raises the question of whether caloric restriction activates pathways which may suppress the NLRP3 inflammasome. Fasting and caloric restriction improve mitochondrial integrity, in part via activation of sirtuin protein, and

blunt systemic inflammation. Nicotinamide riboside (NR), a naturally occurring form of vitamin B3, has been found to activate Sirt3, a fasting sensing mitochondrial sirtuin protein. The purpose of this study was to evaluate whether pharmacologic activation of Sirt3 by nicotinamide riboside, via enhancing mitochondrial integrity, will blunt sterile-inflammation linked NLRP3 inflammasome activation.

We are conducting a prospective, randomized, double-blinded, crossover placebo-controlled trial of 58 healthy human subjects to explore whether NR administration will blunt the NLRP3 activation of feeding in healthy subjects.

Preliminary data in the first 12 study subjects reveal two distinct patterns of IL1 β secretion after activation of monocytes with ATP, which confirm the study's hypothesis. The expected increase in IL1 β release with refeeding has been seen in one arm of all the subjects; however, there is a blunted increase in IL1 β levels in the opposing arm, which suggests that NR modulates IL1 β secretion. TNF α secretion follows a similar trend.

These preliminary data suggest that: there is (i) a blunted effect of inflammation through the NLRP3 pathway due to administration of NR in vivo and (ii) a blunted effect of TNF α increase with NR administration which suggests a broader effect on the inflammatory pathway.



Therese S. Korndorf

School: University of Illinois College of Medicine Peoria

Mentor: Heidi H. Kong, M.D., Investigator, and Keisuke Nagao, M.D., Ph.D., Stadtman Investigator; Dermatology Branch.

Institute: National Cancer Institute (NCI)

Research: Hidradenitis Suppurativa-Like Lesions Associated with Pharmacologic Inhibition of Gamma-Secretase

Hidradenitis suppurativa is a chronic skin disease characterized by follicular occlusion that presents as painful nodules and abscesses in apocrine gland-rich areas, such as the axillae, buttocks, medial thighs, and groin. While the molecular details of pathogenesis remain unclear, familial hidradenitis suppurativa is primarily associated with mutations in gamma-secretase (GS), a protease complex. Notably, conditional GS knockout mice develop abnormalities in the hair follicle, supporting a role for GS and its downstream signaling target, Notch, in maintenance of the pilosebaceous unit. However, it remains to be seen whether GS-dependent follicular pathology arises early in hair follicle development, occurs as a puberty-dependent process, or can be reproduced in adult skin simply by inhibiting GS function.

dependent process, or can be reproduced in adult skin simply by inhibiting GS function.

We investigated skin findings in a cohort of 17 adults receiving a targeted GS inhibitor in a Phase II trial to treat desmoid tumors/aggressive fibromatosis. We found that the majority of patients (86%) reported skin adverse events during treatment, most frequently follicular and cystic lesions in intertriginous locations (axilla, inguinal crease, labia, buttocks, medial thigh). Of the 17 patients, 71% had CTCAE (v4.0) grade 1 or 2 skin adverse events. The involvement of sites commonly afflicted by hidradenitis suppurativa links GS loss of function to disease pathogenesis. Moreover, our results suggest that the emergence of hidradenitis suppurativa-like lesions does not require GS insufficiency in development or puberty, but rather can be recapitulated in developmentally normal skin with pharmacologic inhibition of GS.

Full Length Publications:

Publications are under her future legal last name Woodring

- O'Sullivan Coyne G*, **Woodring T***, Chen A, Kong H. Hidradenitis suppurativa-like lesions associated with pharmacologic inhibition of gamma-secretase. [Submitted]
- Nagao K, Kitashima D, Kobayashi T, **Woodring T**, Idouchi K, Ouchi T, et al. Langerhans cells prevent autoimmunity via expansion of keratinocyte antigen-specific regulatory T cells. [Submitted]
*co-first author

Travel to Professional Meetings:

- Society For Investigative Dermatology 76th Annual Meeting. Portland, OR; Apr. 26-29, 2017.

Abstract Publications:

- **Woodring T**, O'Sullivan Coyne G, Chen A, Kong H. Dermatologic toxicity associated with chronic gamma-secretase inhibitor treatment for desmoid tumor. Society For Investigative Dermatology 76th Annual Meeting. Portland, OR; Apr. 26-29, 2017. *J Invest Dermatol* 137(S5): S52.
- Kobayashi T, Truong A, Shih H, Doebel T, Voisin B, **Woodring T**, Sohn S, Kennedy E, Jo J, Moro K, Leonard W, Kong H, Nagao K. Spatial heterogeneity and functional diversity of innate lymphoid cells in the skin. Society For Investigative Dermatology 76th Annual Meeting. Portland, Oregon; Apr. 26-29, 2017. *J Invest Dermatol* 137(S5): S104.



Ira L. Kraft

School: University of Utah School of Medicine

Mentor: Brigitte Widemann, M.D.; Jack Shern, M.D.; John Glod, M.D./Ph.D., Center for Cancer Research, Pediatric Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Outcomes and Mechanisms of Disease Progression in MEN2B Patients with Advanced Metastatic Medullary Thyroid Carcinoma Treated with Vandetanib

Childhood medullary thyroid carcinoma (MTC) generally arises from a germline mutation in the *RET* proto-oncogene. Children with advanced MTC are treated with *RET*-targeting inhibitors such as vandetanib. We sought to characterize outcomes, vandetanib tolerability, patterns of disease progression, and clonal evolution of childhood MTC. We monitored toxicities, disease burden, and natural history of patients taking vandetanib for advanced MTC (NCT00514046, NCT01660984). Where feasible, germline/tumor samples were analyzed by genome and transcriptome sequencing.

Seventeen patients [8 male; 13 (9-17)* years] enrolled; 16 had a *RET* p.M918T germline mutation. Patients received vandetanib for 5.5 (0.1-9.2+)* years. Treatment is ongoing in 8 patients. Best response was partial response in 10, stable disease in 6, and progressive disease in 1 patient. Response duration was 5.1 (0.6-8.6+)* years. Six patients died from disease 2.1 (0.4-4.3)* years after stopping vandetanib. Progression free survival was 6.2 years (95% CI 3.0-na) and overall survival was 7.9 years (95% CI 5.9-na). No patients discontinued vandetanib for toxicity.

Panel DNA sequencing (12 samples, 7 patients) identified a change in DNA copy number (CN) from 10.1±1.9% in primary tumors to 29.7±9.4% in metastatic lesions ($p = 0.002$) and a somatic *RET* p.L790F mutation as potential mechanisms of disease progression. Whole exome and transcriptome sequencing of sequential tumors from one patient (4 samples) confirmed accumulation of CN aberrations over time and showed genome-wide changes in RNA expression. Whole exome and genome sequencing was also used to examine clonality of MTC tumors (7 samples, 2 patients). Evolutionary models, k-means, and hierarchical clustering predicted relationships between lesions within individual patients, and suggest that some lesions may be new primary tumors rather than metastatic MTC.

We found that vandetanib is safe and results in sustained responses in children with advanced MTC. We propose that genomic instability may have a role in MTC progression and suggest that some lesions may be new primary tumors rather than MTC metastases.

*median (range)

Abstract Publications:

- **Kraft IL***, Akshintala S*, Killian KJ, Hufnagel RB, Glod JW, Zhu Y, Stevenson H, Derse-Anthony C, Bradford D, Merino MJ, Balis FM, Fox E, Widemann BC, Shern JF, Meltzer PS. Genomic mechanisms of disease progression in pediatric medullary thyroid cancer (MTC). American Association for Cancer Research (AACR) Annual Meeting, Washington, DC; Apr. 1-5, 2017.
- Del Rivero J, Fontana JR, Bradford D, Derse-Anthony C, **Kraft IL**, Madan RA, Lodish MB, Widemann BC, Glod JW. Characterization of pulmonary function in patients with multiple endocrine neoplasia type 2B. Endocrine Society Annual Meeting. Orlando, FL; Apr. 1-4, 2017.
- **Kraft IL***, Gross A*, Akshintala S, Bradford D, Killian KJ, Lei H, Zhu Y, Stevenson H, Bednarova S, Turkbey B, Derse-Anthony C, Merino MJ, Waguespack SG, Meltzer PS, Widemann BC, Shern JF, Glod JW. Clinical and genomic characterization of prostate lesions in multiple endocrine neoplasia 2B. American Society for Pediatric Hematology and Oncology. Montreal, Canada; Apr. 26-29, 2017.
- **Kraft IL***, Akshintala S*, Derse-Anthony C, Steinberg SM, Venzon DJ, Dombi E, Waguespack SG, Kapustina O, Fox E, Balis FM, Shern JF, Glod JW, Widemann BC. Outcomes of children with hereditary medullary thyroid carcinoma treated with vandetanib. American Society for Clinical Oncology (ASCO). Chicago, IL; June 1-6, 2017.
*Equal contribution

Travel to Professional Meetings:

- Rare Tumors Initiative Symposium, National Institutes of Health, Bethesda, MD; Oct. 6-7, 2016 *Participated in the Clinical Trials Study Section.
- American Association for Cancer Research, Washington, DC; Apr. 1-5, 2017.
- American Society for Pediatric Hematology and Oncology Annual Meeting, Montreal, Canada; Apr. 26-29, 2017.
- American Society for Clinical Oncology, Chicago, IL; June 1-6, 2017.

Awards:

- Best Student/Post-Bac Poster: Pediatric Oncology Branch Annual Research Round-Up.



Daniel L. Kuhr

School: Jacobs School of Medicine and Biomedical Sciences, University at Buffalo
Mentor: Enrique F. Schisterman, Ph.D., Chief and Senior Investigator, Epidemiology Branch, Division of Intramural Population Health Research
Institute: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Research: Vitamin D and the Bioavailability of Androgens

Prior studies are mixed regarding relationships between vitamin D, androgens, and sex hormone binding globulin (SHBG) in patients with polycystic ovary syndrome (PCOS). However, less is known regarding associations in healthy premenopausal women. Our objective was to assess the relationship between vitamin D, androgens, SHBG, other hormonal markers, and anovulation in a cohort of healthy, regularly cycling women with proven fecundity.

This was a secondary analysis of the EAGeR trial (2006-2012), a prospective cohort study which followed women for anovulation for up to 2 cycles. Serum vitamin D (25-hydroxyvitamin D), and hormone concentrations were measured at baseline. 1191 participants, aged 18-40, were attempting to conceive; they had a history of 1-2 documented prior pregnancy losses and no history of infertility. Baseline concentrations of total and free testosterone, free androgen index (FAI), SHBG, dehydroepiandrosterone sulfate (DHEAS), and sporadic anovulation were all the main outcome measures.

Vitamin D was negatively associated with FAI (β -coefficient [95% confidence interval]: -0.05 [-0.08, -0.02] per 10 ng/mL increase), and positively associated with SHBG (0.04 [0.02, 0.07]), though not with total or free testosterone and DHEAS after adjusting for age, body mass index, smoking, race, income, exercise, season, and treatment arm. Vitamin D was not associated with the risk of anovulation (RR [95% CI]: 1.04 [0.94, 1.15]).

Overall, vitamin D was associated with SHBG and FAI in healthy, premenopausal women, suggesting that vitamin D may play a critical role in SHBG homeostasis and, consequently, the bioavailability of androgens in healthy women.

Full Length Publications:

- Sjaarda LA, Radin RG, Swanson C, **Kuhr DL**, Mumford SL, Galai N, Silver RM, Wactawski-Wende J, Perkins NJ, Schisterman EF. Prevalence and contributors to low-grade inflammation in three U.S. populations of reproductive age women. *Paediatr Perinat Epidemiol*. [In press]
- **Kuhr DL**, Alkhalaf Z, Sjaarda LA, Kim K, Omosigbo UR, Perkins NJ, Silver RM, Schisterman EF, Holland TL, Mumford SL. Vitamin D is associated with bioavailability of androgens in healthy women attempting pregnancy. [In review]
- Sjaarda LA, Mumford SL, **Kuhr DL**, Holland T, Plowden TC, Perkins NJ, Schisterman EF. Association of higher androgen and anti-Müllerian hormone with fecundability: a study of PCOS-related endocrine markers in fecund women attempting pregnancy. [In review]
- Connell MT, Sjaarda LA, Radin RG, **Kuhr DL**, Mumford SL, Plowden TC, Silver RM, Schisterman EF. EAGeR Trial: A Story of Discovery. [In review]

Abstract Publications:

- **Kuhr DL**, Sjaarda LA, Kim K, Omosigbo UR, Perkins NJ, Silver RM, Schisterman EF, Holland TL, Mumford SL. Vitamin D and bioavailability of androgens in women with proven fecundity. Society for Pediatric and Perinatal Epidemiologic Research. Seattle, WA; June 2017. [Poster]
- Mumford SL, **Kuhr DL**, Sjaarda LA, Kim K, Omosigbo UR, Silver RM, Perkins NP, Holland TL, Schisterman EF. Vitamin D and anovulation in women with proven fecundity. Society for Pediatric and Perinatal Epidemiologic Research. Seattle, WA; June 2017. [Oral presentation]

- Sjaarda LA, Mumford SL, **Kuhr DL**, Holland TL, Silver RM, Plowden TC, Perkins NJ, Schisterman EF. Association of higher androgen and anti-Müllerian hormone with fecundability: a study of PCOS-related outcomes in fecund women attempting pregnancy. Society for Pediatric and Perinatal Epidemiologic Research. Seattle, WA; June 2017. [Oral presentation]
- Holland TF, Sjaarda LA, **Kuhr DL**, Omosigbo UR, Perkins NJ, Schisterman EF. Large scale placental tissue collection procedures for epidemiologic studies. Society for Pediatric and Perinatal Epidemiologic Research. Seattle, WA; June 2017. [Poster]
- Omosigbo UR, Kim K, **Kuhr DL**, Plowden TC, Connell MT, Sjaarda LA, Schisterman EF, Galai N, Perkins NJ, Holland TL, Mumford SL. Maternal preconception vitamin D and neonatal outcomes. Society for Pediatric and Perinatal Epidemiologic Research. Seattle, WA; June 2017. [Poster]

Travel to Professional Meetings:

- American Medical Association Interim Meeting, Orlando, FL; Nov 2016.
- Society for Pediatric and Perinatal Epidemiologic Research, Seattle, WA; June 2017.



Clare C. Landefeld

School: Cleveland Clinic Lerner College of Medicine at Case Western Reserve University

Mentor: David Goldman, M.D., Section of Human Neurogenetics

Institute: National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Research: Short Tandem Repeat Variants at the Vasopressin Receptor 1a Gene are Associated with Externalizing Behavior

Vasopressin is an ancient multifunctional neuropeptide whose many effects are mediated by the varied distribution of its three distinct receptors. Short tandem repeat (STR) polymorphisms in the flanking region of the vasopressin receptor 1a (*AVPR1a*) gene have attracted interest in social neuroscience due to their association with altered *AVPR1a* expression in the brain and with a number of social behaviors including pair-bonding, altruism, and aggression. The RS1 STR is a tetranucleotide repeat situated upstream from the transcription start site. Shorter RS1 alleles are associated with autism, lower *AVPR1a* promoter activity, and increased amygdala activation. Here, we investigated whether the RS1 alleles are associated with externalizing behaviors in subjects with history of violent crime, and in non-psychiatric controls.

The sample consisted of 311 Finns: 127 were incarcerated criminal offenders with severe externalizing behaviors, and 184 were population controls. The RS1 STR was genotyped by size with an ABI 3730 Capillary Sequencer, using primers that equivalently amplified the various RS1 alleles. Gene effects on externalizing behaviors were tested in logistic regression models and chi-square analyses.

7 RS1 alleles were detected with lengths ranging from 306 to 330 bp (9 to 15 repeats). In a logistic regression model controlling for gender, the RS1 STR was significantly associated with violent offending ($p=0.003$). The short (306) allele was associated with an increased prevalence of violent offending in a dose-dependent manner (Odds Ratios (95% Confidence Intervals) for subjects with one and two copies of the 306 allele respectively: 2.04 (1.20, 3.50) and 5.12 (1.38, 24.2)).

Variation in the number of repeats of the RS1 allele, particularly the presence or absence of the short 306 bp allele, may contribute to aggression. This effect may be due to altered expression of the *AVPR1a* gene in different regions of the brain, a hypothesis we are currently testing.

Abstract Publications

- Landefeld CC, Spagnolo P, Hodgkinson C, Shen P, Goldman D. Variation in short tandem repeats of vasopressin receptor 1a are associated with violent offending. ASCI/AAP/APSA Joint Meeting. Chicago, IL; Apr. 2017.
- Landefeld CC, Spagnolo P, Schwandt M, Goldman D. Vasopressin (AVP) gene modulates risk of alcohol dependence via effects on stress and anxiety. Society for Biological Psychiatry Annual Scientific Program and Convention. San Diego, CA; May 2017.

Travel to Professional Meetings:

- AAP/ASCI/APSA Joint Meeting, Chicago, IL; Apr. 21-23, 2017.
- Society for Biological Psychiatry, San Diego, CA; May 18-20, 2017.



John M. Le

School: University of Michigan School of Dentistry

Mentor: Janice S. Lee, D.D.S., M.D., M.S., Clinical Director and Chief, Craniofacial Anomalies and Regeneration Section

Institute: National Institute of Dental and Craniofacial Research (NIDCR)

Research: *In Vivo* Analysis of Stromal Cell Osteogenic Capacity in a Murine Model

Bone regenerative capacity decreases with age, and the aging microenvironment may alter the differentiation pathway of multipotent bone marrow stromal cells (BMSCs) that reside in the marrow niche. As a result, the ability for bone to heal and regenerate in an aged individual is impaired. The purpose of our study was to define the role of aging on the osteogenic potential of human BMSCs (hBMSCs) coupled with an osteoconductive scaffold within a variable age murine model.

Six hBMSC cell lines were used for the *in vivo* transplantation assay. The hBMSCs were from skeletally growing and skeletally mature subjects. Mean age of young and old donors was 16 (range 12-19) and 46 (range 38-55) years. Primary cell lines were expanded and at 80% confluence, hBMSCs were combined with hydroxyapatite and tricalcium phosphate particles and loaded into either a 12-well Teflon combinatorial cassette (n=4 per cell line) or directly transplanted into subcutaneous dorsal pockets in young (6-10 weeks) and old (32-36 weeks) immunocompromised mice (n=4 transplants per cell line). Transplants were harvested at 8 weeks for analysis of bone formation.

Four cell lines are analyzed to date, consisting of 2 transplants per cell line (n=8) derived from young and old donor mice. Utilizing BIOQUANT® Osteo software, transplants retrieved from younger animal recipients demonstrated a mean (\pm SD) percentage of bone formation volume to total transplant volume of $9.63 \pm 7.65\%$, vs $2.54 \pm 1.62\%$ in transplants harvested from older animals, regardless of the age of the donor cells. Results are pending from the remaining transplants and the 12-well combinatorial cassette transplants. RNA was extracted from the transplants for genomic sequencing.

These preliminary findings demonstrate that the marrow microenvironment contributes to the osteogenic capacity of hBMSCs, regardless of the age of the donor cells. Our results should contribute to the development of bone tissue engineering modalities for restoration and reconstruction of the skeletal complex in the aging niche.



Melissa A. Levoska

School: Wayne State University School of Medicine

Mentor: Kenneth H. Kraemer, M.D., Chief, and John J. DiGiovanna, M.D., Senior Research Physician; DNA Repair Section, Laboratory of Cancer Biology and Genetics

Institute: Center for Cancer Research (CCR), National Cancer Institute (NCI)

Research: Deep Phenotyping of Patients with Xeroderma Pigmentosum and Trichothiodystrophy

Xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and XP/TTD are rare autosomal recessive diseases that can be caused by mutations in the same gene, *XPD (ERCC2)*, a DNA repair/transcription helicase. XP and TTD are associated with multi-system clinical abnormalities and increased mortality. Even though both XP and TTD patients are photosensitive, XP patients have a 10,000-fold increased risk of skin cancer while TTD patients do not. XP/TTD patients have features of both diseases. We performed “deep phenotyping” followed by statistical analysis to gain insights into the relationship between molecular defects and clinical phenotypes and to determine the features most associated with reduced survival.

We gathered clinical information from multidisciplinary NIH visits and outside medical records, and assembled a cohort of 67 patients (30 XP, 13 XP/TTD, and 24 TTD) with mutations in the *XPD (ERCC2)* gene. For each patient, we entered 299 clinical and laboratory variables into a database. Hierarchical clustering and principal component analysis (PCA) successfully separated patients according to their previously assigned clinical diagnoses and survival status. Sun burning and blistering were features that clustered among XP and XP/TTD patients. Hair abnormalities, decreased hair sulfur content, abnormal growth, and failure to thrive clustered among TTD and XP/TTD patients. TTD patients had reduced survival compared to XP ($p < 0.0001$) or XP/TTD patients ($p = 0.003$). Median XP survival was 42.9 years compared to 32.3 years for XP/TTD patients and to 15 years for TTD patients. Using PCA, we determined that cataracts, cryptorchidism and peripheral osteopenia were features associated with reduced survival among TTD patients ($p = 0.02, 0.01, 0.047$, respectively).

Deep phenotyping with statistical analysis can identify important phenotypic differences that may improve clinical diagnosis, predict disease prognosis, and guide treatment for patients with complex disorders.

Full Length Publications:

- **Levoska MA**, Nicholson CL, Hamzavi IH. A retrospective review of light- and laser-based management of hidradenitis suppurativa. *Semin Cutan Med Surg* 2017; 36(2):67-74.
- **Levoska MA**, Cohen JI, Manoli I, Lee CR, Ching SST, Shand J, Tamura D, Kraemer KH, DiGiovanna JJ. Recurrent scarring papulovesicular lesions on sun-exposed skin in a 22-year-old man. *J Am Acad Dermatol*. [Submitted]
- **Levoska MA**, Mohammad TF, Hamzavi IH. Lasers in pigmentary disorders. In: *Pigmentary Skin Disorders*, P. Kumarsinghe ed., Springer. [In Press, publication date Nov. 2017]

Abstract Publications:

- **Levoska M**, Pugh J, Bembry R, Hanona P, Khan SG, Heller ER, Nelson G, Scheibye-Knudsen M, Tamura D, DiGiovanna JJ, Kraemer KH. Deep phenotyping of patients with xeroderma pigmentosum and trichothiodystrophy. *J Invest Dermatol* 2017; 137(5): S46. Society of Investigative Dermatology Annual Meeting. Portland, OR; Apr. 28, 2017.
- **Levoska MA**, Pugh JM, Nelson G, Bembry R, Hanona PF, Tamura D, Khan SG, Heller ER, Scheibye-Knudsen M, DiGiovanna JJ, Kraemer KH. Using principal component analysis to determine phenotypic differences in patients with mutations in the *XPD (ERCC2)* gene. American Academy of Dermatology Annual Meeting. Orlando, FL; Mar. 3-7, 2017. [Invited discussant]
- **Levoska MA**, Cohen JI, Manoli I, Lee CR, Ching SST, Shand J, Tamura D, Kraemer KH, DiGiovanna JJ. A 22-year-old male with hydroa vacciniforme and chronic active Epstein Barr virus infection. American Academy of Dermatology Annual Meeting. Orlando, FL; Mar. 3-7, 2017. [Invited discussant]

Travel to Professional Meetings:

- Laboratory of Cancer Biology and Genetics (LCBG) and Women’s Malignancies Branch (WMB) Scientific Retreat, Rockville, MD; May 4-5, 2017. Presented poster on Deep Phenotyping Study.
- Society of Investigative Dermatology Annual Meeting, Portland, OR; Apr. 26-29, 2017.
- American Academy of Dermatology Annual Meeting, Orlando, FL; Mar. 3-7, 2017.



Jeffrey Lin

School: David Geffen School of Medicine at UCLA

Mentor: Andrea Apolo, M.D., Chief, Bladder Cancer Section; NIH Lasker Clinical Research Scholar, Genitourinary Malignancies Branch

Institute: National Cancer Institute (NCI)

Research: Combined Fludeoxyglucose (FDG) and Sodium Fluoride (NaF) Positron Emission Tomography/Computed Tomography (PET/CT) Study in Patients with Metastatic Genitourinary Tumors (mGU) Treated with Cabozantinib + Nivolumab +/- Ipilimumab

18F-NaF PET/CT has reemerged as a valuable imaging method for detecting osseous metastasis, and 18F-FDG PET/CT is well-established to detect metastatic disease, particularly soft tissue disease. These scans are typically done on separate days to clear the radiotracer; however, there are data to support the clinical utility of obtaining both scans sequentially on the same day.

We conducted a single-arm, multicenter, phase I trial of cabozantinib, ipilimumab, and/or nivolumab in patients with mGU. Patients had a FDG PET/CT followed within 1-hour by a NaF PET/CT at baseline and at 8 weeks. We captured the number and location of metastatic lesions on FDG and on combined FDG/NaF. The concordance of bone disease was compared between the FDG and combined FDG/NaF scans.

49 patients with mGU had combined FDG/NaF scans. Median age of subjects was 58 years and 85% were male. 784 lesions were detected on the FDG scans with the majority found in bone (29.5%), lymph node (29.2%) and lung (27.7%). A patient-based analysis revealed that of the 49 patients, the majority of patients had lymph node (77.8%), lung (46.7%), and bone (35.6%) disease. For the combined FDG/NaF scans, 396 lesions were detected, with the majority of lesions found in the spine (27%) and rib (26%). A concordance analysis analyzing how well FDG or NaF could detect metastatic bone disease found that of 405 lesions analyzed, FDG detected 62% of the lesions, and NaF detected 94% of the lesions.

Combination FDG/NaF scans adequately detected metastatic disease in mGU patients treated with targeted therapy and immunotherapy. Most lesions were found in bone, lymph node, and lung, and most bone lesions were found in the spine and rib. NaF detected more bony lesions than FDG alone. There were no instances of where the uptake from the prior FDG scan affected the determination of metastatic disease in the sequential NaF scan.

Abstract Publications:

- Lin J, et al. Assessing bone response to cabozantinib in patients with metastatic urothelial carcinoma using 18 F-Sodium Fluoride PET/CT. *J Clin Oncol*; 2017 Feb. 16-18; Orlando, FL: Genitourinary ASCO; Abstract 328.
- Lin J, et.al. Combined FDG and NaF PET/CT study in patients with metastatic genitourinary tumors treated with cabozantinib and nivolumab +/- ipilimumab (CaboNivo+/-Ipi). *J Clin Oncol*; 2017 June 2-6; Chicago, IL; American society for Clinical Oncology (ASCO); Abstract 16017.
- Civelek AC, et al. FDG PET-MRI in the management of patients with muscle invasive bladder cancer. *J Nucl Med*; 2017 June 10-14; Denver, CO; Society of Nuclear Medicine and Molecular Imaging (SNMMI). Abstract 753.
- Merna E, et al. Value of combined 18F-FDG/18F-NaF PET/CT in tumor detection and therapy response in patients with advanced bladder cancer treated with cabozantinib plus nivolumab alone or in combination with ipilimumab. *J Nucl Med*; 2017 June 10-14; Denver, CO; Society of Nuclear Medicine and Molecular Imaging (SNMMI); 2017. Abstract 754.

Travel to Professional Meetings:

- Genitourinary Cancers Symposium; Orlando, FL; Feb. 16-18, 2017.
- American Association of Neurological Surgeons Annual Scientific Meeting, Los Angeles, CA; Apr. 22-26 2017.
- American Society of Clinical Oncology Annual Meeting, Chicago, IL; June 2-6, 2017.



Anna D. Louie

School: University of Nevada, Reno School of Medicine

Mentor: Christian Hinrichs, M.D., Lasker Clinical Research Scholar, Experimental Transplantation and Immunology Branch (ETIB), NCI/CCR

Institute: National Cancer Institute (NCI)

Research: Creating an Immunocompetent Mouse Model to Investigate Inhibitors of the PD1/PDL1 Immune Checkpoint on T-Cell Cancer Immunotherapy

Human papilloma virus (HPV) causes cervical, anal and oropharyngeal cancers. Only diseased cells express HPV viral proteins, allowing for selective immune targeting. Engineered T cells can directly recognize and kill viral antigen-expressing tumor cells. However, some tumors inactivate immune cells and evade killing. Upregulated expression of immune checkpoints in tumors can contribute to tumor immune resistance. When engaged by its ligands, PDL1 and PDL2, the checkpoint inhibitor receptor, PD1, limits the activity of T cells in peripheral tissues. The blockade of immune checkpoints can unleash the potential of the antitumor immune response.

Our lab uses engineered T cells targeting HPV proteins to treat metastatic cancers. However, these engineered T cells are not always active after infusion into patients. We developed a mouse model to understand the importance of the PD1 immune checkpoint inhibitor on T cell immunotherapy. The C57Bl/6 mouse model is syngeneic and immunocompetent. B16F0 mouse melanoma cells were retrovirally transduced to express ovalbumin, a non-self antigen, and PDL1. Tumors were implanted subcutaneously in irradiated mice. Seven days later, mice were treated with OT1 T cells that specifically target ovalbumin. Some mice also received PD1 or PDL1 blocking antibodies.

The addition of PDL1 did not change the untreated tumor growth curve, and showed a trend to decreased antitumor effects of OT1 T cells. Adding either PDL1 or PD1 blocking antibodies to the system removed the T-cell inhibitory effects of the tumors. The combination of OT1 T cells and blocking antibody caused tumor regression. These results confirm the role of the PD1 axis in tumor immune evasion. This mouse model will probe the effects of checkpoint inhibitors on T cell activation and serve as a model for testing new disruptors of the PD1 checkpoint inhibitor pathway. These insights may result in better clinical outcomes in autologous T cell therapy.

Travel to Professional Meetings:

- American College of Surgeons Clinical Congress, Washington, DC; Oct. 16-20, 2016.



Rachel Marchalik

School: Georgetown University School of Medicine

Mentor: Jennifer Kanakry, M.D., Staff Clinician, and Juan Gea-Banacloche, M.D., Senior Clinician; Experimental Transplantation and Immunology Branch

Institute: National Cancer Institute (NCI)

Research: Characterization of Hepatic Dysfunction in Patients with Chronic GVHD and an Evaluation of the NIH Consensus Criteria for the Diagnosis of cGVHD

Graft vs host disease (GVHD), a serious complication of allogeneic hematopoietic stem cell transplant (HSCT), is a clinical diagnosis defined by the 2014 National Institutes of Health consensus criteria (NCC). The hepatic component is based on liver function tests (LFTs), and is frequently a diagnosis of exclusion. We aimed to characterize different patterns of LFT and cytokine profiles associated with hepatic dysfunction in hepatic chronic GVHD (HcGVHD), to evaluate the agreement between clinical and histologic findings, and to explore predictors for HcGVHD in order to improve the diagnostic capability of the clinical criteria.

A cross-sectional prospective study of cGVHD was performed in patients recruited under an NIH-sponsored natural history protocol of cGVHD. Three hundred and two patients were evaluated at the NIH from 2004 to 2014. Half were diagnosed with HcGVHD by the NCC. Thirty-four patients had liver tissue available for histopathological analysis. They were divided into clinically suspected and not suspected hepatic cGVHD groups, with 17 patients in each. Eight patients (47%) in the suspected and 6 (35%) in the non-suspected group had histologic features of HcGVHD. Overall sensitivity, specificity, PPV and NPV of the NCC criteria for HcGVHD were 57%, 52.6%, 47% and 62.5%, respectively. On univariate analysis, HcGVHD was associated with younger age, higher ALT, ALKPhos, total cholesterol and LDL ($p=0.046$, 0.019 , 0.003 , 0.002 , 0.0086 , respectively). On multivariate analysis, ALKPhos and total cholesterol were associated with HcGVHD ($p=0.0071$ and 0.017 , respectively). ALKPhos above 200 or total cholesterol above 240 could predict 75% of hepatic cGVHD ($p=0.0002$). Incorporating total cholesterol into the pre-existing NCC increased specificity to 84.2% and PPV and NPV to 72.7%.

Although LFTs are commonly abnormal in the post-HSCT population, it is challenging to make a diagnosis of HcGVHD. Total cholesterol over 240 can improve the diagnostic capability of the NCC, but these findings should be validated in a larger and more diverse population.

Full Length Publications:

- Day CP, **Marchalik R**, Merlino G, Michael H. Mouse models of UV-induced melanoma: genetics, pathology, and clinical relevance. *Lab Invest* 2017; 97:698-705.



Matthew R. McCord

School: University of Florida College of Medicine

Mentor: Mark Gilbert, M.D., Senior Investigator and Chief, Neuro-Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Therapeutic Use of Vascular Endothelial Growth Factor for Blood-brain Barrier Modulation

The presence of the blood-brain barrier (BBB) poses a significant hindrance in delivering effective chemotherapy to malignant brain tumors. Previous studies utilizing vascular endothelial growth factor (VEGF) to induce transient permeability of the BBB have failed to investigate a role for its use in brain tumor treatment. Our study goals were to look at the effects of VEGF on brain endothelial cells and on drug delivery in animal models. In-vitro studies of brain endothelial cell junctional/cytoskeletal proteins were performed via Western blotting, immunofluorescence, and electrical cell-cell impedance. In-vivo studies involved use of rodents receiving VEGF and chemotherapy (temozolomide) to investigate the effect of VEGF on drug delivery.

Both recombinant mouse (rm) and recombinant human (rh) VEGF demonstrated effects on cell-cell adhesion, resulting in approximately a 30% decrease in electrical impedance. These effects were controlled and reversed with Bevacizumab, a human VEGF monoclonal antibody. Western blotting and immunofluorescence indicated that rmVEGF decreased the expression of junctional proteins, including claudin-5 and VE-cadherin; while altering cytoskeletal arrangement of actin filaments. Systemic administration of rmVEGF to rodents affected the integrity of CNS endothelial tight junctions, demonstrated by transmission electron microscopy. However, pre-treatment with a single dose of intravenous rmVEGF failed to demonstrate increased CNS delivery of temozolomide in healthy mice.

Our in-vitro results are consistent with the known properties of VEGF and its effects on vasculature, particularly its role in vasogenic edema. Our animal studies demonstrate that systemically administered VEGF does affect the BBB on the cellular level, but fails to improve chemotherapy penetration. This is possibly due to the renal vascular changes of systemic VEGF, which cause increased excretion of temozolomide. In summary, in-vitro VEGF studies demonstrated an impact on cellular integrity, but further animal studies are needed to evaluate the effect of direct VEGF administration on CNS vasculature, in an effort to improve chemotherapy delivery.

Abstract Publications:

- **McCord M**, Vezina A, Gilbert M, Jackson S. Therapeutic use of VEGF for blood-brain barrier modulation. Annual Blood-brain Barrier Consortium Meeting, Stevenson, WA; Mar. 2-4, 2017.
- Vezina A, **McCord M**, Gilbert M, Jackson S. Transient modulation of the blood-brain barrier with time dependent adenosine receptor agonism. Annual Blood-brain Barrier Consortium Meeting, Stevenson, WA; Mar. 2-4, 2017.
- **McCord M**, Vezina A, Gilbert M, Jackson S. Use of vasoactive agents for transient blood-brain barrier modulation in malignant glioma therapy. ACEA™ Cancer and Immunotherapy Symposium, Arlington, VA; Mar. 31-Apr. 1, 2017.
- **McCord M**, Vezina A, Gilbert M, Jackson S. Therapeutic use of VEGF for blood-brain barrier modulation. American Association for Cancer Research Annual Meeting, Washington, DC; Apr. 1-5, 2017.
- Vezina A, **McCord M**, Gilbert M, Jackson S. Transient modulation of the blood-brain barrier with time dependent adenosine receptor agonism. American Association for Cancer Research Annual Meeting, Washington, DC; Apr. 1-5, 2017.

Travel to Professional Meetings:

- Annual Blood-brain Barrier Consortium, Stevenson, WA; Mar. 2-4, 2017.
- ACEA™ Cancer and Immunotherapy Symposium, Arlington, VA; Mar. 31-Apr. 1, 2017.
- American Association for Cancer Research Annual Meeting, Washington, DC; Apr. 1-5, 2017.

Awards:

- ACEA™ Cancer and Immunotherapy Symposium, Award for best late-breaking abstract.



Megan V. Morisada

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

Mentor: Clint Allen, M.D., Principal Investigator, Translational Tumor Immunology Program

Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)

Research: The Effect of Low Dose Fractionated Versus High Dose Hypofractionated Radiotherapy on Antitumor Immunity

Ionizing radiotherapy (IR) has many applications in contemporary cancer management. Single or hypofractionated high-dose IR enhances responses to experimental immunotherapies. However, standard-of-care clinical management of many cancers involves low-dose, fractionated (daily) IR. The effect of low-dose fractionated IR on anti-tumor immunity remains unclear. This year, we compared the impact of 2 fractions of 8 Gy (hypofractionated high-dose, 48 hours apart) versus 10 fractions of 2 Gy (fractionated low-dose, daily) on tumor infiltrating lymphocyte (TIL) accumulation and activation, peripheral immune cell densities and activation, and tumor-draining lymph node (TDLN) T-lymphocyte antigen-specific IFN γ

responses in T-cell inflamed syngeneic murine models of oral cavity (MOC1) and colon (MC38-CEA) carcinoma. Tumors, TDLNs and spleens were collected at 5, 10 and 20 days after the start of either IR regimen. Both IR schemas delayed primary tumor growth to a similar degree and neither regimen enhanced CD8 TIL accumulation over time. However, TIL CD107a positivity and tumor-draining lymph node T-lymphocyte antigen-specific responses were significantly increased in the high-dose IR cohort. While both IR regimens limited the accumulation of tumor-infiltrating myeloid-derived suppressor cells with tumor progression, both also resulted in increased peripheral and tumor-infiltrating T regulatory cells. Tumors that received high-dose IR also demonstrated significantly increased TIL PD-1 and tumor cell PD-L1 expression, suggesting that adaptive immune resistance may be limiting responses. Experiments combining high-dose hypofractionated or low-dose fractionated IR with systemic PD-1 mAb are underway. In addition to providing biologic insight into the effects of low-dose and high-dose IR on anti-tumor immunity, the results of these experiments will critically inform the design of clinical trials utilizing concurrent IR and PD-based checkpoint inhibition.

Full Length Publications:

- **Morisada M**, Moore E, Hodge R, Friedman J, Cash H, Hodge, J, Mitchell, J, Allen, C. Dose-dependent T-lymphocyte priming and CTL lysis following ionizing radiation in an engineered model of oral cancer. *Oral Oncol* 2017. [In press]

Abstract Publications:

- **Morisada M**, Moore E, Friedman J, Allen C. Impact of low-dose fractionated vs high-dose hypofractionated radiation on anti-tumor immunity. American Association for Cancer Research (AACR) Annual Meeting, Washington, DC; Apr. 1-5, 2017. [Poster]
- **Morisada M**, Moore E, Friedman J, Allen C. The effect of low dose fractionated versus high dose hypofractionated radiotherapy on antitumor immunity. AACR-American Head and Neck Society (AHNS) Head and Neck Cancer Conference, San Diego, CA; Apr. 23-25, 2017. [Podium presentation]

Travel to Professional Meetings:

- American Association for Cancer Research (AACR) Annual Meeting, Washington, DC; Apr. 1-5, 2017.
- AACR-American Head and Neck Society (AHNS) Head and Neck Cancer Conference, San Diego, CA; Apr. 23-25, 2017.



Sachin Nair

School: University of Missouri-Kansas City School Of Medicine (UMKC-SOM)

Mentor: Bruno Averbeck, Ph.D., Chief, Section on Learning and Decision Making, Laboratory of Neuropsychology

Institute: National Institute of Mental Health (NIMH)

Research: The Effect of Periaqueductal Gray (PAG) Lesions on Pain Processing and Cardiovascular Regulation in Rhesus Macaques

The periaqueductal gray (PAG) is located in the midbrain, immediately surrounding the cerebral aqueduct. It plays an important role in mediating defensive behaviors and it influences functions including pain processing, fear and anxiety, cardiovascular control, vocalization, and lordosis. Although there has been considerable work on the PAG in rodents, there is minimal work on this structure in monkeys. We therefore examined the effects of ibotenic acid lesions of the PAG in rhesus monkeys (*Macaca mulatta*) on both pain processing and cardiovascular control. We examined both of these functions through four separate assessments each, two pre-operative and two post-operative. Pain was measured through the use of a von Frey (VF)

filament-based nociception assay and vital signs were obtained using standard procedures.

Our preliminary results indicate there may be a significant difference between the change in pre-operative and post-operative arterial pulse measurements (pulse in experimental animals pre-operative = 132, in experimental post-operative animals = 137.7, in control pre-operative animals = 133.3, and in control post-operative animals = 152.3 beats/min, $F = 6.63$, $p = 0.04$). The PAG-lesioned monkeys did not show a significant change from baseline whereas the surgical controls did. However, we did not find a significant difference between the lesioned animals and the controls in pre-operative vs post-operative measurements ($F = 0.03$, $p = 0.87$) of pain assessments.

The PAG primarily modulates pain through a descending inhibitory system. This system inhibits pain mainly through the release of opioids. Thus, we did not expect to see any changes in our baseline pain assessments, as supported by our data. However, we are still evaluating our results regarding changes in pulse and blood pressure. Further acquisition and analysis of data are ongoing.

Abstract Publications:

- **Nair S**, Browning PG, Murray EA, Averbeck BB. The role of periaqueductal gray (PAG) lesions on pain processing and cardiovascular regulation. Society for Neuroscience Annual Meeting, Washington, DC; Nov. 11-15, 2017. Abstract No. 14703.

Travel to Professional Meetings:

- Society for Neuroscience Annual Meeting, Washington, DC; Nov. 11-15, 2017.



Jannett Nguyen

School: University of California Irvine School of Medicine

Mentor: Isaac Brownell, M.D., Ph.D., Investigator, Dermatology Branch

Institute: National Cancer Institute (NCI)

Research: Identifying New Markers to Distinguish Merkel Cell Carcinoma and Small Cell Lung Cancer

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin. Diagnosis requires biopsy. Histologically, MCC appears similar to small cell lung cancer (SCLC). Discriminating between MCC and cutaneous metastases from SCLC is imperative for management. Thus, immunohistochemistry (IHC) is also required. Currently, CK20 and TTF-1 are the most useful markers for MCC and SCLC, respectively. However, the sensitivities of CK20 and TTF-1 for detecting MCC and SCLC are only 85%. Additionally, there is lack of specificity, as 6% of SCLCs express CK20, and there are cases of MCCs expressing TTF-1. Therefore, additional markers are needed to accurately diagnose neuroendocrine tumors from a skin biopsy. The objectives of our study were to identify new markers to distinguish MCC and SCLC, compare

the sensitivities and specificities of new markers to those used in clinical diagnostics, and to identify a diagnostic panel with the highest sensitivity and specificity.

Microarray transcriptome analysis of MCC and SCLC identified highly differentially expressed genes, which served as candidate markers. Antibodies to these gene products were systematically characterized and staining conditions were optimized on MCC and SCLC cell lines. Markers were then applied to 10 MCC and 59 SCLC tumors.

We identified MATH1 and TFAP2B as new MCC markers. 100% of MCC tumors stained positively for MATH1 and TFAP2B. These markers were 100% specific, and did not stain SCLC tumors. All MCC expressed the standard marker, CK20. We also identified CEACAM-P as a new marker for SCLC. 83% (49/59) of SCLC expressed CEACAM-P, and 80% (47/59) were positive for the standard marker, TTF-1. A panel combining CEACAM-P and TTF-1 increases sensitivity to 93% (55/59, $p < 0.05$). Both markers were 100% specific for SCLC.

We conclude that MATH1 and TFAP2B are additional markers with high sensitivity and specificity for MCC and could be adjuncts to CK20 in a diagnostic panel. CEACAM-P and TTF-1 are comparably sensitive and specific for SCLC, and a panel combining both antibodies increases sensitivity.

Full Length Publications:

- Eid M, **Nguyen J**, Brownell I. Seeking standards for the detection of Merkel cell polyomavirus and its clinical significance. *J Invest Dermatol.* 2017;137(4):797-799.
- **Nguyen J**, Alexander T, Jiang H, Hill N, Abdullaev Z, Pack SD, Hsu AP, Holland SM, Hickstein DD, Brownell I. Melanoma in GATA2 deficient patients. [Under Review]

Travel to Professional Meetings:

- American Academy of Dermatology Annual Meeting, Orlando, FL; Mar. 2017.



Ukpebo R. Omosigho

School: University of Tennessee Health Science Center

Mentor: Sunni Mumford, Ph.D., Stadtman Investigator, Epidemiology Branch

Institute: Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

Research: Preconception Serum Vitamin D and Neonatal Outcomes

Vitamin D deficiency is increasingly becoming a public health concern especially among reproductive aged women. Currently, evidence is limited regarding the potential link between preconception maternal 25-hydroxyvitamin D (25(OH)D) status and neonatal anthropometric parameters. Additionally, the effects of preconception maternal vitamin D on neonatal features may be sex specific and have yet to be elucidated. Thus, we aimed to investigate the association between maternal preconception vitamin D concentrations and neonatal and obstetric outcomes. This was a secondary analysis of participants in the EAGeR trial, which was designed to evaluate the effect of preconception-initiated low dose aspirin on reproductive outcomes across four academic medical centers in the U.S. 1191 women aged

18-40, with 1-2 prior pregnancy losses, were included in the analysis. Preconception 25(OH)D was measured from serum collected at baseline. Main outcomes were birth weight, length, head circumference, ponderal index, pre-term birth, gestational diabetes mellitus (GDM), low birthweight, preeclampsia, and neonatal intensive care unit (NICU) admissions. Preconception 25(OH)D concentrations were not associated with neonatal outcomes overall. However, preconception 25(OH)D was positively associated with birth weight only among female neonates. Specifically, increases in 25(OH)D were associated with increases in birth weight (β 37.0 g; 95% CI -3.0 to 77.0 per 10 ng/mL), and female neonates born to mothers with sufficient levels were larger in comparison to infants born to mothers with insufficient levels (β 110.6 g; 95% CI 19.2, 202.12). There was no association between 25(OH)D and preterm birth, GDM, low birthweight, preeclampsia, NICU admissions or head circumference, length, and ponderal index by infant sex. In conclusion, maternal preconception 25(OH)D status was associated with birth weight in a sex specific manner. These data suggest that female fetuses respond differently to maternal 25(OH)D status in utero which may reflect differences in intrauterine growth adaptations in response to 25(OH)D bioavailability.

Abstract Publications:

- **Omosigho UR**, Kim K, Kuhr D, Plowden TC, Connell MT, Sjaarda LA, Schisterman EF, Galai N, Perkins NJ, Holland T, Mumford SL. Preconception vitamin D and neonatal outcomes. Society for Pediatric and Perinatal Epidemiologic Research Annual Meeting, Seattle, WA; June 21-24, 2017.
- **Omosigho UR**, Kim K, Kuhr D, Plowden TC, Connell MT, Sjaarda LA, Schisterman EF, Galai N, Perkins NJ, Holland T, Mumford SL. Preconception vitamin D and neonatal outcomes. Society for Epidemiologic Research Annual Meeting, Seattle, WA; June 20-21, 2017.

Travel to Professional Meetings:

- Society for Pediatric and Perinatal Epidemiologic Research Annual Meeting, Seattle, WA; June 21-24, 2017.
- Society for Epidemiologic Research Annual Meeting, Seattle, WA; June 20-21, 2017.



John W. Ostrominski

School: University of Texas School of Medicine at San Antonio

Mentor: Cynthia Dunbar, M.D., Senior Investigator, Molecular Hematopoiesis Section;
Manfred Boehm, M.D., Senior Investigator, Laboratory of Cardiovascular Regenerative
Medicine

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: CRISPR/Cas9-mediated Introduction of the Sodium/Iodide Symporter Gene
Enables Noninvasive *in vivo* Tracking of Rhesus iPSC-derived Cardiomyocytes in Murine
Model of Myocardial Infarction

Due to the limited regenerative capacity of mature cardiomyocytes, cardiac cell therapies constitute an exciting strategy for myocardial repair. However, numerous challenges remain, including limited understanding of cell graft behavior long-term. Hence, there is considerable demand for technologies enabling longitudinal monitoring of transplanted cells. Sodium-iodide symporter (NIS)-based *in vivo* imaging has many advantages, including predicted safety and immunotolerance due to reliance on an endogenous gene, and on widely available imaging technologies. Furthermore, because of their close physiologic similarity to humans, we believe that non-human primates represent ideal models for investigating the biology of allogeneic or autologous cell therapies. We report the development of NIS-based *in vivo* imaging to detect and track rhesus induced pluripotent stem cell (RhiPSC)-derived cardiomyocytes (CMs) in a murine model of myocardial infarction (MI). NIS-RhiPSCs were generated by CRISPR/Cas9-mediated integration of the rhesus NIS cDNA within the *AAVS1* safe harbor locus. NIS was robustly expressed and radiotracer (^{18}F -TFB) uptake by NIS-RhiPSCs was demonstrated *in vitro*. NIS-RhiPSCs exhibited significantly greater uptake than NIS-negative controls ($p < 0.01$). Using our previously established differentiation protocol, NIS-RhiPSC-CMs were derived with high purity, exhibited spontaneous beating in culture, and retained functional NIS expression. Immediately following induction of MI by 90-minute occlusion of the left anterior descending (LAD) artery, 2×10^6 NIS-RhiPSC-CMs were introduced into the putative infarct region by intramyocardial injection. To track the injected cells *in vivo*, positron emission tomography/computed tomography was used with ^{18}F -TFB. Transplanted cells could be clearly visualized for up to five weeks post-injection. To investigate their electrophysiologic profile, NIS-RhiPSC-CMs underwent both whole-cell patch clamp and optical imaging studies. All electrophysiologic parameters assessed were within normal limits, and no significant deviations were seen in the presence of sodium iodide. Taken together, our results further demonstrate the utility of NIS as a safe and robust tool for imaging of cell therapies.

Full Length Publications:

- Yada RC, **Ostrominski JW**, Tunc I, Hong SG, Zou J, Dunbar CE. CRISPR/Cas9-based safe harbor gene editing in rhesus iPSCs. *Curr Protocols Stem Cell Biol*. [Under review]

Abstract Publications:

- **Ostrominski JW**, Yada RC, Sato N, Palisoc M, Pittaluga S, Lin Y, Zou J, Peng K, Hong SG, and Dunbar CE. CRISPR-mediated introduction of the sodium-iodide symporter to enable non-invasive monitoring of macaque iPSC-derived cardiomyocytes. American Heart Association Basic Cardiovascular Sciences, Scientific Sessions, Portland, OR; Jul. 10-13, 2017. [Podium presentation]
- Yada RC, **Ostrominski JW**, Sato N, Lin Y, Zou J, Palisoc M, Pittaluga S, Peng K, Hong SG, Dunbar CE. Generation and functional characterization of sodium iodide symporter transgenic rhesus induced pluripotent stem cells. International Society of Stem Cell Research Annual Meeting, Boston, MA; Jun. 14-17, 2017. [Podium presentation]
- **Ostrominski JW**, Yada RC, Sato N, Palisoc M, Pittaluga S, Lin Y, Zou J, Peng K, Hong SG, Dunbar CE. CRISPR/Cas9-mediated introduction of the sodium-iodide symporter gene enables non-invasive *in vivo* tracking of rhesus iPSC-derived cells. American Society of Gene and Cell Therapy 20th Annual Meeting, Washington, DC; May 10-13, 2017. [Podium presentation]

Travel to Professional Meetings:

- American Society of Gene and Cell Therapy 20th Annual Meeting, Washington, DC; May 10-13, 2017.
- American Heart Association Basic Cardiovascular Sciences. Scientific Sessions, Portland, OR; Jul. 10-13, 2017.

Awards:

- American Society of Gene and Cell Therapy Meritorious Abstract Travel Award.



Oyetewa B. Oyerinde

School: University of Illinois at Chicago College of Medicine

Mentor: Thomas Darling, M.D., Ph.D., Chair, Dermatology Department, Uniformed Services University of the Health Sciences; Joel Moss, M.D., Ph.D., Senior Investigator, Cardiovascular and Pulmonary Branch, NHLBI

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Disseminated Disease Despite Low Mutant Allele Fractions: The Variable Phenotype of Mosaic Tuberous Sclerosis Complex

Mosaicism is caused by a mutation occurring during prenatal development, resulting in an organism composed of two (or more) genetically distinct cell lineages. Mosaicism has been shown to cause mild disease in tuberous sclerosis complex (TSC) and is often missed by standard genetic testing, leading to assignment of no mutation identified (NMI). Patients with unilateral angiofibromas (AFs) have been hypothesized to be mosaic, but this had not been confirmed genetically. The objective of our study was to identify mosaicism and its phenotypic spectrum in TSC. Thirty patients were selected for mutational analysis for mosaicism using

skin tumor and control tissues. Selection of these patients was based on clinical examination showing cutaneous lateralization of skin findings, mild phenotype or NMI in previous evaluation. We performed massively parallel sequencing (MPS) on DNA isolated from TSC skin tumors. Mosaicism was identified in 19 patients, by identification of mutations in TSC2. Patients ranged in age from 24 to 75 years (median age 40). Four had unilateral or asymmetric AFs, four had fewer than 20 AFs, and 11 had numerous bilateral facial AFs. The mutant allele fractions (MAF) in whole tumors ranged from 1-20%. The median MAF in blood samples was 1.23% (range 0-19, n=16), well below the 50% allelic fraction expected for germline mutations. Several significant correlations were observed: number of skin features with number of internal features ($r=0.58$, $P=0.009$), number of skin features with blood MAF ($r=0.64$, $P=0.008$), and sum of skin and internal features with blood MAF ($r=0.51$, $P=0.046$). Overall, these results show that 1) analysis of DNA from whole skin tumors or cultured tumor cells, in addition to blood, enables identification of low-level mosaicism using MPS and 2) the phenotype of mosaic TSC patients varies from those with unilateral AFs and mild disease, to those with a disseminated phenotype that may be indistinguishable from those with germline mutations.

Full Length Publications:

- Bongiorno MA, Nathan N, **Oyerinde O**, Wang J, Lee CR, Brown GT, Moss J, Darling TN. Clinical characteristics of connective tissue nevi in tuberous sclerosis complex with special emphasis on Shagreen patches. *JAMA Dermatol*. Published online April 26, 2017. doi:10.1001/jamadermatol.2017.0298

Abstract Publications:

- Nathan N, Hamieh L, Tyburczy M, Wang J, **Oyerinde O**, Moss J, Kwiatkowski D, Darling T. Disseminated disease despite low mutant allele fractions: The variable phenotype of mosaic tuberous sclerosis complex. Society for Investigative Dermatology 76th Annual Meeting; Portland, OR; Apr. 26-29, 2017. *J Invest Dermatol*, Apr. 2017. [Poster]
- Oyerinde O**, Buccine D, Moss J, Darling TN. Fibrous cephalic plaques in tuberous sclerosis complex. TS Alliance International Research Conference on TSC & LAM; Washington, DC; June 22-24, 2017. [Poster]
- Oyerinde O**, Buccine D, Moss J, Darling TN. Clinical characteristics of fibrous cephalic plaques in tuberous sclerosis complex. National Medical Association Annual Convention and Scientific Assembly; Philadelphia, PA; July 29-Aug. 2, 2017. [Oral]

Travel to Professional Meetings:

- American Academy of Dermatology Annual Meeting, Orlando, FL; Mar. 3-7, 2017.
- Society for Investigative Dermatology 76th Annual Meeting, Portland, OR; Apr. 26-29, 2017.
- TS Alliance International Research Conference on TSC & LAM, Washington, DC; June 22-24.
- National Medical Association Annual Convention and Scientific Assembly, Philadelphia, PA; July 29-Aug. 2, 2017.

Awards:

- A. Paul Kelly, M.D., National Medical Association 2017 Medical Student Dermatology Symposium Travel Award: Award to travel to symposium and give 20 minute oral presentation.



Varun Padmanaban

School: Drexel University College of Medicine

Mentor: Heather Cameron, Ph.D., Chief, Section of Neuroplasticity

Institute: National Institute of Mental Health (NIMH)

Research: Investigation of Single-Session Deep Brain Stimulation to Increase Adult Hippocampal Neurogenesis and Improve Stress Resiliency

Deep brain stimulation (DBS) is increasingly being investigated as a therapeutic tool to ameliorate emotional and cognitive symptoms of several psychiatric disorders. Interventions generally involve chronic stimulation over long periods of time and have had mixed results partly due to a lack of understanding of how DBS works. Studies in rodents have shown that DBS increases hippocampal neurogenesis, suggesting increased neurogenesis as a possible mediator of behavioral improvement. Neurogenesis or the formation of new neurons occurs throughout adult life within the dentate gyrus of the hippocampus in both humans and rodents. These adult-generated neurons have been implicated in the regulation of corticosteroids and play an important role in stress response. Interestingly, production of adult generated neurons

are exquisitely sensitive to the environment. External stress reduces the formation and life-span of adult-generated granule cells and this reduction may contribute to the underlying pathophysiology of stress-related mood disorders. We sought to evaluate whether single-session DBS can recover stress resiliency after a traumatic stressor.

We first validated a model of deep brain stimulation (DBS) in rodents and showed that single-session DBS, using human DBS parameters, increases neurogenesis as compared to sham surgery. We then validated a rodent model for post-traumatic stress disorder (PTSD). We show that rodents who undergo a single stressor display decreased exploratory behavior (in open field and contextual fear testing) and increased depressive-like behavior (in forced swim testing) one month after that initial stressor. These symptoms may be analogous to those found in patients with PTSD. We are currently testing whether we can rescue these behavioral deficits utilizing single session DBS. Finally, we are utilizing transgenic rodents who are modified to have no appreciable adult hippocampal neurogenesis to investigate whether DBS effects, if any, are neurogenesis dependent. Parallel studies are underway investigating possible mechanisms of how DBS may increase neurogenesis.

Full Length Publications:

- Schoenfeld TJ, McCausland H, Morris HD, **Padmanaban V**, Cameron HA. Chronic stress and inhibition of neurogenesis independently reduce hippocampal volume. *Biol Psychiatry*, 2017; doi: 10.1016/j.biopsych.2017.05.013.
- **Padmanaban V***, Shepard MJ*, Edwards N, Chittiboyna P, Butman JA, Ray-Chaudhury A, Heiss JD. Discovery of aquaporin-1 and aquaporin-4 expression in an intramedullary spinal cord ependymal cyst: case report. [In review]
*Co-first author

Abstract Publications:

- **Padmanaban V**, Schoenfeld TJ, Cameron HA. Using deep brain stimulation to study the role of induced adult neurogenesis in hippocampal subregions. American Association of Neurological Surgeons (AANS), Los Angeles, CA; Apr. 22-26, 2017. [Poster presentation]

Travel to Professional Meetings:

- Society for Neuroscience, San Diego; Nov. 12-16, 2016.
- American Association of Neurological Surgeons, Los Angeles, CA; Apr. 22-26, 2017.



Chandana Papudesu

School: Medical College of Georgia at Augusta University

Mentor: Emily Chew, M.D., Deputy Clinical Director, NEI; Deputy Director, Division of Epidemiology and Clinical Applications, NEI

Institute: National Eye Institute (NEI)

Research: Association of Mortality with Ocular Diseases in the Age-Related Eye Disease Study 2 (AREDS2)

Age-related eye disease and visual impairment are growing public health concerns in the increasing aged population. The Age-Related Eye Disease Study 2 (AREDS2) is a clinical trial that demonstrated that persons assigned to daily intake of the high-dose antioxidants lutein and zeaxanthin, and zinc, had reduced risk of developing advanced age-related macular degeneration (AMD). Participants with at least intermediate AMD were enrolled in the AREDS2 follow-up trial for treatment of AMD and cataract. Ocular disorders including AMD and cataract, and impaired visual acuity, have previously been reported to have a significant effect on mortality.

To further investigate the association of mortality with ocular diseases, we assessed the risk of all-cause and cause-specific mortality using adjusted Cox proportional hazards models. Comprehensive eye exams that included bestcorrected visual acuity (BCVA) assessments, slit lamp examinations, and stereoscopic fundus photographs were conducted at baseline and at annual study visits. A central reading center determined the development of late AMD (central geographic atrophy or neovascular AMD).

We found that participants with advanced AMD in one eye at baseline had a statistically significant increased risk for mortality compared to participants with early AMD (risk ratio [RR] 1.52, 95% confidence interval [CI], 1.062.02).

The association between all-cause mortality and AREDS2 treatment, whether assessing the main or individual treatment effects, was not significantly different [ω -3 fatty acids main effect RR 1.19, 95% CI 0.97-1.46; lutein/zeaxanthin main effect RR 1.03, 95% CI 0.84-1.27]. In the AREDS2 population, the data suggest that development of advanced AMD, bilateral cataract surgery, and visual acuity <20/40 were all associated with decreased survival. Oral supplementation with ω 3 fatty acids, lutein/zeaxanthin, zinc, or betacarotene had no statistically significant impact on mortality.

Abstract Publications:

- **Papudesu C**, Clemons T, Agron E, Chew E. Association of mortality with age-related macular degeneration and cataract surgery in AREDS2. Association for Research in Vision and Ophthalmology (ARVO), Baltimore, MD; May 7-11, 2017. [Poster presentation]
- **Papudesu C**, Hasan, J., Agron E., Keenan, T., Clemons, T., Cukras, C., Wong, W., Chew, E. Natural history of age-related macular degeneration: A twenty-year follow-up in the Age-Related Eye Disease Study (AREDS). American Academy of Ophthalmology, New Orleans, LA; Nov. 11-14, 2017. [Submitted]

Travel to Professional Meetings:

- Association for Research and Vision in Ophthalmology (ARVO), Baltimore, MD; May 7-11, 2017.



Alexandra A. Pietraszkiewicz

School: University of Connecticut School of Medicine

Mentor: Anand Swaroop, Ph.D., Chief, Neurobiology Neurodegeneration and Repair Laboratory; Emily Chew, M.D., Deputy Director, Division of Epidemiology and Clinical Applications; Deputy Clinical Director, NEI

Institute: National Eye Institute (NEI)

Research: Whole-Genome Sequencing of AREDS and AREDS2 Subjects Reveals Rare Loss of Function Variants that Accelerate the Progression of Age-Related Macular Degeneration and Increase Risk of Specific Sub-Phenotypes

Age-Related Macular Degeneration (AMD) is a multifactorial neurodegenerative disease that disproportionately affects elderly individuals. Despite the progress that has been made in AMD genetics, variants at risk loci explain only approximately 50% of disease heritability. The genes that have been identified belong to a variety of biological pathways, including complement, lipids, and extracellular matrix (ECM).

The purpose of this study was to investigate associations between rare loss-of-function (LoF) variants within previously identified AMD risk loci and sub-phenotypes characteristic of intermediate or advanced disease, including geographic atrophy (GA), choroidal neovascularization (CNV), pseudoreticular drusen, calcified drusen, drusen area in grid, and the AREDS Extended AMD Severity Scale.

We performed whole-genome sequencing (WGS) on AMD cases and age and sex-matched controls from the Age-Related Eye Disease Study (AREDS), AREDS2, and the Michigan Genomics Initiative (MGI). Rare LoF variants were defined by Ensembl's Sequence Ontology terms with moderate or high impact and allele frequency $<0.1\%$ in the study population, and were called from 100kb regions around the previously identified 52 independent risk variants. Variants were assigned to either the complement, ECM, lipid, cell survival, immune system, metabolism, or unknown/other pathway.

We found an increased risk of GA (OR=1.4, $p<0.05$), CNV (OR=1.4, $p<0.05$), and higher scores on the AREDS Extended AMD Severity Scale ($p<0.01$; Standardized Coefficient Beta (B)=0.08) in rare variant carriers. We also observed a faster rate of progression to advanced disease with a hazard ratio of 1.25 ($p<0.05$). We found associations between the complement pathway and GA (OR=2.4, $p<0.05$), the complement pathway and calcified drusen (OR=4.8, $p<0.001$), the ECM pathway and CNV (OR=2.0, $p<0.05$), and the ECM pathway and higher scores on the AREDS extended severity scale ($p=0.01$; B=0.07).

Our study demonstrates that rare LoF variants increase the rate of AMD disease progression, and that variants in the complement and ECM pathways modify the clinical course of AMD and increase the risk of developing specific sub-phenotypes.

Abstract Publications:

- Pietraszkiewicz AA, Van Asten F, Kwong A, Ratnapriya R, Abecasis G, Swaroop A, Chew E. Rare variant pathway analysis in age-related macular degeneration. Association for Research in Vision and Ophthalmology (ARVO), Baltimore, MD; June 7-11, 2017. [Poster]

Awards:

- Outstanding Research Award, Spring Awards Ceremony, University of Connecticut School of Medicine: recognizes a third year medical student for making significant contributions to the field of clinical research and/or laboratory research beyond their Phase 1 year summer experience.

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology (ARVO), Baltimore, MD; June 7-11, 2017.



Jacqueline M. Pires

School: University of Massachusetts Medical School

Mentor: Richard J. Youle, Ph.D., Biochemistry Section, Surgical Neurology Branch

Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research: Endogenous Tagging of POLG2 Via Split GFP Fluorescence: Using CRISPR Mediated Gene Editing to Study Mitochondrial DNA Replication

Mitochondria respond to a particular tissue's energy demands through oxidative phosphorylation (OXPHOS) to generate ATP. Mitochondria depend on their 16.6 kb genome to faithfully replicate and transcribe the 13 integral membrane proteins encoded within mitochondrial DNA (mtDNA), which are vital components of OXPHOS function. The nuclear genome controls replication, transcription and maintenance of mtDNA. *POLG* is the nuclear gene that encodes the 140kDa catalytic subunit of the mtDNA polymerase γ and is dependent on its accessory subunit, P55, also encoded by a nuclear gene (*POLG2*). The P55 homodimer binds asymmetrically to the catalytic subunit of *POLG* and each monomer plays a different role: either increasing affinity of the polymerase to mtDNA or accelerating nucleotide incorporation

into the new daughter strand. As excessive overexpression of any protein can impair cellular function.

We developed a GFP split fluorescence technique, used previously to visualize cytosolic proteins, to label endogenous mitochondrial proteins such as *POLG2*. We generated a stable cell line that expressed the first 10 beta-strands of GFP to the mitochondrial matrix using a COX8 mitochondrial matrix targeting sequence (COX8-GFP1-10). In this COX8-GFP1-10 cell line, we directed sequence specific CRISPR guide RNAs to induce double strand breaks at the end of *POLG2* to insert the last beta-strand of GFP at the end of *POLG2* via homology-directed DNA repair. After homologous recombination (HR), we used various techniques including confocal microscopy to confirm that endogenously tagged GFP *POLG2* did not interfere with mitochondrial morphology and identified replicating mtDNA nucleoids. This knock-in reporter is a novel tool that allows for high detailed spatiotemporal visualization of endogenous mitochondrial proteins that would otherwise interfere with their function when overexpressed.

Abstract Publications:

- **Pires JM**, Pickrell AM, Kanfer G, Sarraf SA, Youle RJ. Endogenous tagging of *POLG2* via split GFP fluorescence: Using CRISPR mediated gene editing to study mitochondrial DNA replication. United Mitochondrial Disease Foundation, Alexandria, Virginia; June, 2017.

Travel to Professional Meetings:

- United Mitochondrial Disease Foundation: Mitochondrial Medicine Symposium 2017. Washington DC; June 28-July 1, 2017.



Stephen J. Raithel

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

Mentor: Andrew Mannes, M.D., Chief, Department of Perioperative Medicine

Institute: Clinical Center (CC)

Research: Spinal Cord Dorsal Horn Transcriptomics After Surgical Incision in Rats

Demonstrates Microglial Activation Signatures despite Analgesia from TRPV1+ Nerve Terminal Inactivation.

Peripheral nociceptors expressing the ion channel TRPV1 play an important role in mediating post-operative pain. Silencing these nociceptors in the peri- and post-operative period is thus a promising target for achieving analgesia. The first goal of this study was to evaluate the efficacy of TRPV1+ nerve terminal inactivation for post-operative pain control. To this end, resiniferatoxin (RTX), an ultrapotent capsaicin analogue, was injected subcutaneously into rat hindpaw several minutes prior to surgical incision to inactivate TRPV1+ nerve terminals. The effects of RTX on post-incisional measures of pain were assessed through post-operative day 10, and RTX was found to attenuate thermal hyperalgesia, mechanical allodynia, and

spontaneous paw guarding throughout the entire post-operative period.

Signaling from nociceptors can lead to plastic changes in the spinal cord, known as central sensitization. However, the transcriptomic changes in the dorsal spinal cord after surgery remain poorly defined. Thus, the second goal of this study was to assess transcriptomic changes in the dorsal spinal cord by RNA-sequencing, after surgical incision with and without TRPV1+ nerve terminal inactivation. Surgical incision induced many genes (70 genes upregulated vs 0 genes downregulated) in the dorsal horn and these changes were specific to the ipsilateral dorsal horn. Surprisingly, RTX pre-treatment did not significantly decrease genes induced by surgical incision despite the robust analgesia it provided. Many of the genes induced were related to microglial activation, such as Cd11b and Iba1.

A single subcutaneous injection of RTX prior to incision can attenuate both evoked and non-evoked measures of post-operative pain. However, many genes related to microglial activation are still induced in the spinal cord after surgical incision. This suggests that the processes leading to pain and microglial activation are independent processes, which can be dissociated with analgesia from TRPV1+ nerve terminal inactivation.

Full Length Publications:

- Aron J, **Raithel S**, Mannes A. Torus Palatinus and airway management. *Anesthesiology*. [In press]
- **Raithel S**, Sapio M, LaPaglia D, Iadarola M, Mannes A. Spinal cord dorsal horn transcriptomics after surgical incision in rats demonstrates microglial activation signatures despite analgesia from TRPV1+ nerve terminal inactivation. *Anesthesiology*. [Under review]
- **Raithel S**, Sapio M, Iadarola M, Mannes A. Thermal A-d nociceptors, identified by transcriptomics, express higher levels of anesthesia-sensitive receptors than thermal C-fibers and are more suppressible by low-dose isoflurane. *Anesth Analg*. [Under review]
- Sapio M, Neubert J, LaPaglia D, Keller J, **Raithel S**, Anderson E, Butman J, Caudle R, Brown D, Heiss J, Mannes A, Iadarola M. Pain control through selective chemo-axotomy of centrally-projecting TRPV1+ sensory neurons. *J Clin Invest*. [Under review]
- LaPaglia D, Sapio M, Burbelo P, Thierry-Mieg J, Thierry-Mieg D, **Raithel S**, Ramsden C, Iadarola M, Mannes A. RNA-Seq investigations of human post-mortem trigeminal ganglia. *Cephalalgia*. [Under review]
- Hall B, Prochazkova M, Sapio M, Minetos P, Kurochkina N, BK B, Amin N, Terse A, Joseph J, **Raithel S**, Mannes A, Pant H, Chung M, Iadarola M, Kulkarni A. Phosphorylation of the transient receptor potential ankyrin 1 by cyclin-dependent kinase 5 affects chemo-nociception. *Proc Natl Acad Sci USA*. [Under review]

Abstract Publications:

- **Raithel S**, Lapaglia D, Sapio M, Iadarola M, Mannes A. (2017). (162) Pre-surgical intraplantar resiniferatoxin decreases post-operative pain in rats with plantar incision. *Journal of Pain*, 18(4): S17. American Pain Society Annual Scientific Meeting, Pittsburgh, PA; May 17-20. [Poster]

Travel to Professional Meetings:

- Society for Neuroscience, San Diego, CA; Nov. 12-16, 2016
- Association of University Anesthesiologists, Washington, DC; May 4-5, 2017. [Two posters presented]
- American Pain Society Annual Scientific Meeting, Pittsburgh, PA; May 17-20, 2017. [One poster presented]
- 12th Annual NIH Pain Consortium Symposium on Multidisciplinary Strategies for Pain, Bethesda, MD; May 31-June 1, 2017. [One poster presented]



Joshua P. Rivers

School: Wayne State University School of Medicine

Mentor: Tiffany M. Powell-Wiley, M.D., M.P.H., Assistant Clinical Investigator, Unit on Social Determinants of Obesity and Cardiovascular Risk; Nehal Mehta, M.D., M.S.C.E., F.A.H.A., Lasker Clinical Research Scholar, Section on Inflammation and Cardiometabolic Diseases

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Visceral Adiposity in Psoriasis is Associated with Vascular Inflammation by 18-FDG PET/CT beyond Cardiometabolic Disease Risk Factors in an Observational Cohort Study.

Psoriasis, a chronic inflammatory skin disease, is associated with vascular inflammation (VI) by 18-fluorodeoxyglucose positron emission tomography/ computed tomography (18-FDG PET/CT) and increased cardiometabolic disease risk including adipose tissue dysregulation. Recently, visceral adiposity was shown to be associated with future cardiovascular events; however, the relationship of visceral (VAT) and subcutaneous adiposity (SAT) with VI in psoriasis has yet to be evaluated. Therefore, we sought to examine the relationship between VAT volume and VI by 18-FDG PET/CT in psoriasis. We further evaluated the impact of psoriasis treatment on VAT volume and VI at 1-year.

Consecutively recruited psoriasis patients (N=77) underwent 18-FDG PET/CT scans to measure VI and abdominal adiposity. A subset of psoriasis patients with severe skin disease was scanned again at 1-year following psoriasis treatment.

At baseline, the cohort was middle aged (51.8 ± 12.6 years; mean \pm SD), predominantly male (44; 57%), with low cardiovascular risk by Framingham risk score [median (interquartile range); 4 (2-7)], and mild-moderate skin disease by psoriasis area severity index (PASI) score [5.2 (3.0-8.5)]. After multivariable analysis, VAT ($\beta=0.55$, $p<0.001$), but not SAT volume ($\beta=0.15$, $p=0.11$) was associated with VI beyond cardiovascular risk factors. A separate analysis revealed that psoriasis disease severity associated with VAT volume ($\beta=0.33$, $p=0.004$) beyond SAT volume ($\beta=0.30$, $p=0.005$). Lastly, in a subset of patients with severe skin disease ($n=13$), there was an improvement in psoriasis severity and VAT volume which was associated with an improvement in VI at 1-year beyond cardiovascular risk factors ($\beta=0.53$, $p=0.049$).

We conclude that volume-based computed tomography measurement of VAT may capture more metabolic risk associated with subclinical atherosclerosis compared to SAT in psoriasis. The treatment of psoriasis associates with a decrease in VAT as well as a decrease in VI, potentially implicating VAT as a relevant biomarker as it relates to VI in psoriasis. However, randomized controlled trials are needed to confirm our findings.

Full Length Publications:

- Adu-Brimpong J, Coffey N, Ayers C, Berrigan D, Yingling LR, Thomas S, Mitchell V, Ahuja C, **Rivers JP**, Hartz J, Powell-Wiley TM. Optimizing score and sampling methods for assessing built neighborhood environment quality in residential areas. *Int J Environ Res Public Health*. 2017 Mar 8;14.
- Dey AK, Joshi AA, Chaturvedi A, Lerman JB, Aberra TM, Rodante JA, Teague HL, Harrington CL, **Rivers JP**, Chung JH, Kabbany MT, Natarajan B, Silverman JJ, Ng Q, Sanda GE, Sorokin AV, Baumer Y, Gerson E, Prussick RB, Ehrlich A, Green LJ, Lockshin BN, Ahlman MA, Playford MP, Gelfand JM, Mehta NN. Association between skin and aortic vascular inflammation in patients with psoriasis: a case-cohort study using positron emission tomography/ computed tomography. *JAMA Cardiol*. 2017 May 31. doi:10.1001/jamacardio.2017.1213. [Epub ahead of print]
- Rivers JP**, Powell-Wiley TM, Dey AK, Rodante JA, Chung JH, Joshi AA, Natarajan B, Sajja AP, Chaturvedi A, Rana A, Harrington CL, Teague HL, Lockshin BN, Ahlman MA, Yao J, Playford MP, Gelfand JM, Mehta NN. Visceral adiposity in psoriasis is associated with vascular inflammation by 18-FDG PET/CT beyond cardiometabolic disease risk factors in an observational cohort study. *JACC Imaging*. [Under review]

Abstract Publications:

- Rivers JP**, Mitchell V, Peters-Lawrence M, Joshi AA, Dey AK, Mehta NN, Powell-Wiley TM. Vascular inflammation as a subclinical marker of atherosclerosis demonstrates high cardiometabolic risk in a resource-limited, community-based population. American Heart Association (AHA) EPI Lifestyle Scientific Session, Portland, OR; Mar. 2017. [Poster]

- Rivers JP**, Dey AK, Chaturvedi A, Chung JH, Kabbany MT, Ahlman MA, Rodante JA, Joshi AA, Harrington CL, Playford MP, Yao J, Powell-Wiley TM, Mehta NM. Visceral adipose tissue but not subcutaneous adipose tissue associates with cholesterol efflux capacity in psoriasis. American Heart Association (AHA) EPI Lifestyle Scientific Session, Portland, OR; Mar. 2017. [Poster]
- Chung JH, Dey A, Chaturvedi A, **Rivers JP**, Lerman JB, Harrington CL, Playford MP, Gordon SM, Remaley A, Chen M, Bluemke D, Mehta NN. Lipid rich plaque by coronary CT angiography associates with cholesterol efflux capacity independent of traditional cardiovascular risk factors in those at risk for myocardial infarction. American Heart Association (AHA) EPI Lifestyle Scientific Session, Portland, OR; Mar. 2017. [Poster]
- Rivers JP**, Dey AK, Chaturvedi A, Chung JH, Kabbany MT, Ahlman MA, Rodante JA, Joshi AA, Harrington CL, Playford MP, Yao J, Powell-Wiley TM, Mehta NM. Visceral but not subcutaneous adipose tissue associates with vascular inflammation by 18-FDG PET/CT in psoriasis. American College of Cardiology Scientific Session, Washington, DC; Mar. 2017. [Poster]
- Kabbany MT, Dey A, Shukla P, Chaturvedi A, Rana A, **Rivers JP**, Chung J, Joshi A, Lerman J, Aberra T, Rodante J, Teague H, Silverman J, Ng Q, Ahlman M, Playford M, Mehta N. Improvement in cholesterol efflux capacity is associated with a reduction in aortic wall thickness by MRI independent of traditional CV risk factors. American College of Cardiology Scientific Session, Washington, DC; Mar. 2017. [Poster]

Continued on the Next Page

- Natarajan B, Chaturvedi A, Dey AK, Chung J, **Rivers J**, Rana A, Rodante J, Teague H, Silverman J, Sanda G, Sorokin A, Baumer Y, Harrington C, Lerman J, Joshi A, Playford M, Mehta N. Small dense low density lipoprotein particle number relates to coronary plaque burden independent of traditional cardiovascular risk factors in psoriasis. American College of Cardiology Scientific Session, Washington, DC; Mar. 2017. [Poster]
- Chaturvedi A, Lerman J, Sandfort V, Chung J, Dey A, **Rivers J**, Joshi A, Rana A, Rodante J, Teague H, Silverman J, Ng Q, Sanda G, Harrington C, Sorokin A, Baumer Y, Gelfand J, Playford M, Ahlman M, Bluemke D, Mehta N. Aortic vascular inflammation by 18-FDG PET/CT associates with high-risk coronary plaques in young psoriasis patients. American College of Cardiology Scientific Session, Washington, DC; Mar. 2017. [Poster]
- Joshi A, Dey AK, Chaturvedi A, Chung J, **Rivers J**, Kabbany MT, Ahlman M, Playford M, Mehta N. Improvement in cholesterol efflux capacity is associated with improvement in vascular inflammation by 18- FDG PET/CT in psoriasis. American College of Cardiology Scientific Session, Washington, DC; Mar. 2017. [Poster]
- **Rivers JP**, Dey AK, Chung JH, Rana A, Chaturvedi A, Rodante JA, Lerman JB, Playford MP, Yao J, Chen MY, Bluemke DA, Powell-Wiley TM, Mehta NM. Visceral adipose tissue associates with coronary plaque burdens beyond cardiovascular risk factors in psoriasis. Atherosclerosis, Thrombosis, and Vascular Biology Scientific Session, Minneapolis, MN; May 2017. [Poster]

Travel to Professional Meetings:

- American Heart Association Epi/Lifestyle Scientific Session, Portland, OR; Mar. 7-10, 2017.
- American College of Cardiology Scientific Session, Washington, DC; Mar. 17-19, 2017.
- New England Science Symposium, Boston, MA; Mar 25, 2017.
- American Federation of Medical Research, Eastern Regional Meeting, Washington DC; Apr. 18, 2017.
- American Heart Association - Arteriosclerosis, Thrombosis, and Vascular Biology Scientific Session, Minneapolis, MN; May 4-6, 2017.

Awards:

- American Heart Association (AHA) Minority Travel Award.
- American Federation of Medical Research (AFMR) Scholar Award.



Hannah R. Robinson

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

Mentor: Adrian Wiestner, M.D., Ph.D., Senior Investigator, Hematology Branch

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: CD19/CD3 Bispecific Antibodies for Treatment of Chronic Lymphocytic Leukemia

Although treatment of chronic lymphocytic leukemia (CLL) has been advanced by introduction of targeted therapies, there remains a need for adjunct treatments capable of inducing deeper initial response, response in the setting of resistance to first-line agents, and/or CLL cure. Bispecific antibodies (bsAbs) can be used to target endogenous T cells against tumor cells via the formation of cytolytic synapses. The anti-CD19/CD3 bsAb blinatumomab is the most clinically advanced bsAb to date, and is approved for treatment of Philadelphia chromosome-negative relapsed/refractory B-cell acute lymphoblastic leukemia. However, due to its half-life of 2.1 hours, blinatumomab requires continuous intravenous dosing for efficacy. We have developed a novel anti-CD19/CD3 bsAb in the single chain-Fv Fc format (CD19/CD3-scFv-Fc). With a half-life approximately 100-fold longer than blinatumomab, CD19/CD3-scFv-Fc may be suitable for weekly dosing, which would provide a significant logistical advantage in the clinic.

We first sought to evaluate the activity of anti-CD19/CD3 bsAbs against CLL by culture of CLL peripheral blood mononuclear cells (PBMCs) with either blinatumomab, CD19/CD3-scFv-Fc, negative control HER2/CD3-scFv-Fc, or medium alone. Compared to negative control, treatment with both CD19/CD3-scFv-Fc and blinatumomab induced potent killing of CLL cells, as measured by flow cytometry ($p = 0.0031$ and 0.0004 , respectively, $n=10$). This response was associated with expansion of autologous CD4+ and CD8+ T cells, as well as increase in T cell activation and granzyme B expression. We next investigated response to CD19/CD3 bsAbs in a NOD/scid/ γ c(null) (NSG) xenograft mouse model. Here, mice were treated weekly with either blinatumomab, CD19/CD3-scFv-Fc, or HER2/CD3-scFv-Fc after established engraftment with human CLL PBMCs. Treatment with CD19/CD3-scFv-Fc resulted in a 99.5% reduction in circulating leukemia burden compared to treatment with control ($p<0.0001$). However, blinatumomab failed to induce a response ($p=0.82$). These data support promise of CD19/CD3-scFv-Fc as a novel immunotherapy for use in CLL.

Abstract Publications:

- **Robinson H**, Qi J, Baskar S, Rader C, Wiestner A. CD19/CD3 bispecific antibodies induce potent response against chronic lymphocytic leukemia cells ex vivo. *J Immunol* 2017; 120:17. *Immunology* 2017, The American Association of Immunologists Annual Meeting, May 12-16.

Awards:

- Best Predoctoral Fellow Pitch Award, National Heart, Lung, and Blood Institute Research Festival; June 9, 2017.

Travel to Professional Meetings:

- Immune Regulation in Autoimmunity and Cancer. Keystone Symposia, Whistler, BC; Mar. 26-30, 2017.
- Immunology 2017, The American Association of Immunologists Annual Meeting. Washington, DC; May 12-16, 2017.



Gregory W. Roloff

School: Jacobs School of Medicine and Biomedical Sciences, University at Buffalo

Mentor: Christopher S. Hourigan, M.D., D.Phil., Chief, Myeloid Malignancies Laboratory, Hematology Branch

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Quantifying measurable residual disease in acute myeloid leukemia by targeted RNA sequencing

Acute myeloid leukemia (AML) is a malignancy of blood-forming stem cells characterized by a high rate of relapse despite initial therapeutic response. Persistent leukemic burden giving rise to relapse is referred to as measurable residual disease (MRD). Due to disease heterogeneity, established MRD PCR assays are only applicable to small patient subsets with recurrent cytogenetic abnormalities.

We have developed a targeted RNA-sequencing assay capable of detecting and tracking MRD in approximately of 70% of cases. Our panel detects important AML wild-type gene expression signatures (WT1, PRAME, ABL), inversions (CBFB-MYH11), insertions (NPM1), and translocations (BCR-ABLp190, BCR-ABLp210, RUNX1-RUNX1T1, PML-RARA). 400 ng of RNA is extracted from peripheral blood and is reverse transcribed in the presence of primers containing 12-bp random barcode sequences to enable individual molecular labeling. Sequencing adapters are attached to targeted amplicons with 26 cycles of PCR and library quality is assessed by a Qubit DNA Fluorometer and 2100 Bioanalyzer. Libraries are sequenced on an Illumina MiSeq using V3 Reagent chemistry with 150bp single-end reads and analyzed using a custom bioinformatics pipeline.

To determine assay sensitivity and limits of detection, we spiked in RNA extracted from leukemia cell lines K-562 and Kas-1 into RNA from a healthy individual. Quantification of AML-specific transcripts (K562: PRAME, WT1, BCR-ABLp210 and Kas-1: RUNX1-RUNX1T1) was detectable in a linear relationship at all points in a dilution series spanning 1pg-800ng of leukemia input. 10,000 copies of ABL1 (control gene) were used as a baseline for healthy-donor expression. We then localized and quantified a pathognomonic 4bp insertion in exon 12 of NPM1 transcripts at all inputs in a dilution series of 20-400 ng RNA from blood extracted from patient samples. Ongoing work involves tracking MRD in a cohort of 50 clinically-annotated AML patients with blood samples available at longitudinal time points.

Full Length Publications:

- **Roloff GW**, Dillon LW, Wong HY, Lai C, Hourigan CS. Technical advances in measurement of minimal residual disease in AML. *J Clin Med* (Review). [In press]

Abstract Publications:

- **Roloff GW**, Dillon LW, Hayati S, Wong HY, Sung AD, Hourigan CS. Detection of measurable residual disease in AML by targeted RNA sequencing. American Society of Hematology (ASH) Annual Meeting, Atlanta, GA; Dec. 2017.

Travel to Professional Meetings:

- American Society of Hematology (ASH) Annual Meeting, Atlanta, GA; Dec. 9-12, 2017.

Awards:

- Best Predoctoral Fellow Pitch Award, National Heart, Lung, and Blood Institute Research Festival; June 9, 2017.



Mohammad R. Siddiqui

School: University of Wisconsin School of Medicine and Public Health

Mentor: Piyush K. Agarwal, M.D., Head, Bladder Cancer Section, Urologic Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Targeting Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor 2 (HER2) Expressing Bladder Cancer Using Combination Photoimmunotherapy (PIT)

Photoimmunotherapy (PIT) involves antibodies (Abs) conjugated to a photoabsorber (PA), IR Dye 700Dx, and then activated by near infra-red light (NIR) to specifically target tumors. Our lab has shown that bladder cancer (BC) tumors expressing high levels of EGFR can be efficiently targeted with PIT. However, PIT is less effective when a tumor lacks “overwhelming” expression of a single target. Our study focused on combinatorial PIT approaches for bladder tumors expressing EGFR and HER2, using Panitumumab-IR700 (PanIR700) and Trastuzumumab-IR700 (TraIR700) antibodies, respectively.

Tissue microarray (TMA) was used to determine the cell-surface expression of EGFR and HER2 in commercially available normal human bladder tissue and BC tissues. BC cell lines were analyzed for expression of EGFR and HER2 using flow cytometry. Concurrent and optimal binding of both PA-labeled Abs were determined using flow cytometry and immunocytochemistry. Efficacy of combination PIT was evaluated *in vivo* and *in vitro*.

Normal bladder urothelium TMAs showed EGFR and HER2 expression in 71% and 9% of control human samples, respectively. In contrast, EGFR and HER2 were expressed in 84% and 46% of BC samples, respectively. The SW780 bladder cancer cell line showed low to moderate cell-surface expression of EGFR and HER2, with 143 fold and 42 fold higher expression than the isotype controls, respectively, such that the ratio of cell surface EGFR to HER2 expression was approximately 3:1, ideal for combination PIT therapy. The *in vitro* NIR lethal dose-50 (LD_{50}) was determined to be 28.66 J/cm² for combination PIT compared to 71.55 J/cm² for the next most potent arm of PanIR700 alone therapy. Combination PIT also showed significant reduction in tumor growth and gross tumor size compared to control treatment arms *in vivo*.

This research demonstrates a novel approach to treating BC with low to moderate expression of different cell surface targets, namely EGFR and HER2.

Full Length Publications:

- **Siddiqui M**, Sanford T, Achuth, N, Zerbe C, Hughes M, Folio L, Brancato S, Agarwal P. Chronic colovesical fistula leading to chronic urinary tract infection resulting in end-stage renal disease in a chronic granulomatous disease patient. *Urol Case Rep*, 2017. [In press]
- **Siddiqui M**, Agarwal P. High Dose BCG for urothelial cell carcinoma is trickier than expected. *Translational Cancer Research*, 2017. [In press]
- **Siddiqui M**, Campbell G, Sanford T, Agarwal P. Current trials in non-muscle invasive bladder cancer (NMIBC). *Urol Oncol Semin Orig Invest*, 2017. [In press]
- Raikar R, Krane S, Li Q, Sanford T, **Siddiqui M**, Haines D, Vounganti S, Brancato S, Choyke P, Kobayashi H, Agarwal P. Epidermal growth factor receptor (EGFR) targeted photoimmunotherapy (PIT) for the treatment of EGFR expressing bladder cancer. *Mol Cancer Ther*, 2017. [In press]
- Stritch J, Brancato S, Dolan R, Mahir M, **Siddiqui M**, Sanford T, Zerbe C, Agarwal P. Case Presentation: Lung consolidation as sequelae of BCG sepsis after combined intravesical and intraurethral BCG. *Urol Case Rep*, 2017. [In press]

Abstract Publications:

- **Siddiqui M**, Raikar R, Sanford T, Agarwal PK. Targeting epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) expressing bladder cancer using combination photoimmunotherapy (PIT). American Urological Association (AUA), Boston, MA; May 12-16, 2017. [Late breaking abstract, podium presentation]
- Hsu I, **Siddiqui MR**, Li Q, Sanford T, Raikar R, Agarwal PK. Targeting Protein Kinase D2 May Represent a Therapeutic Strategy for Bladder Cancer. American Urological Association (AUA), Boston, MA; May 12-16, 2017. [Poster]
- **Siddiqui MR**, Raikar R, Sanford T, Agarwal PK. Targeting epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) expressing bladder cancer using combination photoimmunotherapy (PIT). American Society of Clinical Oncology (ASCO), Chicago, IL; June 2-6, 2017. [Poster]

Travel to Professional Meetings:

- American Urological Association (AUA), Boston, MA; May 12-15, 2017.



Richard M. Smith

School: Drexel University College of Medicine

Mentor: Frances T. Sheehan Gavelli, Ph.D., Functional & Applied Biomechanics Section, Rehabilitation Medicine Department

Institute: Clinical Center (CC)

Research: The Contributions of Pathological Volume and Kinematics to the Etiology of Adolescent Patellofemoral Pain Syndrome

One in eight active adolescent females suffer from idiopathic patellofemoral pain (PFP). Early to mid-adolescence is unique in maturation due to the greater potential of bone to grow and remodel due to external stressors (such as muscle and force imbalances). The etiology of PFP in this age group is not completely understood but current theories point to patellar maltracking and neuromuscular deficits. However, other factors such as the role of morphology (size and shape) have not been fully elucidated. The goal of this study is to determine if alterations in patellofemoral morphology contribute to PFP and kinematic abnormalities in this population.

Thirty-four adolescent females (ages 11-16, 17 with PFP and 17 asymptomatic controls) were enrolled in an ongoing IRB-approved study. Two sets of MRI scans were obtained for analysis: three-dimensional static T1-weighted gradient recalled echo acquired with the lower leg in an anatomically neutral position, and 3D dynamic MRI captured during cyclical flexion-extension volitional movements of the lower extremity. Patellar and femoral models were created using custom in-house algorithms and commercial software. Next, volume and shape measurements were calculated from these models.

Overall, the patellar volume was 13% larger in the cohort with PFP relative to controls ($p < 0.05$). Likewise, in the PFP cohort, a larger patellar volume was moderately correlated with a medial patellar tilt ($r = 0.50$, $p < 0.05$). Additionally, we observed that subjects with PFP had a 7% smaller femoral trochlear width ($p < 0.01$). The current study builds on our understanding of morphological factors in PFP. The increase in patellar bone volume in PFP may be the cause or a reactionary result of force imbalances and patellofemoral kinematic abnormalities. Future prospective studies with a larger sample size are warranted to make further conclusions.

Full Length Publications:

- **Smith RM**, Sheehan FT. Cross Platform Comparison of Imaging Technologies for Measuring Musculoskeletal Motion. In: Müller B, Wolf SI, Brueggemann G-P, et al., eds. *Handbook of Human Motion*. Springer International Publishing, Cham, Switzerland, 2017.
- Sheehan FT, **Smith RM**. 3D Musculoskeletal Kinematics Using Dynamic MRI. In: Müller B, Wolf SI, Brueggemann G-P, et al., eds. *Handbook of Human Motion*. Springer International Publishing, Cham, Switzerland, 2017.

Travel to Professional Meetings:

- Movement is Life 2016, Washington, DC; Nov. 10-11, 2016.
- American Academy of Orthopaedic Surgeons Annual Meeting 2017, San Diego, CA; Mar. 16-18, 2017.
- Orthopaedic Research Society Annual Meeting, San Diego, CA; Mar. 18-22, 2017.

Abstract Publications:

- **Smith RM**, Alexandridi NA, Boden BP, Alter KA, Sheehan FT. The contributions of pathological volume and kinematics to the etiology of adolescent patellofemoral pain. Orthopaedic Research Society Annual Meeting; San Diego, CA; Mar. 2017. [Poster]
- **Smith RM**, Boden BP, Sheehan FT. Another piece off the puzzle: adolescent patellofemoral pain and bone volume. National Medical Association Annual Meeting; Philadelphia, PA; July 2017. [Submitted]
- Smith RM, Sheehan FT, Boden BP. Shape matters: correlating femoral shape with kinematics in adolescents with patellofemoral pain. American Academy of Orthopaedic Surgeons Annual Meeting 2018. New Orleans, LA; Mar. 2018. [Submitted]



Katie K. Spielbauer

School: Michigan State University College of Human Medicine

Mentor: Lisa Cunningham, Ph.D., Chief, Section on Sensory Cell Biology

Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)

Research: Statin Use May Prevent Cisplatin-Induced Ototoxicity

Cisplatin therapy, while integral to the management of many solid tumors, often results in permanent hearing loss for cancer survivors. Currently no FDA approved therapy to prevent this hearing loss exists. Previous studies from our group have shown that upregulation of heat shock proteins (HSPs), specifically HSP32 (also called heme oxygenase 1), can ameliorate cisplatin-induced ototoxicity *in vitro*. We hypothesized that statins, known inducers of HSP32, administered during cisplatin chemotherapy might help prevent hearing loss *in vivo*.

Thirty nine CBA/Cal mice underwent hearing testing by far-field physiologic recording of auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs). The mice were then pretreated with either 40 or 60 mg/kg/day lovastatin by oral gavage for

two weeks followed by three rounds of cisplatin, during which daily statin use was continued. Cisplatin, lovastatin only, and vehicle control groups were used for comparison. ABR and DPOAE measures were repeated following cisplatin treatment. Cisplatin levels in the inner ear were measured using inductively-coupled plasma mass spectroscopy (ICP-MS). RT-qPCR for Hsp mRNA induction in the cochlea was performed.

Forty mg/kg lovastatin partially protected against cisplatin-induced hearing loss at 16kHz (36.9±22.6 vs. 55.0±4.3 dB SPL, p<0.01). DPOAE amplitudes were also partially preserved at 14.4 and 16 kHz with lovastatin co-administration (-4.4±20.6 vs -19.0±11.3 dB μV, p<0.05 and -6.6±21.1 vs -19.6±5.4 dB μV, p<0.05, respectively). This protection was most robust in male mice. ICP-MS demonstrated less cisplatin accumulation in the stria vascularis of male animals co-administered lovastatin (17.2±6.8 vs 23.1±3.5 pg platinum/ng sulfur, p<0.05). Hsp32 mRNA expression in the cochlea increased 32.8 fold following lovastatin administration.

These data indicate that lovastatin may protect against cisplatin-induced hearing loss and may do so through HSP induction and/or decreased cisplatin accumulation. Further studies to understand the protective mechanisms as well as evaluate efficacy in human patients are underway.

Full Length Publications:

- Breglio A, Rusheen A, Shide E, Fernandez K, **Spielbauer K**, McLachlin K, Hall M, Amable L, Cunningham L. Cisplatin ototoxicity is associated with long-term drug retention in the cochlea. *J Clin Invest*. [Under review, June 2017]
- Tran L, Allen C, Xiao R, Moore E, Davis R, Park S, **Spielbauer K**, Van Waes C, Schmitt N. Cisplatin alters anti-tumor immunity and synergizes with PD-1/PD-L1 inhibition in head and neck squamous cell carcinoma. *Cancer Immunol Res*. [Under review, May 2017]

Abstract Publications:

- Ryals M, May L, **Spielbauer K**, Kelly M, Burns J, Kelley M, Boger E, Morell R, Cunningham L. Transcriptional analysis of heat-shocked mouse protein: Attempting to align transcriptome to drug response. Association for Research in Otolaryngology, 40th MidWinter Meeting, Baltimore, MD; Feb. 11-15, 2017.
- Fernandez K, Allen P, Orlando M, Mulford D, Li C, Rusheen A, **Spielbauer K**, Brewer C, Schmitt N, Newlands S, Cunningham L. Concurrent use of cholesterol-lowering drugs may reduce the incidence of ototoxicity in cisplatin-treated patients. Association for Research in Otolaryngology, 40th MidWinter Meeting, Baltimore, MD; Feb. 11-15, 2017.

Travel to Professional Meetings:

- Association for Research in Otolaryngology, 40th Annual MidWinter Meeting, Baltimore, MD; Feb. 11-15, 2017.



Dordaneh E. Sugano

School: Albert Einstein College of Medicine

Mentor: Peter Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Index Tumor Volume on MRI as a Predictor of Clinical and Pathologic Outcomes Following Radical Prostatectomy

Index lesion tumor volume (ITV), measured on post-prostatectomy whole-mount pathology, has been demonstrated to correlate with adverse clinical and pathologic outcomes. ITV has been shown in prior studies to be significantly associated with systemic progression, prostate cancer (PCa)-specific mortality, and all-cause mortality. An accurate pathologic volume determination is time-consuming and can only be performed on patients who undergo prostatectomy. Moreover, ITV is difficult to measure preoperatively based on percent involvement on needle biopsy specimens alone.

Recent advances in MRI technology have rendered it a powerful tool in directing prostate biopsies, with a sensitivity and specificity of 90% and 88% for clinically significant cancers. Prior research has already established that tumor volume can be measured on MRI. We hypothesized that ITV measured on preoperative MRI could play a role in the prediction of extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node invasion (LNI), positive surgical margins (PM), and biochemical recurrence (BCR). In this study, we measured ITV of index lesions on preoperative MRI to determine how well it predicted prognosis.

On the creation of multivariate regression models, ITV was found to be an independent predictor of EPE (OR: 1.22, $p=0.010$), LNI (OR: 1.39, $p=0.001$), and SVI (OR: 1.28, $p=0.009$), but not PM (OR: 1.03, $p=0.522$). Although, five year BCR-free survival was higher for patients with $ITV < 2cc$ (84.1% vs 58.5%, $p=0.001$), ITV was not found to be an independent predictor of BCR (HR 1.69, $p=0.130$).

We demonstrate that Index Tumor Volume measured on preoperative MRI is a novel factor that has comparable predictive ability for pathologic outcomes when compared to pathologic ITV. We believe that the strength of the association between ITV and EPE, SVI, and LNI merits further investigation as a potential predictive factor for consideration prior to surgery and radiation therapy.

Full Length Publications:

- **Sugano D**, Sidana A, Calio B, Cobb K, Turkbey B, Pinto PA. MRI-targeted biopsy: Is systematic biopsy obsolete? *Can J Urol*. [In press]
- **Sugano D**, Sidana A, Calio B, Gaur S, Jain AL, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto PA. Index tumor volume on MRI as a predictor of clinical and pathologic outcomes following radical prostatectomy. *J Urol*. [Under review]

Abstract Publications:

- **Sugano D**, Sidana A, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Index tumor volume on MRI as a predictor of pathologic outcomes following radical prostatectomy. American Urological Association Annual Meeting, Boston, MA; 2017. [Podium presentation]
- **Sugano D**, Sidana A, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Effect of hypogonadism on prostate imaging and cancer detection. American Urological Association Annual Meeting, Boston, MA; 2017. [Poster presentation]
- **Sugano D**, Sidana A, Wright C, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Technique and case series of MRI guided in-bore biopsy for patients without rectum. American Urological Association Annual Meeting, Boston, MA; 2017. [Poster presentation]

- **Sugano D**, Xu S, Seifabadi R, Bakhutashvili I, Glossop N, Choyke P, Pinto P, Bale R, Wood BJ. Transperineal MR-guided prostate needle interventions using a patient-specific template. American Urological Association Annual Meeting, Boston, MA; 2017. [Poster presentation]
- **Sugano D**, Sidana A, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Can index lesion tumor volume on T2 weighted MRI predict biochemical recurrence following radical prostatectomy? Genitourinary Cancers Symposium, Orlando, FL; 2017. [Poster presentation]
- **Sugano D**, Sidana A, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood BJ, Pinto P. Index lesion tumor volume on MRI to predict adverse pathologic outcomes following radical prostatectomy. Genitourinary Cancers Symposium, Orlando, FL; 2017. [Poster presentation]
- **Sugano D**, Sidana A, Wright C, Calio B, Gaur S, Jain A, Maruf M, Merino M, Choyke P, Turkbey B, Wood B, Pinto P. MRI guided in-bore prostate biopsy for patients without rectum. Society of Urologic Oncology, San Antonio, TX; 2016. [Poster presentation]

Travel to Professional Meetings:

- American Urological Association Annual Meeting, Boston, MA; 2017.
- Genitourinary Cancers Symposium, Orlando, FL; 2017.
- Society of Urologic Oncology, San Antonio, TX; 2016.



Samiksha Tarun

School: Saint Louis University School of Medicine

Mentor: Terry J. Fry, M.D., Head, Hematologic Malignancies Section, Pediatric Oncology Branch

Institute: National Cancer Institute (NCI)

Research: Pre-Clinical Evaluation of Potency and Efficacy of Anti-CD33 and Anti-CD123 Chimeric Antigen Receptor Expressing T Cells for Treatment of Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive malignancy with a poor prognosis and limited treatment options. Chimeric antigen receptor expressing T (CART) cell therapy has been highly successful against refractory B cell acute lymphoblastic leukemia. Effective use of CART cells in AML has not yet been established. Here, we evaluated the pre-clinical potency and efficacy of anti-CD123 and anti-CD33 CART cells against AML.

Anti-CD33 and anti-CD123 CART cells were developed using CD33 and CD123 single chain fragment variable sequences and cloning into a third-generation lentiviral plasmid containing a CD8 transmembrane domain, a co-stimulatory signaling domain (either CD28 or 41BB) and a CD3-zeta domain. CART surface expression on T cells was measured by flow cytometry, staining with allophycocyanin (APC)-conjugated anti-FLAG for anti-CD123 CART cells or APC-Protein L/streptavidin for anti-CD33 CART cells. Enzyme-linked immunosorbent assay kits for interleukin-2 (IL2) and interferon-gamma (IFN-gamma) were used to assess *in vitro* CART functionality; 10^5 tumor cells were co-incubated with 10^5 transduced CART cells or mock T cells for 16 hours in 96-well plates. Killing assays using IncuCyte live cell analysis were completed to assess killing potency of CART; 10^5 tumor cells were co-incubated with 10^5 transduced CART cells or mock T cells for 36 hours in 96-well plates.

Anti-CD33 and anti-CD123 CART cells show *in vitro* functionality through robust production of IL2 and IFN-gamma against various AML cell lines. Anti-CD33 CART cells produced 2000 pg/mL of IL2 when co-incubated with THP1 cell line (derived from a one-year-old male patient with relapsed AML). Anti-CD33 CART cells also produced about 2000 pg/mL of IFN-gamma against THP1 and also MOLM14 (derived from a 20-year-old male with M5 AML). Anti-CD123 CART produced about 2500 pg/mL of IFN-gamma against both MOLM14 and THP1, and 1000 pg/mL of IL2 against MOLM14. CART cells targeting both antigens showed *in vitro* killing activity against MOLM14 and THP1 AML cell lines.

CART cell therapy targeting surface antigens CD33 and CD123 in AML is promising. Pre-clinical AML models indicate *in vitro* activity of anti-CD33 and anti-CD123 CART cells against AML, showing lysis of leukemic cells and continued presence of CART cells. Further experiments are needed to characterize any associated toxicity of anti-CD33 and anti-CD123 CART cells.

Abstract Publications:

- **Tarun S**, Qin H, Chien CD, Kohler EM, Fry TJ. Pre-clinical evaluation of potency and efficacy of anti-CD33 and anti-CD123 chimeric antigen receptor expressing T cells for treatment of acute myeloid leukemia. American Society of Hematology (ASH) Annual Meeting, Atlanta, GA; Dec. 9-12, 2017.

Travel to Professional Meetings:

- American Society of Clinical Oncology, Chicago, IL; Jun. 2-6, 2017.



Kevin H. Terashima

School: UCLA David Geffen School of Medicine

Mentor: Daniel S. Reich, M.D., Ph.D., Chief, Translational Neuroradiology Section, Neuroimmunology Branch

Institute: National Institute of Neurological Diseases and Stroke (NINDS)

Research: Gadolinium Deposition After Contrast-Enhanced Magnetic Resonance Imaging: A Retrospective Study of Multiple Sclerosis Patients

Gadolinium-based contrast agents (GBCAs) are essential in magnetic resonance imaging (MRI) for the diagnosis and monitoring of multiple sclerosis (MS). Patients who receive many doses of certain GBCAs have prolonged deposition of gadolinium in deep gray matter structures of the brain including the cerebellar dentate nuclei (DN), detectable on T1-weighted MRI. The clinical significance of this phenomenon is undefined. We compared longitudinal changes in T1 signal intensity of the DN and clinical disability measures in a closely monitored MS cohort after repeat administrations of a GBCA over a mean of 5.2 ± 2.9 years.

We retrospectively analyzed data from MS patients followed at the National Institutes of Health who received five or more administrations of the linear GBCA gadopentetate dimeglumine (Magnevist). Disability was assessed with the Expanded Disability Status Scale (EDSS), a global measure of MS disease severity, and the 9-hole peg test (9-HPT), a measure of manual dexterity. DN signal intensity ratios were calculated from non-enhanced T1-weighted brain MRIs. Linear mixed effects models corrected for differences in T1 protocols and allowed for estimation of subject-specific slopes of signal intensity ratio over time. The Pearson's correlation coefficient was used to evaluate the association between estimated subject-specific T1 signal intensity ratio slopes and clinical variables.

Mean rate of change of DN-to-middle cerebellar peduncle signal intensity ratio for 48 MS patients (28 females, 20 males) who received 6-71 doses of GBCA was 0.0117/year (std dev 0.0072/year). However, subject-specific rate of T1 change showed no correlation with annual change in EDSS ($p=0.29$) or 9-HPT performance ($p=0.66$).

MS patients who received multiple doses of gadopentetate dimeglumine demonstrated a progressive increase in T1 signal in the DN, likely due to gadolinium deposition. This imaging finding did not correlate with change in EDSS or 9-HPT performance. The clinical significance of prolonged intracranial gadolinium deposition remains unknown.

Full Length Publications:

- Terashima KH, Reich DS. Gadolinium deposition: practical guidelines in the face of uncertainty. *Lancet Neurol.* 16:495-97, 2017.

Abstract Publications:

- Terashima KH, Reich DS. Dentate nucleus T1 signal changes after linear vs. macrocyclic gadolinium contrast exposure: are multiple sclerosis patients at risk? American Society of Neuroradiology, Long Beach, CA; Apr. 23-27, 2017.

Travel to Professional Meetings:

- Consortium of Multiple Sclerosis Centers: MRI Consensus Meeting; Jan. 11-12, 2017.
- American Society for Neuroradiology, Long Beach, CA; Apr. 23-27, 2017.



Ankita H. Tippur

School: Emory University School of Medicine

Mentor: Kareem Zaghoul, M.D., Ph.D., Chief, Functional and Restorative Neurology Unit, Surgical Neurology Branch

Institute: National Institute of Neurological Diseases and Stroke (NINDS)

Research: Spectral Analysis of Complex Partial and Focal to Bilateral Tonic-Clonic Seizures Reveals a Decreasing, Low Frequency Power Contour

It is theorized that the ictal wavefront, a slow-moving wave of tonic neuronal firing, is responsible for the recruitment of cortical areas into a seizure by producing low-frequency synaptic barrages that synchronize neuronal population firing. Though easily identified in multielectrode recordings, this wavefront is difficult to characterize in electrocorticography (ECoG) recordings of seizures. However, we may be able to indirectly pinpoint the ictal wavefront's passing in ECoG spectrally due to its low frequency effects.

We used a short-time Fourier transform (STFT) analysis of ECoG recordings from refractory epilepsy patients undergoing intracranial seizure monitoring to identify the low-frequency (0.5 – 16 Hz) power changes that occur during complex partial seizures (CPS) and focal to bilateral tonic-clonic seizures (F2BTCS). We then extracted dominant power contours from spectrograms using a custom-built, automated contour extraction algorithm for analysis.

In seizures from 10 patients, average raw power spectrograms showed maximum power contours initiating in the 4-8 Hz range at seizure recruitment. This power contour stabilized in frequency initially, but slowly and consistently decreased in frequency during post-recruitment, reaching the 1-2 Hz range at termination. We observed that power localized along this contour initially, de-localized during post-recruitment, and re-localized along this frequency contour as termination approached. Individual ictal channels also demonstrated these trends, with the caveat that they showed timing variabilities in power localization during the post-recruitment epoch.

This work shows that low frequency power is concentrated in the same frequency range at seizure initiation as the frequency of neuronal firing following ictal wavefront passage, suggesting that the wavefront's passage may be defined in ECoG via a spectral approach. It also supports current literature regarding seizure synchronization, with high synchronization at initiation and termination and desynchronization at post-recruitment. Future work will explore the mechanisms behind this power contour, giving us insights into how seizures spread in cortical networks.

Abstract Publications:

- Vaz A, **Tippur AH**, Inati SK, Zaghoul KA. Cortical neural correlates of major depressive disorder. Society for Neuroscience 2017, Washington, DC. [Submitted]
- **Tippur AH**, Diamond JM, Chapeton JI, Inati SK, Zaghoul KA. Spectral analysis of focal to bilateral tonic-clonic seizures reveals a dominant, decreasing low frequency power contour. American Epilepsy Society Annual Meeting 2017, Washington, DC. [Submitted]

Travel to Professional Meetings:

- 2017 American Association of Neurological Surgeons Annual Scientific Meeting, Los Angeles, CA; Apr. 22-26, 2017.



Giacomo C. Waller

School: Emory University School of Medicine

Mentor: Richard Childs, M.D., R.A.D.M., U.S.P.H.S., Senior Investigator, Laboratory of Transplantation Immunology, Hematology Branch; Clinical Director, Division of Intramural Research, NHLBI

Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research: Development of an Optimized Toolkit for High-Efficiency Lentiviral Genetic Modification of Human Natural Killer Cells

Natural Killer (NK) cells are a subset of immune cells with antiviral and antitumor activity that have the innate ability to lyse tumor cells without the need to recognize specific MHC-bound peptide sequences. Infusion of large numbers of NK cells, expanded *in vitro*, represents a promising immunotherapeutic intervention in cancer. To augment the function and homing of NK cells with expression of particular genes, we developed and optimized a protocol for lentiviral transduction of primary human NK cells. Stimulation of NK cells with IL-2 alone for two to four days was found to be necessary and sufficient to achieve high transduction efficiency, while the addition of other cytokines had negligible or transient effects. Identical off-the-shelf lentiviral constructs with eight different promoter sequences driving expression of EGFP were examined, and three of the promoters were found to consistently facilitate transduction efficiencies in the range of 25-60% with minimal loss of expression over two weeks of culture in our clinical-grade feeder-based *in vitro* expansion protocol. Transduced and expanded primary NK cells did not show functional deficiencies in degranulation, IFN γ , or TNF α production. To permit identification, tracking, and isolation suitable for scalable use under GMP, constructs expressing both the gene of interest and a truncated CD34 marker are being examined, both as 2A-fusions and expressed from independent promoters. The goal of this research is to enable the production of large numbers (>1010) of uniformly modified NK cells suitable for infusion in our clinical NK cell treatment protocol.

Abstract Publications:

- **Waller G**, Allan D, Chinnasamy D, Chakraborty M, Hochman M, Reger R, Childs R. Development of an optimized toolkit for high-efficiency lentiviral genetic modification of human natural killer cells. 15th Annual NHLBI Department of Intramural Research Festival. Bethesda, MD; June 9, 2017.

Travel to Professional Meetings:

- American Society of Hematology 59th Annual Meeting. Atlanta, GA; Dec. 9-12, 2017. [Planned]



Suzanne C. Ward

School: University of Cincinnati College of Medicine

Mentor: Edward Cowen, M.D., Senior Clinician and Head, Dermatology Consultation Service, Dermatology Branch

Institute: National Cancer Institute (NCI)

Research: Beyond the Triad: Correlating Mucocutaneous Phenotype, Inheritance Patterns, and Survival in Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a telomere biology disorder characterized by the clinical triad of reticulate hyperpigmentation, nail dystrophy, and oral leukoplakia, as well as a high risk of bone marrow failure, cancer, pulmonary fibrosis, and other medical problems. Although many telomere biology genes have been linked to DC, there are limited data on genotype-phenotype relationships, particularly regarding the mucocutaneous manifestations of DC.

In this study, we sought to assess the diagnostic utility of the clinical triad, identify additional mucocutaneous features of DC, investigate genotype-phenotype correlations, and determine the value of mucocutaneous features as a prognostic marker.

We examined the mucocutaneous phenotype of a large cohort (n=60) of patients with genetically-proven DC. Patients were assessed for triad features as well as eight additional mucocutaneous features which have been reported in association with DC. The complete DC triad manifested in only 37% (22/60) of patients. In contrast, 10% (6/60) lacked all DC triad features. Six additional non-triad mucocutaneous features were present in more than 20% of the cohort. Patients with more than one triad feature or more than five total mucocutaneous features were more likely to have autosomal recessive or heterozygous TINF2 mutations as the cause of DC ($p < 0.01$), as well as greater cumulative incidence of bone marrow failure and increased mortality compared with patients with fewer mucocutaneous features ($p < 0.001$).

Although DC presents with a broad spectrum of cutaneous signs/symptoms, identification of mucocutaneous features has both diagnostic and prognostic implications and can be useful for early intervention and management of DC.

Full Length Publications:

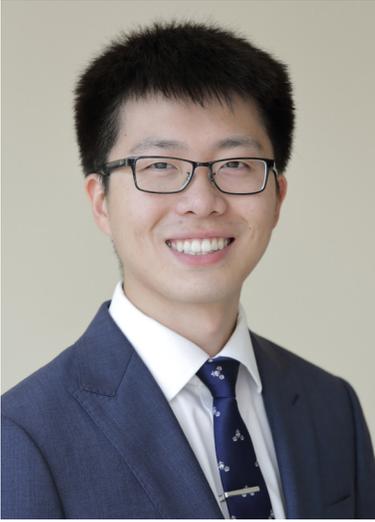
- **Ward SC**, Savage SA, Giri N, Alter BP, Rosenberg PS, Pichard DC, Cowen EW. Beyond the triad: correlating inheritance, mucocutaneous phenotype, and mortality in dyskeratosis congenita. [Submitted]
- **Ward SC**, Savage SA, Giri N, Alter BP, Cowen EW. Progressive reticulate skin pigmentation and onychia in a patient with bone marrow failure. [Submitted]
- **Ward SC**, Townsley DM, Weinstein B, Young NS, Dunbar CE, Pichard DC, Cowen EW. Cutaneous and oral hypersensitivity syndrome associated with eltrombopag in patients with severe aplastic anemia. [Submitted]

Abstract Publications:

- **Ward SC**, Savage SA, Giri N, Alter BP, Pichard DC, Cowen EW. TINF2 mutations are associated with severe mucocutaneous disease in dyskeratosis congenita. Society for Investigative Dermatology Annual Meeting, Portland OR; Apr. 26-29, 2017. [Poster]
- **Ward SC**, Savage SA, Giri N, Alter BP, Pichard DC, Cowen EW. Beyond the triad: the spectrum of mucocutaneous findings in dyskeratosis congenita. World Congress of Pediatric Dermatology. Chicago, IL; Jul. 6-9, 2017. [Poster]

Travel to Professional Meetings:

- Society for Investigative Dermatology Annual Meeting. Portland, OR; Apr. 26-29, 2017.
- World Congress of Pediatric Dermatology. Chicago, IL; Jul. 6-9, 2017.



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Research: Novel Dual cIAP1/XIAP Antagonist ASTX660 Activity in Preclinical Models of Human Papillomavirus(+) and (-) Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer with a five-year survival of approximately 50%. HNSCC is linked to human papillomavirus (HPV+) and tobacco carcinogenesis (HPV-). Nearly 30% of HNSCC overexpress FADD (Fas-Associated Death Domain), with or without BIRC2/3 genes encoding the cellular Inhibitor of Apoptosis Proteins 1/2 (cIAP1/2), critical components of the Tumor Necrosis Factor (TNF) Receptor signaling pathways. The frequency of such mutations provides a window for therapeutics, as IAP antagonists can switch TNF α signaling from pro-survival to pro-apoptotic. ASTX660 (developed by Astex Pharmaceuticals) is a novel dual cIAP1/XIAP antagonist in clinical trials

for advanced solid tumors and lymphomas. Our objective was to determine the therapeutic effects of ASTX660 in HPV+/- HNSCC preclinical models.

ASTX660 at nanomolar concentrations was found to potently inhibit cell proliferation (XTT assays) and induce apoptosis (Annexin/7-AAD flow cytometry), and displayed combinatorial activity with TNF α , TRAIL, and cisplatin in multiple human HPV+/- HNSCC cell lines, as well as several Murine Oral Cancer (MOC) cell lines. Western blotting showed near complete degradation of cIAP1 expression at nanomolar concentrations in human HNSCC cell lines, as well as cleavage of caspases 3 and 8. Furthermore, cytotoxic T lymphocyte assays have demonstrated significant stimulation of T-cell killing of MOC-1 cells expressing surface ovalbumin through both perforin/granzyme B and TNF α as mechanisms of killing. Using both HPV+/- human HNSCC xenografts and syngeneic MOC mouse models, we observed anti-tumor effects of ASTX660 as a monotherapy and in combination with cisplatin, PD-1 blockade, and/or radiation. The greatest tumor regression of HPV+/- human HNSCC xenografts was observed in combination with radiation, whereas the greatest tumor regression of MOC-1 tumors was observed in combination with both radiation and PD-1 blockade. Our results demonstrate that ASTX660 sensitizes HPV+/- HNSCC to TNF α and causes significant tumor regression in combination with radiation.

Full Length Publications:

- **Xiao R**, Van Waes C, Schmitt NC. Putting T cells to work - outsourcing neoantigen detection in head and neck cancer? *Oral Dis* 2016 Oct 31. doi: 10.1111/odi.12604. [Epub ahead of print]
- Tran L, Allen CT, **Xiao R**, Moore EC, Davis RJ, Park S, Spielbauer K, Van Waes C, Schmitt NC. Cisplatin alters anti-tumor immunity and synergizes with PD-1/PD-L1 inhibition in head and neck squamous cell carcinoma. *Cancer Immunol Res*. [Under review]

Abstract Publications:

- **Xiao R**, An Y, Derakhshan A, Chen Z, Schmitt NC, Van Waes C. Novel dual cIAP1/XIAP antagonist ASTX660 activity in preclinical models of human papillomavirus(+) and (-) head and neck squamous cell carcinoma. American Association for Cancer Research (AACR) Annual Meeting. Washington, DC; Apr. 1-5, 2017.
- Tran L, Allen CT, Park S, **Xiao R**, Van Waes C, Schmitt NC. Anti-tumor activity of cisplatin is enhanced by anti-PD-1 blockade in preclinical models of head and neck squamous cell carcinoma. American Association for Cancer Research (AACR) Annual Meeting. Washington, DC; Apr. 1-5, 2017.

Travel to Professional Meetings:

- American Association for Cancer Research (AACR) Annual Meeting. Washington, DC; Apr. 1-5, 2017.

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