



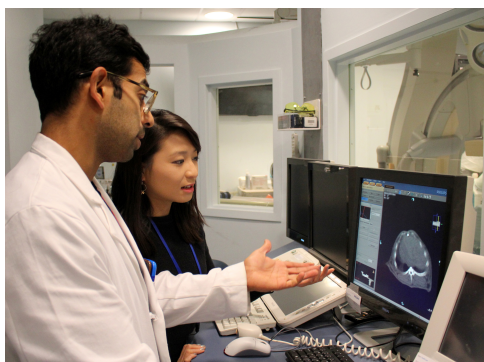
The National Institutes of Health's Medical Research Scholars Program

2018-2019 Scholars & Abstracts



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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.

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 2018-2019 Scholars of the National Institutes of Health’s (NIH) Medical Research Scholars Program (MRSP) and outlines their research studies and accomplishments 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 healthcare 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, 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 advice 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 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.

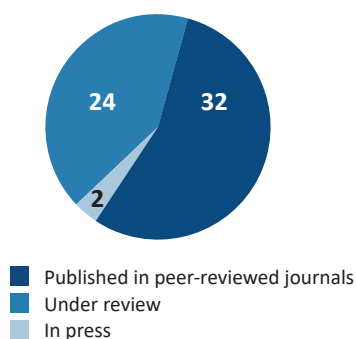
For more information about the MRSP or to learn about opportunities to support the program, please contact the Development Office at Development@fnihi.org.

Research Achievements and Scholarly Output

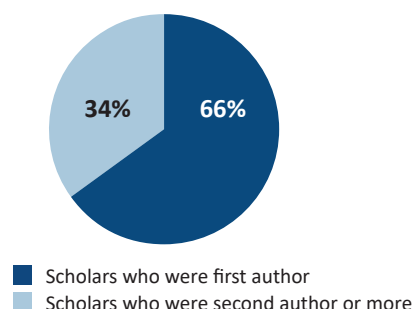
MRSP Class of 2018-2019

During the 2018-2019 MRSP year, the scholars celebrated many research accomplishments, as shown by the number of manuscripts they produced (**Graph 1**); the number of scholars who were first authors (**Graph 2**); the number of scholars who presented at professional meetings (**Graph 3**); and the number of scholars who traveled to professional meetings (**Graph 4**). Specifically, 21 scholars (57 percent) produced a total of 58 manuscripts for peer-reviewed publication; 34 scholars (92 percent) attended 62 professional meetings where they presented a total of 71 abstracts; and 14 scholars (38 percent) received a **total of 18 awards**.

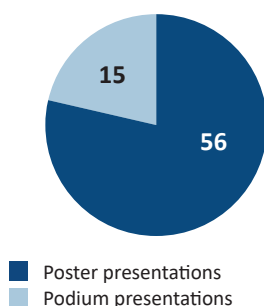
Graph 1. Completion of 58 MRSP Manuscripts



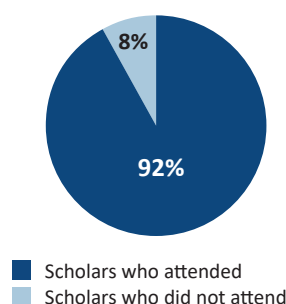
Graph 2. Authorship of MRSP Publications



Graph 3. Presentations at Scholarly Meetings



Graph 4. Attendance at Professional Meetings



Below are MRSP publications, awards and honors, as of August 2018:

In Print

- **Bauer TM**, Giles AV, Sun J, Femnou A, Covian R, Murphy E, Balaban RS. Perfused murine heart optical transmission spectroscopy using optical catheter and integrating sphere: Effects of ischemia/reperfusion. *Anal Biochem*. 2019 Dec 1; 586: 113443. doi: 10.1016/j.ab.2019.113443. Epub 2019 Sep 17.
- Groenendyk JW, Shukla P, Dey AK, Elnabawi YA, Aksentijevich M, **Choi H**, Genovese LD, Harrington CL, Natarajan B, Goyal A, Reddy AS, Rodante JA, Kabbany MT, Sadek A, Al Najafi M, Playford MP, Joshi AA, Ahlman MA, Gelfand JM, Bluemke DA, Mehta NN. Association of aortic vascular uptake of 18FDG by PET/CT and aortic wall thickness by MRI in psoriasis: A prospective observational study. *Eur J Nucl Med Mol Imaging*. 2019 Aug 5. doi: 10.1007/s00259-019-04454-w [Epub ahead of print]
- Elnabawi YA, Oikonomou EA, Dey AK, Mancio J, Rodante JA, Aksentijevich M, **Choi H**, Keel A, Erb-Alvarez J, Teague HL, Joshi AA, Playford MP, Lockshin B, Choi AD, Gelfand JM, Chen MY, Bluemke DA, Shirodaria C, Antoniadis C, Mehta NN. Association of biologic therapy with coronary inflammation in patients with psoriasis as assessed by perivascular fat attenuation index. *JAMA Cardiol*. 2019 Jul 31; 4(9): 885-891

- **Cruz Walma DA**, Collins JW. Western blotting with solutions containing nanoliter volumes of antibody. *Curr Protoc Cell Biol.* 2019 May; 84:e87
- Yamada KM, Collins JW, **Cruz Walma DA**, Doyle AD, Morales SG, Lu J, Matsumoto K, Nazari SS, Sekiguchi R, Shinsato Y, Wang S. Extracellular matrix dynamics in cell migration, invasion and tissue morphogenesis. *Int J Exp Pathol.* 2019 Jun; 100(3): 144-152. Review.
- **Fick CN**, Fratzl-Zelman N, Roschger P, Klaushofer K, Jha S, Marini JC, Bhattacharyya T. Melorheostosis: a clinical, pathological and radiological case series. *Am J Surg Pathol.* 2019 Jul 26. doi: 10.1097/PAS. [Epub ahead of print]
- Sun L, Clavijo PE, Robbins Y, Patel P, Friedman J, **Greene S**, Das R, Silvin C, Van Waes C, Horn LA, Schlom J, Palena C, Maeda D, Zebala J, Allen CT. Inhibiting myeloid-derived suppressor cell trafficking enhances T cell immunotherapy. *JCI Insight.* 2019 Apr 4; 4(7): eCollection 2019 Apr 4.
- **Greene S**, Patel P, Allen CT. How patients with an intact immune system develop head and neck cancer. *Oral Oncol.* 2019 May; 92: 26-32. Review.
- **Hong GH**, Ortega-Villa AM, Hunsberger S, Chetchotisakd P, Anunnatsiri S, Mootsikapun P, Rosen LB, Zerbe CS, Holland SM. Natural history and evolution of anti-interferon-gamma autoantibody-associated immunodeficiency syndrome in Thailand and the U.S. *Clin Infect Dis.* 2019 Aug 20. doi: 10.1093/cid/ciz786. [Epub ahead of print]
- Caplash S, Gangaputra S, **Kesav N**, Akanda M, Vitale S, Kodati S, Marques A, Sen HN. Usefulness of routine Lyme screening in patients with uveitis. *Ophthalmology.* 2019 Jun 27. doi: 10.1016/j.ophtha.2019.06.014. [Epub ahead of print]
- **Lampert EJ**, Hays JL, Kohn EC, Annunziata C, Minasian L, Yu M, Gordon N, Sissung TM, Chiou VL, Figg WD, Houston N, Lee JM. Phase I/II study of olaparib and carboplatin in heavily pretreated recurrent high-grade serous ovarian cancer at low genetic risk. *Oncotarget* 2019 Apr 23; 10(30): 2855-2868.
- Davidson ERW, Thomas TN, **Lampert EJ**, Paraiso MFR, Ferrando CA. Route of hysterectomy during minimally invasive sacrocolpopexy does not affect postoperative outcomes. *Int Urogynecol J.* 2019 Apr; 30(4): 649-655.
- Tamura K, **Langerman SD**, Ceasar JN, Andrews MR, Powell-Wiley TM. Neighborhood social environment and cardiovascular disease risk. *Curr Cardiovasc Risk Rep.* 2019 Apr (13)4:7.
- Xiao Z, Qiu Y, Lin Y, **Medina R**, Zhuang Z, Rosenblum JS, Cui J, Li Z, Zhang X, Guo L. Blocking lncRNA H19-miR-19a-Id2 axis attenuates hypoxia/ischemia-induced neuronal injury. *Aging.* 2019 Jun 15; 11(11): 3585-3600.
- **Pithadia DJ**, Treichel AM, Lee CR, Cowen EW, Linehan WM, Moss J, Darling TN. Birt-Hogg-Dubé syndrome initially diagnosed as tuberous sclerosis complex. *JAAD Case Rep.* 2019; 5(4): 368-371.
- Flannagan KS, Sjaarda LA, Hill MJ, Connell MT, Zolton JR, Perkins NJ, Mumford SL, Plowden TC, Andriessen VC, **Radoc JG**, Schisterman EF. Pilot randomized trial of short-term changes in inflammation and lipid levels during and after aspirin and pravastatin therapy. *Reprod Health.* 2019 Sep 2; 16(1): 132. doi: 10.1186/s12978-019-0794-6.
- **Sackett J**, Choyke PL, Turkbey B. Prostate imaging reporting and data system version 2 for MRI of prostate cancer: Can we do better? *Am J Roentgenol.* 2019 Jun; 212(6): 1244-1252.
- **Seehra GK**, Solomon B, Ryan E, Steward A, Roshan Lal T, Tanima Y, Lopez G, Sidransky E. Five-parameter evaluation of dysphagia: A novel prognostic scale for assessing neurological decline in Gaucher disease type 2. *Mol Genet Metab.* 2019 Jul; 127(3): 191-199.
- Eghbali A, Hassan S, Seehra GK, Fitzgibbon E, Sidransky E. Ophthalmological findings in Gaucher disease. *Mol Genet Metab.* 2019 May; 127(1): 23-27.
- Ryan E, **Seehra GK**, Sharma P, Sidransky E. GBA1-associated parkinsonism: new insights and therapeutic opportunities. *Curr Opin Neurol.* 2019 Aug; 32(4): 589-596.
- Ryan E, **Seehra GK**, Sidransky E. Mutations, modifiers and epigenetics in Gaucher disease: Blurred boundaries between simple and complex disorders. *Mol Genet Metab.* 2019 Aug 20. doi: 10.1016/j.ymgme.2019.08.006. [Epub ahead of print]
- Park SJ, **Ye W**, Xiao R, Silvin C, Padget M, Hodge JW, Van Waes C, Schmitt NC. Cisplatin and oxaliplatin induce similar immunogenic changes in preclinical models of head and neck cancer. *Oral Oncol.* 2019 Aug; 95: 127-135.
- **Ye W**, Schmitt NC. Pembrolizumab for recurrent/metastatic head and neck cancer: equally promising for Asian patients? *Ann Transl Med.* 2019 Mar; 7(Suppl 1):S14. doi: 10.21037/atm.2019.01.46. [Epub ahead of print]
- Xiao R, An Y, **Ye W**, Derakhshan A, Cheng H, Yang X, Allen C, Chen Z, Schmitt NC, Van Waes C. Dual antagonist of cIAP/XIAP ASTX660 sensitizes HPV(-) and HPV(+) head and neck cancers to TNF α , TRAIL, and radiation therapy. *Clin Cancer Res.* 2019 Jul 2. doi: 10.1158/1078-0432.CCR-18-3802. [Epub ahead of print]
- **Ye W**, Schmitt NC, Ferris R, Allen C. Improving the therapeutic ratio in head and neck cancer. R. Kimble (Ed.), *Improving responses to immunotherapy in head and neck squamous cell carcinoma*. Philadelphia: Elsevier; 2019. [In press]

In Press

- Elinoff JM, Mazer AJ, Cai R, **Lu M**, Graninger G, Harper B, Ferreyra G, Sun J, Solomon MA, Danner RL. Meta-analysis of blood genome-wide expression profiling studies in pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol.* [In press]
- **Ye W**, Schmitt NC, Ferris R, Allen C. Improving the therapeutic ratio in head and neck cancer. R. Kimble (Ed.), *Improving responses to immunotherapy in head and neck squamous cell carcinoma*. Philadelphia: Elsevier; 2019. [In press]

Under Review

- **Bauer TM**, Murphy E. A current perspective on the identity of the permeability transition pore: Are we there yet? [Under review, submitted to *J Mol Cell Cardiol*, 2019]
- Papanicolaou K, Deepthi A, Liu T, **Bauer TM**, Li Z, Da Costa E, Crepy D'Orleans C, Nathan S, Lefer DJ, Murphy E, Paolocci N, Foster BD, O'Rourke B. Global, but not cardiac-specific, knockout of ROMK potassium channels worsens cardiac ischemia-reperfusion injury. [Under review, submitted to *J Mol Cell Cardiol*, 2019]
- **Choi H**, Dey AK, Aksentjevich M, Rodante JA, Elnabawi YA, Khalil N, Playford MP, Gelfand J, Chen M, Bluemke DA, Buckler A, Mehta NN. Treatment of psoriasis with biologic therapy is associated with improvement of coronary artery plaque necrotic core and positive remodeling: results from a prospective, observational pilot study. [Under review, submitted to *Circulation*, 2019.]
- Munger E, **Choi H**, Dey AK, Elnabawi YA, Groenendyk JW, Khalil N, Rodante JA, Aksentjevich M, Reddy A, Argueta-Amaya J, Playford MP, Hasan A, Jafri M, Sandfort V, Chen MY, Bluemke DA, Gelfand JM, Mehta NN. Application of machine learning to determine top predictors of non-calcified coronary plaque burden in psoriasis. [Under review, submitted to *Am J Cardiol*, 2019.]
- Dey AK, Gaddipati R, Elnabawi YA, Ongstad E, Goyal A, Rodante JA, Sajja A, Sorokin A, Teague HL, Aksentjevich M, **Choi H**, Khalil N, Reddy A, Argueta-Amaya J, Shukla P, Baumer Y, Joshi AA, Sandfort V, Playford MP, Chen M, Bluemke DA, Karathanasis S, Gelfand JM, Gupta R, Mehta NN. Soluble lectin-like oxidized low-density lipoprotein receptor-1 is associated with subclinical coronary artery disease in psoriasis. [Under review, submitted to *JAMA Dermatol*, 2019]
- **Fick CN**, Grant C, Sheehan FT. Adolescent patellofemoral pain: an envelope of pathology. [Under review, submitted to *Am J Sports Med*, 2019]
- Friedman J, Moore EC, Zolkind P, Robbins Y, Clavijo PE, Sun L, **Greene S**, Morisada M, Mydlarz W, Schmitt N, Hodge J, Schreiber H, Van Waes C, Uppaluri R, Allen CT. Neoadjuvant PD-1 immune checkpoint blockade reverses functional immunodominance among tumor-antigen specific T cells. [Under review, submitted to *J Clin Invest*, 2019]
- Ruan X*, Li P*, Ma Y, Jiang C, Chen Y, Shi Y, **Gupta N**, Seifuddin F, Pirooznia M, Suemizu H, Ohnishi Y, Yoneda N, Nishiwaki M and Cao H. Multilevel integrative transcriptome analyses in humans and humanized mice define in vivo human lncRNA metabolic regulators. [Under review, submitted to *Cell Metab*, 2019]
- **Kesav N**, Kaplan A, Hwang C, Okeagu C, Sen HN. Tattoo-associated cases of Vogt-Koyanagi-Harada disease. [Under review, submitted to *Retin Cases Brief Rep*, 2019]
- Knickelbein K, Jeffrey B, Wei M, Cheng S, **Kesav N**, Sen HN. Reproducibility of full-field electroretinogram measurements in birdshot chorioretinopathy patients: an intra- and inter-visit analysis. [Under review, submitted to *Ocul Immunol Inflamm*, 2019]
- Sapio MR, Iadarola MJ, Loydpierson AJ, **Kim JJ**, Maric D, Mannes AJ. Dynorphin and enkephalin opioid peptides and transcripts in spinal cord during peripheral inflammatory hyperalgesia and allodynia. [Under review, submitted to *J Pain*, 2019]
- Sapio MR, **Kim JJ**, Loydpierson AJ, Maric D, Goto T, Vazquez FA, Muhly WT, Iadarola MJ, Mannes AJ. Opioid and non-opioid neuronal opponent processes in spinal cord dorsal horn controlling hyperalgesia and pain sensitization. [Under review]
- Andrews MR, Tamura K, Claudel S, Xu S, Ceasar JN, Collins B, **Langerman SD**, Mitchell V, Baumer Y, Powell-Wiley TM. Geospatial analysis of neighborhood deprivation index (NDI) for the United States by county. [Under review]
- Andrews MR, Ceasar JN, Tamura K, **Langerman SD**, Mitchell V, Collins B, Baumer Y, Gutierrez-Huerta C, Key A, Playford MP, Mehta NN, Powell-Wiley TM. Neighborhood environment perceptions associate with depression levels and cardiovascular risk: data from the Washington, DC Cardiovascular Health and Needs Assessment. [Under review]
- Powell-Wiley TM, Dey AK, Rivers J, Chaturvedi A, Mitchell V, Andrews MR, Ceasar JN, Ayers C, Baumer Y, Tamura K, **Langerman SD**, Gutierrez-Huerta C, Yu Q, Collins B, Ahlman M, Goyal A, Joshi AA, Teague H, Chung S, Sumner A, Playford MP, Mehta NN. Chronic stress-related neural activity associated with subclinical cardiovascular disease in a community-based cohort: data from the Washington, D.C. Cardiovascular Health and Needs Assessment. [Under review]
- **Lee DH**, Hwang CK, Cukras CA, Wiley HE, Malik FF, Chew EY, Keenan TD. Two cases of severe Purtscher-like retinopathy demonstrating recurrence and progression to neovascularization and vitreous hemorrhage. *Retin Cases Brief Rep*. [Under review]
- **Lu M**, Blaine KP, Cullinane A, Hall C, Dulau-Florea A, Sun J, Chenwi HF, Graninger G, Harper B, Brusca SB, Elinoff JM, Solomon MA. Pulmonary arterial hypertension patients display normal kinetics of clot formation using thrombelastography [Under review]
- **Nguyen QC**, Duverger O, Mitnik GL, Jani P, Mishra R, Guerrero P, Lee JS. Oral health-related quality of life in Loeys-Dietz Syndrome, a rare connective tissue disorder: A retrospective cohort study. [Under review, submitted to *Orphanet J Rare Dis*, 2019]
- **Pithadia DJ**, Treichel AM, Jones AM, Julien-Williams P, Machado T, Moss J, Darling TN. Dermatologic adverse events associated with oral mTOR inhibitor therapy in a cohort of individuals with tuberous sclerosis complex. [Under review, submitted to *Br J Dermatol*]
- Treichel AM, **Pithadia DJ**, Lee CR, Oyerinde O, Moss J, Darling TN. Histologic analysis of fibrous cephalic plaques in tuberous sclerosis complex. [Under review, submitted to *J Am Acad Dermatol*]
- Connell MT, Kim K, White MV, **Radoc JG**, Sjaarda LA, Mumford SL, Plowden TC, Kuhr DL, Omosigbo UR, Holland TL, Pollack AZ, Silver RM, Schisterman EF. Occupational exposures in women and their relationship with time to pregnancy and pregnancy loss in a U.S. cohort. [Under review, submitted to *Paediatr Perinat Epidemiol*]
- Plowden TC, Zarek SM, DeVilbiss EA, **Radoc JG**, Kim K, Sjaarda LA, Schisterman EF, Silver RM, Kuhr DL, Omosigbo UR, Yeung EH, Mumford SL. Preconception leptin and fecundability, pregnancy, and live birth among women with a history of pregnancy loss. [Under review, submitted to *J Clin Endocrinol Metab*]
- Levine LD, Kim K, Purdue-Smithe A, Sundaram R, Schisterman EF, Connell MT, DeVilbiss EA, Alkhalaf Z, **Radoc JG**, Buck Louis GM, Mumford SL. Urinary phytoestrogens and menstrual cycle length and variability among healthy, eumenorrheic women. [Under review, submitted to *J Clin Endocrinol Metab*]
- Purdue-Smithe AC, Kim K, Nobles C, Schisterman EF, Schliep KC, Perkins NJ, Sjaarda LA, Freeman JR, Robinson SL, **Radoc JG**, Mills JL, Silver RM, Ye A, Mumford SL. The role of maternal preconception vitamin D status in human sex ratio aberration. [Under review]

- Flannagan K, **Radoc JG**, Mumford SL, Zolton J, Enrique F Schisterman EF. Preconception opioid use and pregnancy outcomes. [Under review]
- Mumford SL, Flannagan K, **Radoc JG**, Plowden TC, Kim K, Purdue-Smithe A, Zolton J, Lindsey Sjaarda, Perkins N, Freeman JF, Alkhalaf Z, Andriessen V, Silver RM, Enrique F Schisterman EF. Preconception marijuana use and pregnancy outcomes. [Under review]
- Sjaarda LA, Flannagan K, **Radoc JG**, Mumford SL, Perkins NJ, Silver RM, Schisterman EF. Antidepressant medication exposure and time to pregnancy and risk of pregnancy loss. [Under review]
- Eubanks AA, Nobles CJ, Mumford SL, Kim K, Hill MJ, DeCherney AH, Sjaarda LA, **Radoc JG**, Perkins NJ, Silver RM, Schisterman EF. The safety of low dose aspirin on the mode of delivery: secondary analysis of the Effect of Aspirin in Gestation and Reproduction (EAGeR) trial. [Under review]
- Robinson SL, Mumford SL, Guan W, Trinh MH, Flannagan K, Kim K, **Radoc JG**, Zeng X, Schisterman EF, Yeung EH. Maternal fatty acid concentrations and newborn DNA methylation. [Under review]
- Theilen LH, Campbell HD, Mumford SL, Purdue-Smithe AC, Sjaarda LA, Perkins NJ, **Radoc JG**, Silver RM, Schisterman EF. Platelet activation and placenta-mediated adverse pregnancy outcomes. [Under review]
- **Seehra GK**, Eghbali A, Sidransky E, Fitzgibbon E. White vitreous opacities in five patients with Gaucher disease type 3. [Under review, submitted to *Mol Genet Metab*]
- Boden BP, Fine KM, **Spencer TA**, Breit I, Anderson SA. Non-traumatic exertional fatalities in football: excess in conditioning kills, Part II. [In review, submitted to *Am J Sports Med*]

Awards and Honors

- NHLBI Best Pre-doctoral Fellow Pitch Award, 2019
- NCI Pediatric Oncology Branch Research Roundup Day, Best student poster, 2019
- NIDCR Fellows' Scientific Training Forum: Best Poster Design and Presentation Award, 2019
- NEI Fellows Three-Minute Talk Competition, Second Place, 2018
- NIDCD Best Graduate Student Trainee Talk, Second Place, 2019
- NHGRI Research Symposium, Scientific Poster Award, 2019
- AANS Annual Scientific Meeting, Top Honors, Neurosurgical Top Gun Competition, 2019
- AFMR, Medical Scholar Award, 2019
- ARVO 2019 Knights Templar Eye Foundation, Travel Grant Award
- American Physiological Society 5th Annual Meeting: Graduate Student Poster Award
- Clinical Immunology Society Annual Meeting, Travel Grant Award, 2019
- American Association for Dental Research /Dentsply Sirona Student Competition for Advancing Dental Research: Second Place Award in Basic and Translational Science Research, 2019
- American College of Physicians Annual Meeting, Student Oral Abstract Award, 2019
- 60th Annual National Student Research Forum, Lefebvre Oral Presentation Award in Aging Research, 2019
- Society for Pediatric Dermatology Annual Meeting, Research Travel Award, 2019
- Other Professional Society Travel Grant Awards



Tyler M. Bauer

School: Sidney Kimmel Medical College at Thomas Jefferson University

Mentor: Elizabeth Murphy, Ph.D., Senior Investigator, Laboratory of Cardiac Physiology

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

Research: Perfused Mouse Heart Optical Transmission Spectroscopy within an Integrating Sphere: Redox Status During Ischemia/Reperfusion

Tissue transmission optical absorption spectroscopy provides dynamic information on metabolism and function. Murine genetic malleability makes it a major model for heart research. The diminutive size of the mouse heart makes optical transmission studies challenging. A method was developed for studying the perfused murine heart, which was center-mounted in an integrating sphere for light collection. A ventricular cavity optical catheter was used as an internal light source. The transmission absorption data were analyzed using model spectra and least squares fitting routines. All data were analyzed as change in optical density (ΔOD) of known chromophores across the heart wall from baseline. This approach generated dynamic optical data with a full-scale signal-to-noise ratio for cytochrome oxidase (COX) of 72.55 ± 11.66

(SD). This technique was applied to the study of cardiac ischemia and ischemia reperfusion which generates extreme heart motion, especially during ischemic contracture. The integrating sphere reduced motion artifact associated with a fixed optical pickup, and methods were developed to compensate for changes in tissue thickness. During ischemia, rapid decreases in myoglobin oxygenation ($\Delta OD_{mb} = -0.28 \pm 0.01$) occurred along with increases cytochrome reduction levels ($\Delta OD_{COX} = 0.251 \pm 0.016$). Surprisingly, when ischemic contracture occurred, myoglobin remained fully deoxygenated, while the cytochromes became more reduced ($\Delta OD_{COX} = 0.025 \pm 0.006$), consistent with a further, and critical, reduction of mitochondrial oxygen tension during ischemic contracture. Furthermore, ischemic contracture correlated with a decrease in mitochondrial membrane potential, as heralded by a drop in reducing equivalents on the bL subunit ($\Delta OD_{bL} = -0.071 \pm 0.005$) and an increase in the reducing equivalents on bH ($\Delta OD_{bH} = 0.027 \pm 0.001$) of complex III. This study has provided new insights on the need for controlling for both motion and tissue thickness in transmission optical spectroscopy. This optical arrangement is an effective method of monitoring murine heart metabolism, particularly mitochondrial membrane potential and cytosolic and mitochondrial oxygen tension.

Full Length Publications:

- **Bauer TM**, Murphy E. A current perspective on the identity of the permeability transition pore: Are we there yet? *J Mol Cell Cardiol.* [Under review, July 2019]
- Papanicolaou K, Deepthi A, Liu T, **Bauer TM**, Li Z, Da Costa E, Crepy D'Orleans C, Nathan S, Lefer DJ, Murphy E, Paolocci N, Foster BD, O'Rourke B. Global, but not cardiac-specific, knockout of ROMK potassium channels worsens cardiac ischemia-reperfusion injury. *J Mol Cell Cardiol.* [Under review, July 2019]

Abstract Publications:

- **Bauer TM**, Giles A, Sun J, Fenmou A, Murphy E, Balaban RS. Transmural absorbance spectroscopy in an integrating sphere used to evaluate murine mitochondria redox status during ischemia/reperfusion. International Society for Heart Research, Beijing, China; June 3–6, 2019. [Poster presentation]
- **Bauer TM**, Sun J, Antonucci S, Amanakis G, Menabò R, di Sante M, Sileikyte J, Devereaux J, Cohen MS, Forte M, Bernardi P, Di Lisa F, Murphy E. *Ex-vivo* testing of a novel small molecule inhibitor of the mitochondrial permeability transition pore. International Society for Heart Research, Beijing, China; June 3–6, 2019. [Poster presentation]
- Antonucci S, Sileikyte J, Di Sante M, Carraro M, Menabò R, **Bauer TM**, Devereaux J, Cohen MS, Forte MS, Murphy E, Bernardi P, Di Lisa F. Novel PTP inhibitors with potent cardioprotective efficacy. International Society for Heart Research, Beijing, China; June 3–6, 2019. [Poster presentation]

Travel to Professional Meetings:

- International Society for Heart Research, Beijing, China; June 3–6, 2019.
- Leducq Mitocardia Meeting, Venice, Italy; April 27–29, 2019.

Awards:

- National Heart, Lung, and Blood Institute (NHLBI) Best Predoctoral Pitch Award 2019.



Trent TsunKang Chiang

School: Case Western Reserve University School of Medicine

Mentor: Wai T. Wong, M.D., Ph.D., Chief, Section on Neuron-Glia Interaction in Retinal Diseases, Laboratory of Retinal Cell and Molecular Biology

Institute: National Eye Institute (NEI)

Research: Macular Thinning occurs in Non-advanced Age-related Macular Degeneration (AMD) and varies with AMD Stage and Presence of Subretinal Drusenoid Deposits (SDD)

Age-related macular degeneration (AMD) is a leading cause of blindness in the U.S. Its pathobiology is poorly understood, particularly during non-advanced stages. We examined eyes with non-advanced AMD to discover disease-related factors influencing macular thickness and thickness change over a four-year period.

One hundred forty three eyes of 143 patients >50 years old with retinal findings ranging from no to intermediate AMD were imaged with optical coherence tomography (OCT) at study baseline; 79 of those eyes were re-imaged at four years. Study eyes were stratified according to a modified severity scale: control eyes with no large drusen (Group 0, n=35), eyes with large drusen but none in the fellow eye (Group 1, n=27), eyes with large drusen in the study eye and large drusen or advanced AMD in the fellow eye (Group 2, n=60), and eyes with subretinal drusenoid deposits (Group SDD, n=20). Multivariate analyses using mixed models were performed to study the association between demographics, macular thickness, and AMD features. Relative to the control group (Group 0), Group 1 eyes demonstrated a higher mean macular thickness whereas Group SDD eyes demonstrated a lower mean macular thickness. Segmentation analysis showed that changes in the inner and the outer retina contributed to intergroup differences in macular thickness. Longitudinal analysis showed that while Group 0 control eyes did not change significantly in macular thickness over 4 years, Group SDD eyes differed significantly from Group 0, demonstrating significant decreases. We conclude from these findings that biphasic alterations in retinal thickness occur during the progression of intermediate AMD.

Abstract Publications:

- **Chiang TK**, Keenan T, Agrón E, Liao J, Klein B, Chew EY, Cukras C, Wong WT. Macular thinning occurs in non-advanced age-related macular degeneration (AMD) and varies with AMD stage and subretinal drusenoid deposit presence. Association of Research in Vision and Ophthalmology, Vancouver, BC; April 26–May 3, 2019. [Poster Presentation]

Awards:

- Second Place, National Eye Institute (NEI) Focus on Fellows Three-Minute Talk Competition, Bethesda, MD, 2018.
- Association for Research in Vision and Ophthalmology Annual Meeting, Knights Templar Eye Foundation Travel Grant Award, 2019.

Travel to Professional Meetings:

- American Academy of Ophthalmology Annual Meeting, Chicago, IL; Oct. 27–30, 2018.
- CHEST Annual Meeting, San Antonio, TX; Oct. 6–10, 2018.
- Association of Research in Vision and Ophthalmology, Vancouver, BC; April 29–May 3, 2019.



Harry Choi

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

Mentor: Nehal N. Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases

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

Research: Treatment of Psoriasis with Biologic Therapy is Associated with Improvement of Coronary Artery Plaque Necrotic Core and Positive Remodeling: Results from a Prospective, Observational Pilot Study

Psoriasis is a chronic inflammatory condition associated with elevated non-calcified coronary plaque, high-risk plaque features, and increased risk of major cardiovascular (CV) events. We recently demonstrated beneficial effects of biologic therapies (anti-TNF, anti-interleukin-12/23 and anti-interleukin-17) on coronary plaque in psoriasis following one year of treatment. However, the components of lipid-rich necrotic core and positive remodeling in response to biologic therapy were not fully characterized.

Consecutive biologic naïve patients (n=92), stratified by biologic therapy, underwent coronary computed tomography angiography at baseline and 1-year. We studied maximal lipid-rich necrotic core area and maximal remodeling ratio for each major coronary vessel using novel histopathology-validated software (vascuCAP Elucid Bioimaging, Wenham, MA). Maximal remodeling ratio was determined as the ratio between the maximum outer vessel wall divided by the reference outer wall area.

Study participants were middle-aged (mean=51 years), predominantly male, with low cardiovascular risk by Framingham risk score and moderate-to-severe psoriasis, in both groups. Positive remodeling ratio but not lipid-rich necrotic core area was associated with psoriasis severity ($\beta=0.16$, $p=0.009$; $\beta=0.05$, $p=0.44$). Patients started on a biologic therapy at baseline experienced a significant decrease in lipid-rich necrotic core area ($3.3 \pm 2.6 \mu\text{m}^2$ vs $2.9 \pm 2.1 \mu\text{m}^2$, respectively, $p=0.038$) and positive remodeling (defined as remodeling ratio >1.4) (% of positive remodeling: 11% vs 6%; $p=0.03$) at 1-year follow-up. In contrast, participants receiving no biologic treatment for 1-year tended towards larger lipid-rich necrotic core area ($2.8 \pm 1.9 \mu\text{m}^2$ vs $2.9 \pm 1.7 \mu\text{m}^2$, respectively, $p=0.11$) and had no change in positive remodeling (11% vs 11%; $p=1.00$).

At one-year of follow-up on therapy, biologic treatment was associated with favorable modification of lipid-rich necrotic core and positive remodeling, whereas non-biologic treatment was associated with worsening or no change in these features. These findings add to the body of literature suggesting that anti-inflammatory therapy may affect CV risk in psoriasis.

Full Length Publications:

- Groenendyk JW, Shukla P, Dey AK, Elnabawi YA, Aksentijevich M, **Choi H**, Genovese L, Harrington CL, Natarajan B, Goyal A, Reddy A, Rodante JA, Kabbany M, Sadek A, Al Najafi M, Playford MP, Joshi AA, Ahlman M, Gelfand J, Bluemke DA, Mehta NN. Association of aortic vascular uptake of ¹⁸F-FDG by PET/CT and aortic wall thickness by MRI in psoriasis: A prospective observational study. *Eur J Nucl Med Mol Imaging*, June 2019 [Epub ahead of print]
- Elnabawi YA*, Oikonomou E*, Dey AK, Mancio J, Rodante JA, Aksentijevich M, **Choi H**, Keel A, Erb-Alvarez J, Teague H, Joshi AA, Playford MP, Lockshin B, Choi A, Gelfand J, Chen M, Bluemke DA, Shirodaria C, Antoniadis C, Mehta NN. Biologic therapy is associated with a reduction in coronary inflammation as assessed by perivascular fat attenuation index in psoriasis. *JAMA Cardiol*. June 2019 [Epub ahead of print]
- Choi H**, Dey AK, Aksentijevich M, Rodante JA, Elnabawi YA, Khalil N, Playford MP, Gelfand J, Chen M, Bluemke DA, Buckler A, Mehta NN. Treatment of psoriasis with biologic therapy is associated with improvement of coronary artery plaque necrotic core and positive remodeling: results from a prospective, observational pilot study. *Circulation*, 2019. [Under Review]
- Munger E, **Choi H**, Dey AK, Elnabawi YA, Groenendyk JW, Khalil N, Rodante JA, Aksentijevich M, Reddy A, Argueta-Amaya J, Playford MP, Hasan A, Jafri M, Sandfort V, Chen M, Bluemke DA, Gelfand J, Mehta NN. Application of machine learning to determine top predictors of non-calcified coronary plaque burden in psoriasis. *Am J Cardiol*, 2019. [Under Review]

- Dey AK, Gaddipati R, Elnabawi YA, Ongstad E, Goyal A, Rodante JA, Sajja A, Sorokin A, Teague H, Aksentijevich M, **Choi H**, Khalil N, Reddy A, Argueta-Amaya J, Shukla P, Baumer Y, Joshi AA, Sandfort V, Playford MP, Chen M, Bluemke DA, Karathanasis S, Gelfand J, Gupta R, Mehta NN. Soluble lectin-Like oxidized low-density lipoprotein receptor-1 is associated with subclinical coronary artery disease in psoriasis. *JAMA Dermatol*, 2019 [Under Review]

*Equal contribution

Abstract Publications:

- Choi H**, Munger E, Dey A, Elnabawi Y, Groenendyk J, Khalil N, Rodante J, Aksentijevich M, Reddy A, Argueta-Amaya J, Playford M, Hasan A, Jafri M, Sandfort V, Chen M, Bluemke D, Gelfand J, Mehta NN. Application of machine learning to determine top predictors of non-calcified coronary plaque burden in psoriasis. American Federation for Medical Research Eastern Regional Meeting, Philadelphia, PA; March 30, 2019. [Oral presentation]
- Choi H**, Dey AK, Goyal A, Rodante J, Keel A, Aksentijevich M, Khalil N, Argueta-Amaya J, Reddy A, Playford M, Ahlman M, Powell-Wiley T, Gelfand J, Mehta NN. Adipose inflammation as assessed by adipose FDG uptake is associated with aortic vascular inflammation in psoriasis. American Heart Association Epidemiology, Prevention, Lifestyle and Cardiometabolic Health Scientific Sessions, Houston, TX; March 5–8, 2019. *Circulation*. 2019;139:AP041 [Poster presentation]

Continued on the Next Page

- Khalil N, Playford M, Dey AK, Elnabawi Y, Chung J, **Choi H**, Aksentijevich M, Argueta-Amaya J, Munger E, Rodante J, Shukla P, Keel A, Teague H, Baumer Y, Sandfort V, Chen M, Bluemke D, Gelfand J, Mehta NN. Circulating levels of interferon- γ and tumor necrosis factor- α are associated with lipid-rich coronary plaque in psoriasis. American College of Cardiology 68th Annual Scientific Session. New Orleans, LA; March 16–19, 2019. *J Am Coll Cardiol*, 2019; 73(9): Suppl 1. [Poster presentation]
- Dey AK, Gaddipati R, Elnabawi Y, Ongstad E, Goyal A, Rodante J, Sajja A, Sorokin A, Teague H, Aksentijevich M, Khalil N, Reddy A, **Choi H**, Argueta-Amaya J, Shukla P, Baumer Y, Joshi A, Sandfort V, Playford M, Chen M, Bluemke D, Karathanasis S, Gelfand J, Gupta R, Mehta NN. Soluble lectin-Like oxidized low-density lipoprotein receptor-1 is associated with subclinical coronary artery disease in psoriasis. American College of Cardiology 68th Annual Scientific Session. New Orleans, LA; March 16–19, 2019. *J Am Coll Cardiol*, 2019; 73(9): Suppl 1. [Poster presentation]
- Argueta-Amaya J, Dey AK, Elnabawi Y, Ling C, Qian S, **Choi H**, Khalil N, Aksentijevich M, Rodante J, Shukla P, Teague H, Keel A, Genovese L, Sandfort V, Chen M, Bluemke D, Gelfand J, Remaley A, Playford M, Mehta NN. High-sensitivity troponin is associated with high-risk coronary plaque in psoriasis. American College of Cardiology 68th Annual Scientific Session. New Orleans, LA; March 16–19, 2019. *J Am Coll Cardiol*, 2019; 73(9): Suppl 1. [Poster presentation]
- Aksentijevich M, Teague H, Playford M, Dey AK, Reddy A, Elnabawi Y, Goyal A, Chaturvedi A, **Choi H**, Khalil N, Argueta-Amaya J, Shukla P, Rodante J, Keel A, Sandfort V, Chen M, Bluemke D, Choi A, Mazhari R, Gelfand J, Mehta NN. Coronary plaque burden is associated with cholesterol efflux capacity partially mediated by the hematopoietic system in psoriasis. American College of Cardiology 68th Annual Scientific Session. New Orleans, LA; March 16–19, 2019. *J Am Coll Cardiol*, 2019; 73(9): Suppl 1. [Poster presentation]
- Shuckla P, Dey AK, Elnabawi Y, **Choi H**, Groenendyk J, Aksentijevich M, Khalil N, Argueta-Amaya J, Joshi A, Reddy A, Rodante J, Playford N, Naqi M, Erb-Alvarez J, Ahlman M, Sandfort V, Chen M, Bluemke D, Gelfand J, Mehta NN. Aortic distensibility by magnetic resonance imaging inversely associates with non-calcified coronary plaque burden by coronary CT angiography in psoriasis. American College of Cardiology 68th Annual Scientific Session. New Orleans, LA; March 16–19, 2019. *J Am Coll Cardiol*, 2019; 73(9): Suppl 1. [Poster presentation]

Travel to Professional Meetings:

- American Heart Association Epidemiology, Prevention, Lifestyle and Cardiometabolic Health Scientific Sessions, Houston, TX; March 5-8, 2019.
- American College of Cardiology 68th Annual Scientific Session, New Orleans, LA; March 16–19, 2019.
- American Federation of Medical Research, Eastern Regional Meeting, Philadelphia, PA; March 30, 2019.

Awards:

- American Federation for Medical Research, Medical Scholar Award, 2019.



Katharina R. Clore-Gronenborn

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

Mentor: Kathleen R. Merikangas, Ph.D., Chief, Genetic Epidemiology Research Branch

Institute: National Institute of Mental Health (NIMH)

Research: Investigating the Interrelationships of Sleep, Emotion, and the Hypothalamic-Pituitary-Adrenal (HPA) Axis using Mobile Technologies in a Community-based Sample.

Prior studies have examined the association between cortisol, a stress hormone and end hormone of the hypothalamic-pituitary-adrenal (HPA) axis, with various health outcomes including mental health disorders, physical health disorders, and emotional and physical states. Cortisol is secreted in a diurnal pattern with flattening of the diurnal cortisol slope (DCS) typically associated with worse health outcomes and a steeper DCS indicative of healthier states. However, there is a paucity of research examining the dynamic relationships between DCS, sleep, and emotional states, especially over prolonged time periods in a naturalistic setting. This study investigated the associations between the HPA axis, sleep, and emotion in a community-based sample of 154 participants ages 11 to 84 (mean age 37.4, 60% female)

who were evaluated at the NIH Clinical Center and completed two weeks of contemporaneous ecological momentary assessments, actigraphy, and salivary cortisol sampling. We found that shorter sleep duration predicted flatter DCS the subsequent day ($\beta = -0.123$, $p = 0.0004$), but did not appreciate an association between DCS and sleep quality. We also found that shorter sleep duration and lower self-reported sleep quality the previous night predicted increased self-reported frequency of sad mood ($\beta = -0.0595$, $p = 0.0595$; $\beta = -0.0668$, respectively, $p < 0.0001$) and anxious mood ($\beta = -0.1277$, $p < 0.0001$; $\beta = -0.0283$, respectively, $p = 0.0409$) the following day. However, DCS was not associated with mood nor anxiety symptoms and DCS was not found to be a mediator between sleep and mood states. While we found no associations between history of mental health disorders and DCS nor between sex and DCS, we did find an association between DCS and age: adolescents and young adults exhibited flatter cortisol slopes (mean DCS = -0.0679) in comparison to adults age 30 and older (mean DCS = -0.1951) ($p < 0.0001$).

Abstract Publications:

- Clore-Gronenborn K, Dey D, Xiao Y, Cui L, Kang SJ, Guo W, Zupunnikov V, Merikangas KR. Investigating the interrelationships of sleep, emotion, and the HPA axis using mobile technologies in a community-based sample. Society for Ambulatory Assessment Conference, Syracuse NY; June 19–22, 2019. [Poster presentation]

Travel to Professional Meetings:

- Society for Adolescent Health and Medicine Annual Meeting, Washington, DC; March 6–9, 2019.
- Society for Ambulatory Assessment Conference, Syracuse, NY; June 19–22, 2019.



David A. Cruz Walma

School: University of Alabama at Birmingham School of Dentistry

Mentor: Kenneth Yamada, M.D., Ph.D., NIH Distinguished Investigator

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

Research: The BTB Domain Family of Proteins and its Emerging Role in Cell Migration

The BTB/POZ domain is a protein-protein interaction domain present in organisms ranging from yeast to humans. Proteins containing this highly evolutionarily conserved domain are involved in hundreds of interactions critical to development, regulation/repair, and cancer. In mammals, these proteins serve crucial roles in biological processes central to hematopoiesis, angiogenesis, immunity, tumor suppression, chromatin remodeling, skeletal and limb development, axon guidance, organogenesis, and others. BTBD7 is one of these BTB/POZ domain containing proteins. Recent publications report that BTBD7 serves as a key regulator of cell dynamics and organogenesis. BTBD7's structure and mechanism of biological impact are unknown.

Our goal was to identify the functions and molecular mechanisms associated with BTBD7. We found varying intracellular protein levels of BTBD7 correlate with altered cell motility and dynamics. Increasing protein levels of BTBD7 correlate with increased cell migration and cell scattering. A hypothesized molecular mechanism of this dynamic control involves BTBD7 interacting with a ubiquitin E3 ligase to regulate degradation/recycling of proteins involved in cellular migration. One initial barrier was the absence of a monoclonal antibody to BTBD7. We developed an ultra-sensitive western blotting system to screen microliter quantities of mouse serum and low-titer hybridoma supernatants. We used this system to identify a hybridoma clone specific for BTBD7. We also developed multiple 2D and 3D assays to allow us to characterize the *in vitro* and 3D culture role of BTBD7 via various imaging modalities. In parallel, we developed workflows capable of identifying and characterizing molecular interactions of BTBD7 *in vitro* and in 3D culture. Together, these techniques will allow us to characterize BTBD7's interactions and function. These studies should facilitate assessing the druggability of BTBD7 and its interacting molecules and the potential to apply such modalities to human care.

Full Length Publications:

- **Cruz Walma DA**, Collins JW. Western blotting with solutions containing nanoliter volumes of antibody. *Curr Protoc Cell Biol.* 2019 May;84:e87
- Yamada K, Collins J, **Cruz Walma DA**, Doyle A, Morales S, Lu J, Matsumoto K, Nazari SS, Sekiguchi R, Shinsato Y, Wang S. Extracellular matrix dynamics in cell migration, invasion, and tissue morphogenesis. *Int J Exp Pathol.* 2019 June 10. doi:10.1111/iep.12329. [Epub ahead of print]

Abstract Publications:

- **Cruz Walma DA**. Western blotting with aliquots containing nanoliter volumes of antibody. National Institute of Dental and Craniofacial Research (NIDCR) Fellows' Scientific Training, Washington, DC; April 4, 2019. [Poster presentation]



Nicole H. Dalal

School: Duke University School of Medicine

Mentor: Lindsay M. Morton, Ph.D., Senior Investigator, Radiation Epidemiology Branch

Institute: National Cancer Institute, Division of Cancer Epidemiology and Genetics (NCI/DCEG)

Research: Cause-specific Mortality in Survivors of Lymphoplasmacytic Lymphoma (LPL) and Waldenström Macroglobulinemia (WM)

Survival after lymphoplasmacytic lymphoma (LPL) and Waldenström macroglobulinemia (WM) has improved, but data on cause-specific mortality for recently-treated patients are lacking. We identified causes of death for 2,826 deceased subjects among 6,659 adults diagnosed during 2000-2015 with incident first primary LPL (n=2,866) or WM (n=3,793) in 17 U.S. population-based cancer registries. Cumulative mortality at 15 years was 22.6% for lymphoma, 9.3% for other malignancies, and 14.4% for non-malignant causes for patients aged <65 years at diagnosis of LPL/WM, versus 33.3%, 11.6%, and 47.8%, respectively, for those aged ≥75 years. Compared with the general population, the combined cohort of LPL/

WM patients had a 20% higher risk of death due to non-malignant causes (n=1194 deaths, standardized mortality ratio [SMR]=1.2; 95%CI, 1.1-1.2), most notably from infectious (n=162; SMR=1.8; 95%CI, 1.5-2.1), respiratory (n=131; SMR=1.2; 95%CI, 1.0-1.5), and digestive (n=76; SMR=1.9; 95%CI, 1.5-2.4) diseases, but no excesses from cardiovascular diseases (n=422, SMR=1.0, 95%CI=0.9-1.1). The highest SMRs (>5) for infectious deaths were for HIV, mycoses/protozoal infections, and viral hepatitis, although based on small numbers of deaths. SMRs were statistically significantly 2-3-fold increased for gastrointestinal bleeds, chronic liver disease/cirrhosis, and vascular diseases of the intestine. Risks were highest for non-malignant causes within one year of diagnosis for all LPL/WM patients (n=225; SMR_{<1year}=1.4; 95%CI, 1.2-1.6), and declined thereafter (n=440; SMR_{≥5years}=1.1; 95%CI, 1.0-1.3). The SMR for myelodysplastic syndrome/acute myeloid leukemia in LPL/WM patients was notably increased (n=42; SMR=4.6; 95%CI 3.3-6.2). In contrast, solid neoplasm deaths in LPL/WM patients were not elevated overall, except among ≥5-year survivors (n=125; SMR=1.3; 95% CI=1.1-1.6). Due to lower baseline risks, SMRs were higher among younger individuals. We also found similar SMRs between LPL and WM patients. The observed risk differences by age at and time since diagnosis allow for identification of specific diseases to target aggressively with preventive, supportive, and treatment measures to reduce mortality.

Full Length Publications:

- Dalal N, Dores GM, Curtis RC, Linet MS, Morton LM. Cause-specific mortality in survivors of lymphoplasmacytic lymphoma (LPL) and Waldenström macroglobulinemia (WM). [In preparation]
- Dores GM, Curtis RC, Dalal N, Linet MS, Morton LM. Cause-specific mortality in survivors of Hodgkin lymphoma. [In preparation]
- Morton LM, Schonfeld S, Dalal N, Advani, PG, Dores GM, Linet MS, Curtis RC. Association of chemotherapy for lymphoma with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. [In preparation]

Abstract Publications:

- Dalal N, Dores GM, Curtis RC, Linet MS, Morton LM. Cause-specific mortality in survivors of lymphoplasmacytic lymphoma (LPL) and Waldenström macroglobulinemia (WM). American Society of Clinical Oncology Annual Meeting, Chicago, IL; May 31–June 4, 2019. [Electronic presentation]

Travel to Professional Meetings:

- Memorial Sloan Kettering Symposium on Lymphoma, New York, NY; May 10–11, 2019.
- American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL; May 31–June 4, 2019.



Timothy R. Donahoe

School: Weill Medical College of Cornell University

Mentor: Amy Berrington de Gonzalez, Ph.D., Chief, Radiation Epidemiology Branch

Institute: National Cancer Institute, Division of Cancer Epidemiology and Genetics (NCI/DCEG)

Research: Evaluating Cancer Risk from Post-trauma Computerized Tomographic (CT) Scanning

The lifetime cancer risk after radiation exposure increases significantly as time since exposure increases, so young people are particularly at risk of harm. Trauma patients in the emergency department tend to be younger, and are frequently exposed to significant radiation via computerized tomographic (CT) scanning. This study used the National Trauma Data Bank to determine the type and number of CT scans trauma patients were exposed to from 2014-2016. The data were examined with the National Cancer Institute's NCICT software to determine the average radiation exposure from these scans, and the Radiation Risk Assessment Tool (RadRAT) to estimate lifetime cancer risk from the measured exposure, with the goal of

roughly estimating the population risk of post-trauma CT scanning, and for identifying particularly harmful CT practices.

Subjects were selected from the National Trauma Data Bank who were less than 30 years old, and received at least one CT scan following their hospital admission for trauma. Over 100,000 patients from a representative sample of 70% of United States emergency departments were included. CT scan characteristics were estimated using American College of Radiology guidelines. CT scans of the head and neck were the most common, followed by abdomen and pelvis, chest, and extremity scans. Radiation exposure doses for various CT scans are currently undergoing evaluation and analysis. Future results will allow correlation of post-trauma CT scanning procedures with lifetime cancer risk for the evaluation of high-risk CT practices in the emergency department.

Abstract Publications:

- **Donahoe TR**, McIntyre A, Chiu C, Mason C. Nanopore genetic sequencing for human spaceflight: Current understanding and potential applications. Aerospace Medical Association Annual Conference, Las Vegas, NV; May 5--9, 2019 (abstract no. 435).

Travel to Professional Meetings:

- Conference on Radiation and Health, Chicago, IL; Sep. 23--25, 2018.
- Aerospace Medical Association Annual Conference, Las Vegas, NV; May 5--9, 2019.

Awards:

- Aerospace Medical Association Young Investigator Award Finalist.



Cameron N. Fick

School: Georgetown University School of Medicine

Mentor: Frances T. Sheehan-Gavelli, Ph.D., Senior Investigator; Functional and Applied Biomechanics Section, Rehabilitation Medicine Department

Institute: NIH Clinical Center (CC)

Research: Adolescent Patellofemoral Pain: Correlating Morphology and Kinematics

Developing bone is highly adaptable and susceptible to pathological shape deformation. Thus, it is imperative to determine if changes in patellofemoral morphology are associated with adolescent-onset patellofemoral pain to improve clinical decision-making. The purpose of this case-control study was to quantify and compare patellar morphology in patients to healthy controls; and evaluate if a relationship exists between shape and kinematics.

This study was a follow-up to a previous study, using an identical cohort, 3D static images, and kinematics. We measured 2D patellar and trochlear width, lateral patellar width, trochlear and patellar depth, Wiberg index, patella alta, lateral trochlear inclination, cartilage length, and lateral femoral shaft length. Student's t-test was used to compare shape parameters across cohorts and Pearson's correlation was used to explore the relationship between morphology, kinematics, and pain.

Relative to controls (n=20), adolescents with patellofemoral pain (n=20) had a larger sulcus depth (0.6mm; p=0.043) and lateral patellar width (1.7mm; p=0.033). Shape correlated with kinematics in both cohorts and in the entire population. In the patellofemoral pain group, lateral shaft length (r=0.518; p=0.019) and Wiberg index (r=0.477; p=0.033) were correlated with medial shift; while patella alta (r=0.582; p=0.007) correlated with lateral shift. A moderate correlation existed between patella alta and lateral patellar tilt (r=0.527; p=0.017). Regression analyses demonstrated that half of the variation in patellar shift in the patellofemoral pain cohort was explained by patella alta and Wiberg index ($R^2 = 0.487$; p = 0.003). No correlations with pain intensity were found.

This study provides the first direct evidence that patellofemoral morphology is altered and influences maltracking in adolescent-onset patellofemoral pain, highlighting the multifactorial etiology of this condition. Neither morphology nor kinematics correlated with pain level, but this does not imply that changes in these parameters do not foster pain. Instead, both increases and decreases in these parameters can lead to pain, negating a direct linear correlation.

Full Length Publications:

- **Fick CN**, Fratzl-Zelman N, Roschger P, Klaushofer K, Jha S, Marini J, Bhattacharyya T. Melorheostosis: a clinical, pathological and radiological case series. *Am J Surg Pathol*. [In press, May 2019]
- **Fick CN**, Grant C, Sheehan FT. Adolescent patellofemoral pain: an envelope of pathology. [Under review, submitted to *Am J Sports Med* April 2019]

Abstract Publications:

- **Fick CN**, Grant C, Sheehan FT. Exploring the form-function relationship in adolescents with patellofemoral pain syndrome. Congress of the International Society of Biomechanics, Calgary, Canada; July 2019. [Podium presentation]



Leah M. Gober

School: Mercer University School of Medicine

Mentor: Beth A. Kozel, M.D., Ph.D. Lasker Clinical Research Scholar, Laboratory of Vascular and Matrix Genetics, Translational Vascular Medicine

Institute: National Heart Lung Blood Institute (NHLBI)

Research: Elastin Insufficiency: A Study of Changes in Vascular Morphometry, Morphology and Functionality

Elastin, a protein that imparts elasticity to blood vessels, is important in accommodation of hemodynamic changes as blood moves throughout the cardiovascular system. Haploinsufficiency for this protein is known to result in vascular stenosis, arterial stiffening and thickening of muscular walls. Because prior studies have focused on large systemic arteries, attention was instead directed at the pulmonary circulation.

To better understand the developmental biology of the pulmonary vasculature, wild type (WT) and Eln^{+/-} mice were studied at P1, P7, P30 and 3 months (adult). The pulmonary artery was cannulated, lungs inflated and the vascular tree perfused with Microfil™ silicone casting material. The lungs were fixed and scanned by micro-computed topography scanner. Using Amira 6.7, vasculature was segmented and skeletonized to allow for analysis of 3D architecture.

Compared to WT mice, Eln^{+/-} mice demonstrated increased segment length in primary pulmonary arterial generations for both left and right lobes in P30 and 3 month old mice. Lung volumes were significantly increased in 3-month old Eln^{+/-} animals, despite overall animal size remaining the same. Lobar artery branching angle was noted to be significantly more acute in Eln^{+/-} animals at P30 and adult time points compared to WT mice. Increased resistance and altered vessel morphology resulted in filling difficulty using traditional arterial casting methods in Eln^{+/-} animal models.

This methodological approach provides anatomic reconstructions of pulmonary vasculature and is a useful tool for quantitative analysis of whole-lung architecture studying the global effects of elastin insufficiency. Alterations in pulmonary vasculature observed in Eln^{+/-} mice provide a correlate to study developmental adaptations in vascular growth and lung disease in elastin haploinsufficient patient populations.

Abstract Publications:

- **Gober LM**, Knutsen R, Sukinik J, Wardlaw A, Liu D, Levin M, Kozel BA. Minoxidil and elastin insufficiency: A study of changes in vascular morphometry, morphology and functionality. American Physiological Society DMV 5th Annual Meeting; Oct. 8, 2018. [Poster presentation]
- **Gober LM**, Knutsen R, Sukinik J, Wardlaw A, Liu D, Levin M, Kozel BA. Use of microCT to define functional and morphometric alterations in pulmonary vascular architecture of elastin haploinsufficient models. Weinstein Cardiovascular Development and Regeneration Annual Meeting. Indianapolis, IN; May 8–11, 2019. [Poster presentation]

Travel to Professional Meetings:

- American Physiological Society - DMV Chapter Meeting, Washington DC; October 8, 2018.
- Weinstein Cardiovascular Development and Regeneration Annual Meeting, Indianapolis, IN; May 8–11, 2019.
- NIMH & NHLBI Heart and Soul Workshop. Bethesda, MD; April 2–3, 2019.

Awards:

- American Physiological Society DMV 5th Annual Meeting: Graduate Student Poster Award.
- Weinstein Cardiovascular Development and Regeneration Annual Meeting, Travel Grant Award Winner.



Sarah E. Greene

School: Duke University School of Medicine

Mentor: Clint T. Allen, M.D., Principal Investigator, Translational Tumor Immunology Program; Carter Van Waes, M.D., Ph.D., Chief, Tumor Biology Section, Head and Neck Surgery Branch

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

Research: Inhibition of Myeloid-Derived Suppressor Cell Trafficking Enhances Natural Killer Cell Immunotherapy

Immunotherapies designed to activate or replace T cell effector immunity, such as immune checkpoint blockade or adoptive transfer of T cells, are limited by the ability of subpopulations of tumor cells to escape T cell immunity. This occurs through genomic alterations that abrogate the ability of tumor cells to present T cell antigens. Immunotherapy designed to activate natural killer (NK) cell immunity may overcome these limitations through MHC class I-independent tumor cell recognition and killing; thus, novel NK-based therapies may be useful in the treatment of non-T-cell inflamed tumors. The therapeutic efficacy of T cell

based immunotherapy is also limited by immunosuppression in the tumor microenvironment, mediated in part by myeloid derived suppressor cells (MDSCs). MDSCs may limit the efficacy of NK cell immunotherapies.

To model NK cellular therapy, we studied how MDSCs alter the ability of murine NK cells to kill oral cancer cells. We used an oral cancer model, MOC2, that has few genomic alterations and forms non-T-cell inflamed tumors in wild-type mice. SX-682 is a small molecule dual inhibitor of CXCR1/2 that inhibits chemokine signaling of MDSCs. KIL, a natural killer cell line, was used as a source of NK cells. We hypothesized that MDSCs limit NK cell killing of tumor cells and that abrogation of MDSC trafficking into the tumor with SX-682 would enhance NK cellular therapy *in vivo*.

Although SX-682 and KIL adoptive transfer as monotherapies produced no tumor growth inhibition (TGI), combination resulted in significant TGI and prolonged survival of mice. Immune correlative analysis revealed increased tumor infiltration of adoptively transferred KIL, with inhibition of MDSC tumor trafficking. These data suggested that the efficacy of NK cellular therapies can be enhanced with inhibition of MDSC trafficking. The combination of chemokine receptor inhibitors such as SX-682 in combination with NK cellular therapy warrants clinical investigation and may be particularly useful in patients harboring non-T-cell inflamed tumors.

Full Length Publications:

- Sun L, Clavijo PE, Robbins Y, Patel P, Friedman J, **Greene S**, Das R, Silvin C, Van Waes C, Horn LA, Schlom J, Palena C, Maeda D, Zebala J, Allen CT. Inhibiting myeloid-derived suppressor cell trafficking enhances T cell immunotherapy. *JCI Insight*. 2019 Apr 4; 4(7): e126853.
- **Greene S**, Patel P, Allen CT. How patients with an intact immune system develop head and neck cancer. *Oral Oncol*. 2019 May; 92:26-32. Review.
- Friedman J, Moore EC, Zolkind P, Robbins Y, Clavijo PE, Sun L, **Greene S**, Morisada M, Mydlarz W, Schmitt N, Hodge J, Schreiber H, Van Waes C, Uppaluri R, Allen CT. Neoadjuvant PD-1 immune checkpoint blockade reverses functional immunodominance among tumor-antigen specific T cells. *J Clin Invest* [Under review]

Abstract Publications:

- **Greene S**, Palena C, Schlom J, Zebala J, Maeda D, Allen CT. Efficacy of natural killer cell therapy is enhanced through inhibition of myeloid-derived suppressor cell trafficking. AACR-AHNS Head and Neck Cancer Conference: Optimizing Survival and Quality of Life through Basic, Clinical, and Translational Research, Austin, TX; Apr 29–30, 2019. [Poster presentation]

Travel to Professional Meetings:

- AACR-AHNS Head and Neck Cancer Conference: Optimizing Survival and Quality of Life through Basic, Clinical, and Translational Research, Austin, TX; Apr 29–30, 2019.



Nikhil Gupta

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

Mentor: Haiming Cao, Ph.D., Stadtman Investigator, Laboratory of Obesity and Metabolic Diseases

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

Research: The Micropeptide ORF60 Modulates Insulin Sensitivity

Although long non-coding RNAs (lncRNAs) are non-protein-coding transcripts by definition, recent studies have shown that a fraction of putative small open reading frames within lncRNAs are translated. The biological significance of these hidden polypeptides is still unclear, although recent studies have demonstrated functional significance for some polypeptides.

Recently, our lab discovered a novel micropeptide ORF60 encoded by a lncRNA. The micropeptide is conserved across species, and RNA transcript expression is nearly ubiquitous across tissues. In mice, ORF60 expression was found to be increased in the setting of high fat diet (HFD). Using CRISPR/Cas9 technology, we developed ORF60 knockout (KO) mice. In both

mice feeding on normal chow diet and HFD, we observed impaired glucose tolerance in KO mice compared to wild type mice (AUC 45,000 (n = 8) vs 35,500 (n = 9), respectively, p = 0.002, among mice fed HFD). ORF60 KO mice also demonstrated impaired response to insulin compared to WT mice on insulin tolerance testing (ITT), suggesting insulin resistance (AUC normalized to baseline, 95 (n = 9) vs 112 (n = 10), respectively, p = 0.015, among mice fed HFD). Mouse tissue harvested under the condition of insulin infusion demonstrated insulin signaling attenuation in white adipose tissue (WAT) and brown adipose tissue (BAT). Preliminary results from mechanistic studies suggest that ORF60 localizes to the nucleus and may play a role in transcriptional regulation. We are currently dissecting the specific molecular mechanism underlying ORF60's influence on insulin signaling pathways.

Full Length Publications:

- Ruan X*, Li P*, Ma Y, Jiang C, Chen Y, Shi Y, **Gupta N**, Seifuddin F, Pirooznia M, Suemizu H, Ohnishi Y, Yoneda N, Nishiwaki M and Cao H. Multilevel integrative transcriptome analyses in humans and humanized mice define in vivo human lncRNA metabolic regulators. *Cell Metab*. [Under review]

**Equal contribution*

Abstract Publications:

- Gupta N**, Shi Y, Li P, Cao H. The micropeptide ORF60 modulates insulin sensitivity. American Diabetes Association 79th Scientific Sessions, San Francisco, CA; June 7–11, 2019. [Poster presentation]

Travel to Professional Meetings:

- American Diabetes Association 79th Scientific Sessions, San Francisco, CA; June 7–11, 2019.



Saadia Hasan

School: Medical College of Georgia at Augusta University

Mentor: Michael Ward, M.D., Ph.D., Investigator, Inherited Neurodegenerative Diseases Unit, Neurogenetics Branch

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

Research: Delineating the Role of Microglia in Frontotemporal Dementia/Amyotrophic Lateral Sclerosis

Microglia, the resident immune cells of the brain, serve to eliminate immature synapses via synaptic pruning during development and modulate synaptic plasticity during learning and memory. Microglia are implicated in disease states ranging from psychiatric to neurodegenerative conditions. Prior studies show that knocking out the CX3CR1 gene, which codes for a fractalkine receptor, in mice results in increased numbers of synapses in adulthood. This may lead to defects in social behavior, similar to those observed in autism and schizophrenia, and disruption of neuroplasticity in adulthood. Microglia therefore provide a new window into identification of non-traditional therapeutic targets.

Whether diseased states are due to microglia acting aberrantly in an autonomous manner or whether synapses are vulnerable to disordered microglial effects due to non-autonomous cell interactions remains to be determined. To address this question, we evaluated proximity biotinylation using antibody recognition as a method for mapping protein localization, both within microglial processes as well as in microglial interactions with neurons. We used purinergic receptor P2Y12 to label the microglia cell surface to determine if our proximity labeling method could identify and isolate microglial proteins. We achieved successful biotinylation of proteins within 5 nm of P2Y12 in wildtype (WT) mouse brain slices, detected after fixation via imaging and dot blot assay. Biotinylated proteins in WT mice were compared to those in progranulin knock-out (PGRN KO) mice by mass spectrometry. Progranulin mutation is common in neurodegenerative diseases such as amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) and has been shown to cause microglial dysfunction. We identified approximately 300 more proteins in proximity to P2Y12 in the PGRN KO compared to the WT samples.

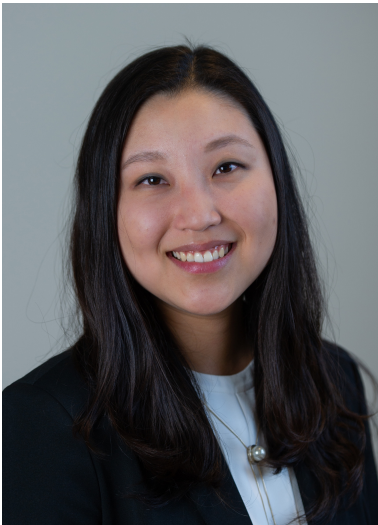
Proximity biotinylation shows promise in identifying the proteome surrounding a protein of interest, in our case, P2Y12. Future studies will use this method to study microglial protein expression in different disease states and neuron-microglia interactions to potentially identify new therapeutic targets.

Abstract Publications:

- Hao L, Prestil R, Fernandopulle M, Humble S, Lee D, **Hasan S**, Parsadanian M, Youle R, Ward M. Multifaceted proteomic evaluation of lysosome dysfunction in neurodegeneration via human iPSC-derived neurons. United States Human Proteome Organization, Washington DC; March 3–6, 2019 [Poster presentation]
- Hao H, Fernandopulle M, **Hasan S**, Parsadanian M, Ward M. Development of a MS-based lysosomal membrane protein proximity label to evaluate lysosome dysfunction in human iPSC-neuron models of neurodegeneration. American Society for Mass Spectrometry, Atlanta, GA; June 1–7, 2019 [Poster presentation]

Travel to Professional Meetings:

- American Academy of Neurology (AAN) 71st Annual Meeting, Philadelphia, PA; May 4–5, 2019.



Gloria H. Hong

School: Johns Hopkins University School of Medicine

Mentor: Steven M. Holland, M.D., Director, Division of Intramural Research

Institute: National Institute of Allergy and Infectious Diseases (NIAID)

Research: Natural History and Evolution of Anti-Interferon-gamma Autoantibody-Associated Immunodeficiency Syndrome in Thailand and the United States

Anti-interferon- γ (IFN- γ) autoantibodies have been strongly associated with severe disseminated nontuberculous mycobacterial and other opportunistic infections in previously healthy adults, predominantly in or from Southeast Asia. However, the natural history of anti-IFN- γ autoantibody-associated immunodeficiency syndrome is poorly understood.

Clinical data of 74 patients with anti-IFN- γ autoantibodies at Srinagarind Hospital in Thailand were collected using standardized forms (median follow-up duration: 7.5 years). Clinical data of 23 patients with anti-IFN- γ autoantibodies at the National Institutes of Health in the U.S. were collected by review of electronic chart records (median follow-up duration: 4.5 years). Anti-IFN- γ autoantibody levels were measured in serial plasma samples.

Ninety-one percent of U.S. patients were of Southeast Asian descent and there was a stronger female predominance (91%) in the U.S. than Thailand (64%). *M. abscessus* (34%) and *M. avium* complex (83%) were the most commonly isolated nontuberculous mycobacteria in Thailand and the U.S., respectively. Skin infections were more common in Thailand ($P=0.001$) whereas bone ($P<0.0001$), lung ($P=0.002$), and central nervous system ($P=0.03$) infections were more common in the U.S. The median time to infection clearance was three years (95% confidence interval [CI]: 2, 4), four years (95% CI: 2, NA), and five years (95% CI: 2, 4) in patients who received antibiotics only, rituximab and antibiotics, and cyclophosphamide and antibiotics, respectively. Twenty-four percent of Thai patients died, mostly from infections, and none of the U.S. patients died during follow-up. Overall, anti-IFN- γ autoantibody levels decreased over time in Thailand ($P<0.001$) and the U.S. ($P=0.017$), as well as with cyclophosphamide ($P=0.01$) and rituximab therapy ($P=0.001$).

Patients with anti-IFN- γ autoantibodies in Thailand and the U.S. had distinct demographic and clinical features. While titers generally decreased with time, anti-IFN- γ autoantibody disease has a chronic clinical course with persistent infections and death. Close long-term surveillance for recurrent or new infections is recommended.

Full Length Publications:

- **Hong GH**, Ortega-Villa AM, Hunsberger S, Chetchotisakd P, Anunnatsiri S, Mootsikapun P, Rosen LB, Zerbe CS, Holland SM. Natural history and evolution of anti-interferon-gamma autoantibody-associated immunodeficiency syndrome in Thailand and the U.S. *Clin Infect Dis*. [Under review]

Abstract Publications:

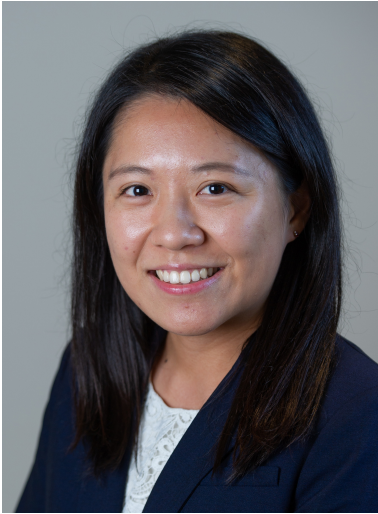
- **Hong GH**, Ortega-Villa AM, Hunsberger S, Chetchotisakd P, Anunnatsiri S, Mootsikapun P, Rosen LB, Zerbe CS, Holland SM. Natural history of anti-interferon-gamma autoantibody-associated immunodeficiency syndrome in Thailand. 2019 Clinical Immunology Society Annual Meeting, Atlanta, GA, April 4–7, 2019. (Podium presentation)

Travel to Professional Meetings:

- Clinical Immunology Society Annual Meeting, Atlanta, GA, April 4–7, 2019.

Awards:

- Clinical Immunology Society Annual Meeting, Travel Grant Award, 2019.



Rebecca Hu

School: University of California, San Diego School of Medicine

Mentor: Ellen Leibenluft, M.D., Chief, Section on Mood Dysregulation and Neuroscience, Emotion and Development Branch; Daniel S. Pine, M.D., Chief, Section on Development and Affective Neuroscience, Emotion and Development Branch

Institute: National Institute of Mental Health (NIMH)

Research: Applications of Morphometric Similarity Networks in Predicting Inter-Individual Cognitive Variation: A Replicability Study

Morphometric similarity network (MSN) mapping is a new MRI imaging technique. Prior research using partial-least squares (PLS) analysis linked MSNs to individual differences in intelligence quotient (IQ). The current study assesses the replicability of these findings both within and across samples of healthy volunteers, as well as in pediatric patients.

Subjects comprised three independent cohorts: 1) Neuroscience in Psychiatry Network (NSPN) healthy volunteers (n=297, mean age=19.1, 50% male), 2) Human Connectome Project (HCP) healthy volunteers (n=1113, mean age=28.8, 46% male), and 3) National Institute of Mental Health (NIMH) transdiagnostic clinical subjects (n=331, mean age=13.6, 46% male). MRI data were processed using FreeSurfer (v5.3.0). IQ was assessed through variable measurement tools. MSN matrices were constructed with varying numbers of features (from T1-weighted imaging alone vs. T1 plus diffusion weighted imaging (DWI)) and either thresholded or unthresholded nodal degree. Within- and between-cohort replicability of MSN topography and associations with IQ were estimated through split-half validation and correlations of regional nodal degree PLS loadings, respectively.

The topography of mean MSN degree was highly reproducible both within and between cohorts and varied little with sample size, MSN features or nodal degree metric ($r > 0.8$). However, the consistency of IQ-MSN associations was highly variable. PLS-derived associations between nodal degree and IQ showed good reproducibility ($0.6 < r < 0.8$) in healthy cohorts when nodal degree was unthresholded and based on MSNs derived from multimodal imaging data (10 features from T1-weighted imaging plus DWI). However, these associations could not be generalized ($r = 0.01$) to a clinical cohort using thresholded, unimodal MSNs (i.e. 7 features from T1 alone). We identify methodological choices that may be able to increase generalizability of MSN-IQ associations from healthy to clinical cohorts.

Abstract Publications:

1. **Hu R**, Cardinale EM, Seidlitz J, Raznahan A, Leibenluft E, Pine D, Kircanski K. Morphometric similarity networks in childhood anxiety and irritability. Society of Biological Psychiatry Annual Meeting, Chicago, IL; May 16–18, 2019. [Poster presentation]

Travel to Professional Meetings:

- Society of Biological Psychiatry 74th Annual Meeting; Chicago, IL; May 16–18, 2019.



Natasha Kesav

School: Northeast Ohio Medical University

Mentor: H. Nida Sen, M.D., Lasker Clinical Research Scholar, Head, Unit on Clinical Translational Immunology, Laboratory of Immunology

Institute: National Eye Institute (NEI)

Research: Association between Laboratory Testing for Latent Tuberculosis (QuantIFERON-TB Gold Test) and Clinical Manifestations of Uveitis in the United States

Determination of a causal relationship between latent tuberculosis (TB) infection and uveitis remains a challenge. Serpiginoid choroiditis, choroidal granulomas, and retinal vasculitis have been suggested as typical findings of ocular TB, a diagnosis often made presumptively. This study investigated the prevalence of latent TB infection and associated clinical features in patients with uveitis.

A cohort of uveitis patients at the National Eye Institute was prospectively tested for latent TB infection using the QuantiFERON-TB Gold (QFT-G) assay. Demographics and clinical features of uveitis were compared between groups testing positive and negative in the assay.

We found that the QFT-G test was positive in 65/450 patients diagnosed with uveitis (14.4%) compared to an annual positive rate of 1.3%-4.3% in greater than four million subjects tested in a study of active service members in the US Army. There were no significant differences in age, gender or laterality of uveitis between QFT-G test-positive and test-negative groups. Asian ethnicity was associated with higher likelihood of a positive test (OR 3.07; $p=0.0008$). Patients who tested QFT-G positive were more likely to have anterior uveitis (OR 1.87; $p=0.036$) and granulomatous uveitis (OR 2.96; $p=0.002$). All but two of the uveitis patients with positive tests for LTBI had a chest X-ray performed, and although one patient had an abnormal chest x-ray, none were found to have systemic TB disease.

Our systematic screening of uveitis patients for latent tuberculosis infection in a low-TB-endemic tertiary referral clinic population using the QFT-G assay demonstrated a significantly higher prevalence of latent TB among uveitis patients compared to an historical population of healthy control subjects. Latent TB infection is more likely to be found in patients of Asian ethnicity and in those with anterior and granulomatous uveitis.

Full Length Publications:

- Caplash S, Gangaputra S, **Kesav N**, Vitale S, Akanda M, Kodati S, Marques A, Sen HN. Utility of routine screening for Lyme disease among patients with ocular inflammation: a Bayesian approach. *Ophthalmology*. [In Press]
- **Kesav N**, Kaplan A, Hwang C, Okeagu C, Sen HN. Tattoo-associated cases of Vogt-Koyanagi-Harada disease. *Retin Cases Brief Rep*. [Under review]
- Knickelbein K, Jeffrey B, Wei M, Cheng S, **Kesav N**, Sen HN. Reproducibility of full-field electroretinogram measurements in birdshot chorioretinopathy patients: an intra- and inter-visit analysis. *Ocul Immunol Inflamm*. [Under review]

Abstract Publications:

- **Kesav N**, Cheng S, Caplash S, Thompson I, Gangaputra S, Sen HN. The association between QuantiFERON-TB Gold Test and clinical manifestations of uveitis in the United States. American Uveitis Society, Vancouver, CA; Apr. 27, 2019. [Oral presentation].
- **Kesav N**, Yang Q, Losert W, Sen HN. Novel automated processing technique for standardization and normalization of fluorescein angiography images in uveitis. Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, CA; Apr. 27–May 2, 2019. [Poster presentation].
- **Kesav N**, Kaplan A, Hwang C, Okeagu C, Sen HN. Linked: a case series of Vogt-Koyanagi-Harada linked to tattoo-associated dermatitis. Ohio Ophthalmological Society Annual Meeting, Columbus, OH; February 18, 2019. [Poster Presentation].

Travel to Professional Meetings:

- Ohio Ophthalmological Society, Columbus, OH; February 18, 2019.
- Forum on Laser-Based Imaging, Silver Spring, MD; April 8, 2019.
- American Uveitis Society Spring Meeting, Vancouver, Canada; Apr. 27, 2019.
- Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, CA; Apr. 27–May 2, 2019.



Jenny J. Kim

School: Stony Brook University School of Medicine

Mentor: Andrew J. Mannes M.D., Chief, Department of Perioperative Medicine; Michael J. Iadarola, Ph.D., Senior Scientist, Department of Perioperative Medicine

Institute: NIH Clinical Center (CC)

Research: RNA-Seq Analysis of Rat Frontal Lobe, Hippocampus, and Amygdala after Sustained Intravenous Administration of Ketamine Anesthesia

Ketamine is an NMDA-receptor antagonist that is increasingly used for the treatment of depression and pain, although the molecular and circuit level mechanisms remain incompletely defined. In the present study, the transcriptional processes induced by ketamine infusion were examined in discrete rat brain regions following sustained femoral vein-infusion titrated to produce immobility and pedal reflexes. Frontal cortex, hippocampus and amygdala, regions known to be affected by anesthetics and analgesics, were obtained from sham-operated (n=7), one-hour infused (n=6), 10-hour infused (n=7), and 10-hour infused+24-hour recovery (n=6) animals. RNA-seq (50-80 million reads per sample) revealed regional

differences in transcriptional signatures that were most accentuated at 10 hours, followed by lower magnitude changes frequently in the opposite direction at recovery. Thirty-six percent, 75%, and 87% of differentially regulated genes were upregulated in the frontal cortex, hippocampus, and amygdala, respectively. Increased expression of immediate early genes such as *Fos*, *Fos12*, and *Maff* was observed across all regions. RNA *in-situ* hybridization of 10-hour samples localized *Fos* upregulation to cortical layer III and layer V pyramidal neurons, indicating involvement of recurrent excitatory and cortical efferent pathways, respectively. The *Fos*⁺ cells also exhibited upregulation of other activity-related genes such as *Nr4a1* and *Bdnf*, the latter being a key transducer of antidepressant effects. Transcriptional regulation of activity-related genes occurred earlier in the hippocampus and amygdala. Canonical pathway analysis revealed upregulation of genes in the *Nrf2*-mediated antioxidant response pathway across all three brain regions, but differential patterns of regulation in other identified pathways including synaptic remodeling, glutamate-receptor complex regulation, and CRH signaling. Upon cessation of ketamine infusion, we observed a rebound downregulation of key activity-related genes and pathways. These data support the idea of NMDA blockade initiating a cascade of molecular regulatory actions leading to establishment of antidepressant and analgesic effects of ketamine.

Full Length Publications:

- Sapio MR, Iadarola MJ, Loydpierson AJ, **Kim JJ**, Maric D, Mannes AJ. Dynorphin and enkephalin opioid peptides and transcripts in spinal cord during peripheral inflammatory hyperalgesia and allodynia. *J Pain*. [Under review].
- Sapio MR, **Kim JJ**, Loydpierson AJ, Maric D, Goto T, Vazquez FA, Muhly WT, Iadarola MJ, Mannes AJ. Opioid and non-opioid neuronal opponent processes in spinal cord dorsal horn controlling hyperalgesia and pain sensitization. [Under review].

Abstract Publications:

- **Kim JJ**, Sapio MR, Loydpierson AJ, Iadarola MJ, Mannes AJ. RNA-seq analysis of rat frontal lobe, hippocampus, and amygdala after long-term administration of ketamine and isoflurane anesthesia. Association for University Anesthesiologists Annual Meeting, Montreal, Quebec, Canada; May 16–17, 2019. [Poster presentation]
- Sapio MR, Loydpierson AJ, Iadarola MJ, **Kim JJ**, Mannes AM. The persistent pain transcriptome: distinct transcriptional signatures of post-surgical and inflammatory models define convergent pathways to the transition to hyperalgesia. American Pain Society Scientific Meeting, Milwaukee, WI; April 3–6, 2019. [Abstract]

- Iadarola MJ, Loydpierson AJ, Sapio MR, Maric D, **Kim JJ**, Fehrenbacher JC, Vasko MR, Gregory MD, Eisenberg DP, Nash TA, Kippenhan JS, Mannes AJ, Mervis CB, Berman KF. Molecular analyses of STX1A and LIMK1 in the Williams-Buren syndrome locus in relationship to reduced pain sensitivity. NIMH-NHLBI Heart and Soul Workshop, Bethesda, MD; April 2–3, 2019. [Abstract]
- Iadarola MJ, Sapio MR, Loydpierson AJ, **Kim JJ**, LaPaglia DM, Raithel SJ, Vazquez FA, Starost JE, Mannes AJ. An RNA-Seq transcriptomic and *in situ* hybridization assessment of mu and kappa opioid receptors and pro-enkephalin and pro-dynorphin transcripts in molecular pain circuits. American College of Neuropsychopharmacology Annual Meeting, Hollywood, FL; Dec. 8–11, 2018. [Abstract]

Travel to Professional Meetings:

- American Pain Society Scientific Meeting, Milwaukee, WI; April 3–6, 2019.
- Association for University Anesthesiologists Annual Meeting, Montreal, Quebec, CA; May 16–17, 2019.



Erika J. Lampert

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

Mentor: Jung-Min Lee, M.D., Lasker Clinical Research Scholar, Women's Malignancies Branch

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

Research: Immune Modulation by Cell Cycle Checkpoint Kinase (CHK)1 Inhibition in High Grade Serous Ovarian Cancer

High-grade serous ovarian cancer (HGSOC) is the most lethal gynecologic malignancy worldwide. HGSOC is characterized by universal TP53 mutations and DNA repair deficiency. Cell cycle checkpoint kinase 1 (CHK1) is overexpressed in nearly all HGSOC, making it a logical target. A phase II study with a CHK1 inhibitor (CHK1i) showed a 33 percent response rate among heavily pretreated BRCA wild-type (BRCAwt) HGSOC patients. Emerging data suggests CHK1i causes DNA damage and induces downstream innate and adaptive immune responses, thereby augmenting antitumor activity. We aimed to characterize the immunomodulatory effects of CHK1 inhibition in BRCAwt HGSOC and identify potential predictive biomarkers.

Twenty four patients with HGSOC were treated with CHK1i on this trial. RNAseq was performed on paired baseline and on-therapy fresh core biopsies to assess changes in the tumoral microenvironment. Multiparametric flow cytometry for DNA damage markers and immune cell subsets was performed on paired blood samples to evaluate changes in the peripheral immune milieu.

We found increased γ -H2AX among peripheral immune cells, indicating CHK1i caused DNA damage (MFI 1.63 vs 1.74, $p=0.034$, CD3+ cells). CHK1i induced innate immune antitumor activity, as evidenced by increased post-treatment monocytes per total cells (31.6 vs 45.6%, $p=0.005$) and improved progression-free survival among patients with increased HLA-DR, a marker of immunocompetence, on monocytes (3.5 vs 9.25 months, $p=0.019$). CHK1i induced lymphodepletion of CD4+ and CD8+ T-cells (25 vs 19.6%, $p=0.008$; 9.49 vs 7.63%, $p=0.005$, respectively), but repopulation with immunostimulatory GITR+ cells (0.32 vs 0.82%, $p=0.0003$). Increased naïve B and resting memory T-cell tumoral infiltration was observed (0.5% vs 14%, $p=0.003$; 19% vs 25%, $p=0.03$, respectively), suggestive of an adaptive immune response.

CHK1i elicits antitumor innate and adaptive immune responses in heavily pretreated BRCAwt HGSOC patients. This work provides novel insights into the biologic activity of CHK1 blockade in ovarian cancer and indicates that this approach warrants further prospective clinical evaluation.

Full Length Publications:

- **Lampert EJ**, Hays J, Kohn E, Annunziata C, Minasian L, Yu M, Gordon N, Sissung T, Chiou V, Figg W, Houston N, Lee JM. Phase I/Ib study of olaparib and carboplatin in heavily pretreated recurrent high-grade serous ovarian cancer at low genetic risk. *Oncotarget* 2019 Apr; 10:2855-2868.

Travel to Professional Meetings:

- American Association of Cancer Research (AACR) Annual Meeting, Atlanta, GA, Mar. 29–Apr. 3, 2019.

Abstract Publications:

- **Lampert EJ**, Lee JS, Lee MJ, Trepel J, Yuno A, Ruppin E, Lee JM. Cell cycle checkpoint kinase (CHK)1 inhibition induces immune modulation in recurrent BRCA wild-type high-grade serous ovarian cancer (HGSOC) patients. American Association of Cancer Research Annual Meeting, Atlanta, GA; Mar. 29–Apr. 3, 2019. [Poster presentation]



Steven D. Langerman

School: George Washington University School of Medicine & Health Sciences

Mentor: Tiffany M. Powell-Wiley, M.D., M.P.H., Chief, Social Determinants of Obesity and Cardiovascular Risk Laboratory

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

Research: Adverse Perceived Neighborhood Social Environment is Associated with Increased Severity of Depressive Symptoms: Data from the Jackson Heart Study

Depression is a major public health issue in the U.S. and is associated with increased risk of cardiovascular disease and mortality, particularly among African-American adults. Neighborhood factors are known contributors to depression, but little is understood about the relationship between neighborhood social environment and depression in African-American populations. The objective of this study was to examine associations between neighborhood social environment and depressive symptoms in African-American adults.

We used baseline data from the Jackson Heart Study, a single-site, prospective, community-based study of African-American adults in Jackson, Mississippi. Perceived neighborhood social environment variables included scores for neighborhood problems, neighborhood violence, and neighborhood social cohesion. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression (CES-D) score as a continuous variable. Multi-level modeling for incorporating the hierarchical nature of the data into analyses was used to estimate associations between neighborhood social environment and depressive symptoms score, adjusting for demographics (e.g., age), health-related factors (e.g., smoking), and built environment variables (e.g., population density).

Our study population (N=3110) was 64.5% female with a mean age of 54 (SD=13) years and a mean depressive symptoms score of 10.9 (SD=8.1). In the fully-adjusted model, we found a positive association between neighborhood problems and depressive symptoms score (B=3.30; 95% CI=1.40, 5.21) and between neighborhood violence and depressive symptoms score (B=4.42; 95% CI=1.65, 7.18). There was no significant association between neighborhood social cohesion and depressive symptoms score.

Higher levels of perceived neighborhood problems and violence were positively associated with depressive symptoms among African-American adults. Policy interventions which seek to mitigate adverse neighborhood perceptions could reduce depression in this population. Further research will investigate potential modifiers in the associations between neighborhood social environment and depressive symptoms.

Full Length Publications:

- Tamura K, **Langerman S**, Ceasar J, Andrews M, Powell-Wiley T. Neighborhood social environment and cardiovascular disease risk. *Curr Cardiovasc Risk Rep*. 2019 Mar 8. doi: 10.1007/s12170-019-0601-5. [Epub ahead of print]
- Andrews M, Ceasar J, Tamura K, **Langerman S**, Mitchell V, Collins B, Baumer Y, Gutierrez-Huerta C, Key A, Playford M, Mehta N, Powell-Wiley T. Neighborhood environment perceptions associate with depression levels and cardiovascular risk: data from the Washington, DC Cardiovascular Health and Needs Assessment. [Under review]
- Andrews M, Tamura K, Claudel S, Xu S, Ceasar J, Collins B, **Langerman S**, Mitchell V, Baumer Y, Powell-Wiley T. Geospatial analysis of neighborhood deprivation index (NDI) for the United States by county. [Under review]
- Powell-Wiley T, Dey A, Rivers J, Chaturvedi A, Mitchell V, Andrews M, Ceasar J, Ayers C, Baumer Y, Tamura K, **Langerman S**, Gutierrez-Huerta C, Yu Q, Collins B, Ahlman M, Goyal A, Joshi A, Teague H, Chung S, Sumner A, Playford M, Mehta N. Chronic stress-related neural activity associated with subclinical cardiovascular disease in a community-based cohort: data from the Washington, D.C. Cardiovascular Health and Needs Assessment. [Under review]

Abstract Publications:

- Langerman S**, Powell-Wiley T, Andrews M, Ceasar J, Sims M, Lee J, Tamura K. Adverse perceived neighborhood social environment is associated with increased severity of depressive symptoms: data from the Jackson Heart Study. Society for Epidemiologic Research Annual Meeting, Minneapolis, MN; Jun 18–21, 2019. [Poster presentation]
- Tamura K, Cromley E, **Langerman S**, Andrews M, Ceasar JN, Claudel SE, Sims M, Powell-Wiley TM. Is perceived neighborhood social environment associated with TV viewing among Jackson Heart Study participants? Society for Epidemiologic Research Annual Meeting, Minneapolis, MN; Jun 18–21,

2019. [Poster presentation]

- Powell-Wiley T, Andrews M, Ayers C, Ceasar J, Tamura K, **Langerman S**, Neeland I, Das S. Social support as a mediator of the relationship between perceived neighborhood environment and physical activity: data from the Dallas Heart Study. International Society of Behavioral Nutrition and Physical Activity Annual Meeting, Prague, Czech Republic; Jun 4–7, 2019. [Poster presentation]
- Powell-Wiley T, Ceasar J, Tamura K, Andrews M, Ayers C, **Langerman S**. Examining the relationship between park availability and self-reported vigorous physical activity in a resource-limited community: data from the Washington, D.C. Cardiovascular Health and Needs Assessment. International Society of Behavioral Nutrition and Physical Activity Annual Meeting, Prague, Czech Republic; Jun 4–7, 2019. [Poster presentation]
- Andrews M, Ceasar J, Tamura K, Mitchell V, **Langerman S**, Collins B, Baumer Y, Gutierrez-Huerta C, Key A, Playford M, Mehta N, Powell-Wiley T. Neighborhood environment perceptions associate with depression levels and cardiometabolic risk: data from the Washington, D.C. Cardiovascular Health and Needs Assessment. American Heart Association Epi-Lifestyle Scientific Sessions, Houston, TX; March 5–8, 2019. [Poster presentation]
- Ceasar J, Powell-Wiley TM, Andrews M, Ayers C, Collins B, **Langerman S**, Mitchell V, Tamura K. Examining the relationship between physical activity resources and self-reported vigorous physical activity in a resource-limited community: data from the Washington D.C. Cardiovascular Health and Needs Assessment. American Heart Association Epi-Lifestyle Scientific Sessions, Houston, TX; March 5–8, 2019. [Poster presentation]

Travel to Professional Meetings:

- Society for Epidemiologic Research, Minneapolis, MN; Jun. 18–21, 2019.



Anthony J. Lee

School: University of Miami Miller School of Medicine

Mentor: Clifton Barry, Ph.D., Chief, Tuberculosis Research Section

Institute: National Institute of Allergy and Infectious Diseases (NIAID)

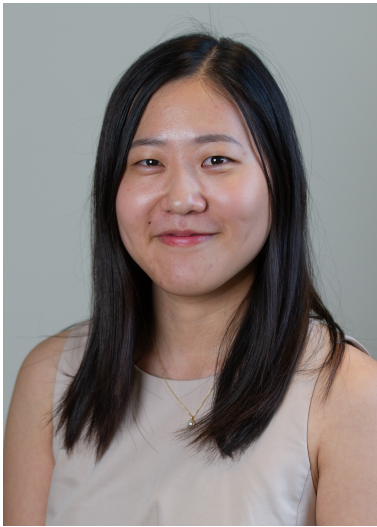
Research: Evaluation of a Quantitative Nucleic Acid Amplification Test (Gene Xpert MTB/RIF Assay) for Capturing Anti-Tuberculosis Treatment Effects and Early Bactericidal Activity

Tuberculosis (TB) is the leading cause of death from a single infectious agent. New anti-TB drug candidates rely on large, costly, and long Phase IIB/III clinical trials to capture sterilizing activity. Commonly, Early Bactericidal Activity (EBA), assessed as mean daily log₁₀ decline of CFU/mL sputum/day, is used as a surrogate of drug activity to triage which drugs proceed to advanced phases of clinical trials. While EBA is attractive due to small sample size and short time span, it does not capture longer-term sterilizing activity.

There is a need for novel biomarkers to measure true sterilizing drug activity in TB. In our parent study, NexGen EBA, the effect of various anti-TB drugs on radiographic and immunologic markers, as measured by PET/CT and immunologic assays, in treatment-naïve subjects (n=160) with pulmonary drug-sensitive TB are characterized. In the current sub-study, a quantitative nucleic acid amplification test (Xpert MTB/RIF assay, Cepheid) that detects *Mycobacterium tuberculosis* (MTB) in sputum with real-time PCR, was evaluated for treatment effects.

Xpert cycle threshold (Ct) value (number of PCR cycles needed to detect TB DNA) strongly correlated with bacterial load at baseline: log CFU ($p < 0.0001$), time-to-culture-positivity ($p < 0.0001$), and EBA ($p = 0.01$); however, Pearson correlations were not strong (-0.52, 0.56, and -0.23, respectively). Delta Ct (Day 14 Ct value – baseline Ct value) did not reflect treatment effects in the first 14 days of treatment. While a strong correlation between Ct and CFU suggests that Xpert captures the decline in bacterial load, the assay cannot distinguish DNA from viable vs. non-viable bacteria. Thus, delta Ct in the first 14 days of treatment was not a useful parameter, as the body requires time to eliminate DNA from non-viable bacteria.

Further analysis is underway to characterize the relationship between Xpert Ct and radiographic biomarkers that may enhance the evaluation of potency of anti-TB drugs.



Debora H. Lee

School: University of California, Irvine School of Medicine

Mentor: Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications; Tiarnan D. Keenan, B.M. B.Ch., Ph.D., Staff Clinician, Division of Epidemiology and Clinical Applications

Institute: National Eye Institute (NEI)

Research: Visual Acuity Outcomes after Cataract Surgery in Persons with Type 2 Diabetes: the Action Control Cardiovascular Risk in Diabetes (ACCORD) Study

Historically, outcomes of cataract surgery have been reported as less favorable in individuals with diabetes. This study evaluated visual acuity (VA) outcomes of cataract surgery and factors associated with good visual outcome in persons with type 2 diabetes.

From 2001 to 2014, the ACCORD Study and the Follow-On (ACCORDION) Study followed 10,251 participants with type 2 diabetes at high risk for cardiovascular disease for a median of 9.2 years. Cataract surgery was documented at annual study visits and VA was measured on

ETDRS charts every two years. Eyes that received cataract surgery during follow-up and VA measurements within two years of surgery were included in the analysis. The outcome assessed was post-operative VA $\geq 20/40$; the association of this outcome with various factors was evaluated using repeated measures logistic regression.

There were 2,748 eyes with incident cataract surgery and, after applying the inclusion criteria, 1,136 eyes (784 participants) remained in the analysis. Of these, 762 eyes (67.1%) achieved post-operative VA $\geq 20/40$. On multivariate analysis, the factors associated with post-operative VA $\geq 20/40$ were education level (reference, some high school; highest, college graduate, adjusted odds ratio (AOR) 2.44 [1.50-4.00]), clinical center network (reference, Northeastern U.S.; highest, Veterans Affairs AOR 3.85 [2.09-7.01]), pre-operative VA (reference, $<20/200$; highest, 20/20+, AOR 9.49 [3.57-25.26]), absence of retinopathy (AOR 2.76 [1.90-3.99]), and bilateral cataract surgery (AOR 1.52 [1.12-2.08]). Factors not significantly associated included age, sex, race, diabetes duration, blood pressure, lipid levels, and HbA1C.

In the ACCORD population, two-thirds of eyes receiving cataract surgery achieved good VA, equivalent to driving-level vision. This suggests that in the modern era of small-incision phacoemulsification and tighter glycemic control, good visual outcomes are attainable despite the presence of diabetes. This appears to hold true irrespective of age, sex, race, or glycemic control. Pre-operative VA and retinopathy are important predictors of visual outcome.

Full Length Publications:

- **Lee DH**, Hwang CK, Cukras CA, Wiley HE, Malik FF, Chew EY, Keenan TD. Two cases of severe Purtscher-like retinopathy demonstrating recurrence and progression to neovascularization and vitreous hemorrhage. *Retin Cases Brief Rep.* [Under review]

Abstract Publications:

- **Lee DH**, Agron E, Keenan TD, Greven CM, Danis RP, Lovato JF, Ambrosius WT, Chew EY. Visual acuity outcomes of cataract surgery in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study. Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, CA; April 27–May 2, 2019. [Poster presentation]

Travel to Professional Meetings:

- Forum on Laser-Based Imaging, Silver Spring, MD; April 8, 2019.
- Association for Research in Vision and Ophthalmology Imaging in the Eye Conference, Vancouver, Canada; April 26–27, 2019.
- Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, CA; April 27–May 2, 2019.



Diane M. Libert

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

Mentor: Jack Shern, M.D., and Nirali Shah, M.D.; Pediatric Oncology Branch

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

Research: Targeting Antigen Expression to Enhance Chimeric Antigen Receptor (CAR) T cell Therapeutic Efficacy for Pediatric B cell Acute Lymphoblastic Leukemia

Ubiquitous expression of CD19 on B-cells renders it an ideal target for immunotherapies, such as chimeric antigen receptor (CAR) T-cells, in pediatric acute lymphoblastic leukemia (ALL). However, antigen modulation is emerging as a mechanism of resistance post-immunotherapy. Knowledge of the evolution of disease CD19 surface expression is essential to assess opportunities for additional CD19 targeting. Furthermore, the ability to pharmacologically increase CD19 expression has the potential to improve responses to targeted therapy. We addressed these issues via a series of clinical and basic research studies.

For the clinical study, the evolution of CD19 expression in clinical flow cytometry reports of patients with relapsed/refractory ALL referred to this institution was retrospectively assessed. Analysis of 56 patients showed that 40 (71%), had no change in CD19 during follow-up while 16 (29%) had ongoing CD19 modulation, including 11 with increases in expression. CD19 loss had previously been assumed permanent; however, our data show that some patients regain CD19 expression after initially losing it, warranting ongoing surveillance for renewed therapeutic susceptibility.

To find a drug that increases CD19 expression, we screened the effects of 96 rationally-selected drugs on the surface expression of CD19 and other CAR targets on leukemia cell lines using flow cytometry. Methotrexate (MTX) was the top hit for a drug that increases CD19, with median fold changes ranging from 1.11- 1.82 on 11 cell lines. Further mechanistic investigation through confocal microscopy and quantitative reverse transcriptase PCR (qRT-PCR) revealed a change in cell morphology without an increase in CD19 RNA with MTX treatment. Current experiments interrogate the hypothesis that MTX increases CD19 expression by promoting protein trafficking to the plasma membrane concomitant with cell cycle arrest. Future efforts involve generating a MTX-resistant CAR to maximize benefit from the synergistic treatment of ALL with both chemotherapy and CAR T-cells.

Full Length Publications:

- **Libert D**, Yuan CM, Masih KE, Shalabi H, Salem D, Yates B, Delbrook C, Fry TJ, Khan J, Shern JF, Stetler-Stevenson M, Shah NN. Evolution of CD19 surface expression in pediatric B-cell malignancies in the era of targeted therapy. (Manuscript in preparation)

Abstract Publications:

- **Libert D**, Yuan CM, Shalabi H, Salem D, Yates B, Delbrook C, Fry TJ, Shern J, Stetler-Stevenson M, Shah N. Evolution of CD19 expression in pediatric B-cell malignancies in the era of targeted therapy. American Association of Cancer Research Annual Meeting, Atlanta, GA; Mar. 29–Apr. 3, 2019. [Poster presentation]

Travel to Professional Meetings:

- American Association of Cancer Research (AACR) Annual Meeting, Atlanta, GA; Mar. 29–Apr. 3, 2019.
- NIH-AACR Cancer, Autoimmunity, and Immunology Conference, Bethesda, MD; Apr. 15–16, 2019.
- Fourth Annual Children's Cancer Foundation Research Symposium, Hyattsville, MD; June 5, 2019.



Mengyun Lu

School: University of North Carolina School of Medicine

Mentor: Michael Solomon, M.D., Head, Cardiology Section, Critical Care Medicine Department, NIH Clinical Center; Jason Elinoff, M.D., Head, Pulmonary Vascular Biology Section, Critical Care Medicine Department, NIH Clinical Center

Institute: NIH Clinical Center (CC)

Research: Effects of Mineralocorticoid Receptor Antagonism on Right Ventricular Function and Pulmonary Vascular Remodeling in a Rodent Model of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a lethal disease that leads to right heart failure and death. Mineralocorticoid receptor (MR) antagonists improve survival in patients with left heart failure but their effects on right heart failure due to PAH are incompletely understood. We tested whether MR antagonists have a beneficial effect on cardiac structure and function after the onset of severe right ventricular (RV) dysfunction in the SU5416/hypoxia rat model of PAH.

To induce PAH, male Sprague-Dawley rats were injected with SU5416 (25 mg/kg), exposed to hypoxia for 3 weeks, and returned to normoxia for the remaining 7 weeks of the study. Animals were fed medicated diets containing spironolactone (SPL; n=15; 40 mg/kg/d), eplerenone (EPL; n=15; 100 mg/kg/d), or placebo (PL; n=13). Cardiac MRI (Bruker 7T) was performed pre- (week 5) and post-treatment (week 10).

Despite evidence of severe RV dysfunction by week 5, MR antagonists prevented further decline in cardiac index (change from weeks 5 to 10: PL = -0.063 ± 0.018 , SPL = 0.002 ± 0.017 , $P = 0.01$; and EPL = -0.0005 ± 0.017 ml/min/g; $P = 0.01$) as well as stroke volume index (PL = -0.14 ± 0.05 , SPL = -0.005 ± 0.05 and EPL = -0.002 ± 0.05 μ l/g; $P = 0.03$ for the combined SPL+EPL group vs PL). EPL also reduced the end-systolic eccentricity index (PL = 0.21 ± 0.17 vs EPL = -0.35 ± 0.16 ; $P = 0.02$) and the RV to LV end-diastolic volume ratio (PL = 0.07 ± 0.08 vs EPL = -0.23 ± 0.08 ; $P = 0.02$).

In the SU5416/hypoxia rat model of PAH, both SPL and EPL maintained cardiac index and stroke volume index when initiated after the onset of RV dysfunction. EPL also improved ventricular interdependence as demonstrated by a reduction in the end-systolic eccentricity index and the RV to LV end-diastolic volume ratio.

Full Length Publications:

- Elinoff JM, Mazer AJ, Cai R, Lu M, Graninger G, Harper B, Ferreyra G, Sun J, Solomon MA, Danner RL. Meta-analysis of blood genome-wide expression profiling studies in pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol*. [Under review]

Travel to Professional Meetings:

- American College of Cardiology 68th Annual Scientific Session, New Orleans, LA; March 16–18, 2019.

Abstract Publications:

- Lu M, Mazer AJ, Anderson SA, Gairhe S, Chen L, Nelson J, Noguchi A, Yu Z, Wang H, Sun J, Danner RL, Solomon MA, Elinoff JM. Mineralocorticoid receptor antagonists prevent further decline in cardiac index and improve ventricular interdependence in a rat model of pulmonary arterial hypertension. American Heart Association Scientific Sessions 2019. Philadelphia, PA; Nov. 2019 [Submitted]
- Lu M, Blaine KP, Cullinane A, Hall C, Dulau-Florea A, Sun J, Chenwi H, Graninger G, Harper B, Elinoff JM, Solomon MA. Pulmonary arterial hypertension patients display normal kinetics of clot formation. American Heart Association Scientific Sessions 2019. Philadelphia, PA; Nov. 2019 [Submitted]



Katherine E. Masih

School: University of Miami Leonard M. Miller School of Medicine

Mentor: Javed Khan, M.D., Deputy Chief, Genetics Branch; Head, Oncogenomics Section

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

Research: Identifying Resistance Mechanisms to CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy in Pediatric B Cell Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and relapsed patient outcome is poor with less than 30 percent overall survival. CD19 CAR T-cell therapy has shown impressive response rates (>80%) in refractory disease. However, long-term survival analysis reveals that durable response rates are closer to 40 percent. Little is known about factors predicting durable response to CAR T therapy. We hypothesized that patients with CD19 CAR T-cell resistant ALL have a distinct disease compared to responders, and that these differences can be identified in pre-treatment leukemia. Utilizing advanced genomic, epigenetic, proteomic and single-cell (sc) techniques, we characterized patient bone marrow aspirates (BMA) to identify mechanisms of resistance.

Patients enrolled in PLAT-02 at Seattle Children's Hospital were categorized according to the durability of response to CD19 CAR T therapy. Pre-treatment therapy-resistant BMAs were analyzed and compared to those with sensitive disease. We performed whole-exome sequencing, RNA-seq, scRNA-seq, sc B cell receptor (BCR)-seq, methylation array, H3K27ac ChIP-seq, and ATAC-seq. Additionally, we developed murine patient-derived xenografts (PDXs) for future studies.

Initial analysis revealed five hotspot mutations in *ABL1*, 2 x *KRAS*, *IKZF1*, and *EP300*. RNA-seq analyses identified 2 *ABL1*, 2 *ETV6*, 2 *ETV5*, *KMT2A* actionable fusions. Interestingly, we identified novel *CREBBP*-fusions in all leukemias resistant to CD19 CAR T induced B-cell aplasia, which have previously been associated with refractory ALL. Integrated gene expression and epigenetic analyses are ongoing to identify genes or pathways associated with resistant disease. scRNA- and scBCR-seq data are being analyzed for mixed lineage and gene expression-based heterogeneity that may predict clonal selection by CAR T pressure. Finally, we developed PDXs (64%), a valuable resource for future studies and developing novel therapies for resistant leukemias.

This study establishes one of the most comprehensive genomic profiling approaches for ALL patient samples. These analyses highlight crucial differences predicting responsiveness to CAR T-cell therapy.

Full Length Publications:

- Libert D, Yuan CM, **Masih KE**, Shalabi H, Salem D, Yates B, Delbrook C, Fry TJ, Khan J, Shern JF, Stetler-Stevenson M, Shah NN. Evolution of CD19 surface expression in pediatric B-cell malignancies in the era of targeted therapy. [Manuscript in preparation]
- Masih KE**, Abdalla A, Gardner R, Adebola S, Jensen M, Wilson A, Gryder BE, Stanton BZ, Lack J, Sindiri S, Song Y, Wang C, Wen X, Rae Z, Kelly M, Cheuk A, Altan-Bonnet G, Wei JS, Orentas R, Khan J. Integrated comprehensive omic analysis of multiply relapsed CD19 CAR T-cell resistant pediatric B-cell acute lymphoblastic leukemia. [Manuscript in preparation]

Travel to Professional Meetings:

- Keystone Symposia on Cancer Immunotherapy: Mechanistic Insights to Improve Clinical Benefit, Whistler, BC; March 10–14, 2019.
- American Association of Cancer Research Annual Meeting, Atlanta, GA; March 29–April 3, 2019.

Awards:

- Distinction in Research Award, University of Miami Miller School of Medicine.

Abstract Publications:

- Masih KE**, Gardner R, Jensen M, Wilson A, Gryder BE, Stanton BZ, Lack J, Sindiri S, Song Y, Wang C, Wen X, Rae Z, Kelly M, Cheuk A, Walton A, Adebola S, Altan-Bonnet G, Wei JS, Orentas R, Khan J. Understanding mechanisms of resistance to CD19 CAR T-cell therapy in pediatric B cell acute lymphoblastic leukemia. Keystone Symposia on Cancer Immunotherapy: Mechanistic Insights to Improve Clinical Benefit, Whistler, BC; March 10–14, 2019 [Poster presentation]
- Masih KE**, Gardner R, Gryder BE, Lack J, Stanton BZ, Wilson A, Finney O, Sindiri S, Song Y, Rae Z, Kelly M, Wang C, Wen X, Cheuk A, Walton A, Wei JS, Jensen M, Orentas R, Khan J. An integrated genomic, epigenetic, proteomic, and single cell analysis of pediatric B cell acute lymphoblastic leukemia to elucidate resistance mechanisms to CD19 CAR T-cell therapy. American Association of Cancer Research Annual Meeting, Atlanta, GA; March 29–April 3, 2019 [Poster presentation]



Grace B. McKay-Corkum

School: University of Massachusetts Medical School

Mentor: Christine Heske, M.D., Head, Translational Sarcoma Biology Group, Pediatric Oncology Branch

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

Research: Exploiting Metabolic Vulnerabilities of Pediatric Rhabdomyosarcoma with Novel Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibitor OT-82

Nicotinamide phosphoribosyltransferase (NAMPT) is an essential NAD salvage pathway enzyme. Tumor cells rely on this pathway to generate NAD for vital metabolic functions. NAMPT may thus be a promising target for cancers requiring novel therapies, such as pediatric rhabdomyosarcoma (RMS). The mean five-year survival rate for pediatric RMS is greater than 70 percent, but is less than 30 percent for patients with relapsed or metastatic disease. Our study investigates the activity and efficacy of novel NAMPT inhibitor OT-82 (OncoTartis) in RMS.

IncuCyte live cell analysis was used to monitor effects of OT-82 on cell proliferation. On-target activity of the drug was determined by NAD assay and rescue experiments using NAD pathway metabolites. Mechanisms of action and downstream effects of OT-82 were investigated using assays for PARP activity, cell cycle and annexin. DNA damage was assessed by comet assay. Western blot analyses characterized expression of NAD pathway enzymes. NAMPT was overexpressed by transfecting cell lines with NAMPT cDNA.

Eight RMS cell lines (five fusion-negative, three fusion-positive) demonstrated profound sensitivity to OT-82, with IC_{50} s below 1 nM. NAD assay showed OT-82 activity was on-target. Addition of nicotinamide mononucleotide (NMN), the product of NAMPT, rescued the effects of OT-82 on proliferation. PARP activity significantly decreased with OT-82; these levels were restored with addition of NMN to OT-82. OT-82 caused DNA damage, demonstrated by gamma H2AX induction and comet assay, and caused G2/M arrest. Apoptosis was detected after 48–72 hours of OT-82 exposure. Expression of NAMPT and NAMPT, an enzyme in the Preiss-Handler pathway, did not correlate with RMS subtype or OT-82 sensitivity. Only cell lines with higher NAMPT expression were rescued by nicotinic acid (NA), the NAMPT substrate. When NAMPT was overexpressed in low/non-expressing cell lines, this restored rescue by NA.

In vitro studies indicate that NAMPT inhibitor OT-82 may be a promising treatment for pediatric RMS and warrants further investigation.

Abstract Publications:

- **McKay-Corkum G**, Yeung C, Ji J, Zhang Y, Heske C. Exploiting metabolic vulnerabilities of pediatric rhabdomyosarcoma with novel nicotinamide phosphoribosyltransferase (NAMPT) inhibitor OT-82. Children's Cancer Foundation Research Symposium, Landover, MD; June 5, 2019. [Podium presentation]

Travel to Professional Meetings:

- Children's Cancer Foundation Research Symposium, Landover, MD; June 5, 2019.

Awards:

- Best student poster, NCI Pediatric Oncology Branch Research Roundup Day 2019.



Rogelio Medina

School: David Geffen School of Medicine at University of California, Los Angeles

Mentor: Zhengping Zhuang, M.D., Ph.D., Senior Investigator, Neuro-Oncology Branch

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

Research: Targeting Metastatic and Central Nervous System Tumors via Mannan-BAM, Toll-like Receptor Ligands and Anti-CD40 Antibody

Immunotherapy based on activation of innate immunity has been tested in syngeneic mouse tumor models via intratumoral administration of the following combined components: phagocytosis-stimulating ligands (Mannan-BAM), toll-like receptor (TLR) agonists, and immunostimulant anti-CD40 antibody (collectively abbreviated as MBTA). In this study, syngeneic colon carcinoma (CT26) and glioma (GL261) mouse models were established to assess MBTA's efficacy in generating immune responses against distal metastatic lesions and central nervous system (CNS) tumors. Additionally, we investigated whether therapeutic delivery of MBTA could be optimized using administration routes other than intratumoral delivery. In the colon carcinoma model, intratumoral injection of MBTA significantly reduced

the growth rate of all metastatic CT26 tumor deposits, compared with saline-injected CT26 metastatic lesions in control animals, and induced complete remission (CR) in 33 percent (3/9) of treated animals. In the glioma model, subcutaneous injection of GL261 cells incubated with MBTA resulted in the complete regression of intracranial gliomas in 87.5 percent (7/8) of treated animals vs zero percent of saline-treated control animals. Therapeutic effect of MBTA was abrogated in CD4+ and CD8+ lymphocyte-depleted mice. Tumor infiltrating leukocyte analyses demonstrated significantly increased CD8+ cytotoxic T-lymphocytes (CTL) in metastatic tumors in treated vs control animals, with higher percentages of TNF α - and IFN γ -positive cells. Further assessments with MHC I tetramers revealed significantly increased CT26-associated peptide (AH1)-specific CTLs in the blood of MBTA-treated vs control animals. All animals that achieved complete remission in the colon carcinoma model resisted subsequent peripheral and intracranial challenges with CT26 cells, confirming the induction of immunological memory against CT26 tumors. Collectively, our investigations demonstrate that MBTA can effectively induce a tumor-specific adaptive immune response that can target tumors located in the periphery and within the CNS.

Full Length Publications:

- Xiao Z, Qiu Y, Lin Y, **Medina R**, Zhuang Z, Rosenblum JS, Cui J, Li Z, Zhang X, Guo L. Blocking lncRNA-miR-19a-Id2 axis attenuates hypoxia/ischemia-induced neuronal injury. *Aging*. June 2019; doi:10.18632/aging.101999 [Epub ahead of print]

Abstract Publications:

- **Medina R**, Lehy T, Maggio D, Mehta GU, Antonios J, Chatain GP, Scott G, Benzo S, Hayes C, Zhuang Z, Heiss JD, Chittiboina P. Etiology of peripheral neuropathy in neurofibromatosis 2. American Academy of Neurological Surgeons Annual Scientific Meeting, San Diego, CA; April 13–17, 2019. (Electronic poster)
- **Medina R**, Wang H, Caisová V, Pacak K, Zhuang Z. Development of anti-tumor immune response via peripheral activation of innate and adaptive immune systems. NIH Graduate Student Symposium. Bethesda, MD; Feb. 21, 2019.

Travel to Professional Meetings:

- American Academy of Neurological Surgeons (AANS) Annual Scientific Meeting, San Diego, CA; April 13–17, 2019.

Awards:

- First Place Peripheral Nerve E-Poster Award, AANS Annual Scientific Meeting 2019.
- Top Honors, Neurosurgical Top Gun Competition, AANS Annual Scientific Meeting 2019.



Quynh C. Nguyen

School: University of Mississippi Medical Center School of Dentistry

Mentor: Janice S. Lee, D.D.S., M.D., Clinical Director; Olivier Duverger, Ph.D., Staff Scientist, Craniofacial Anomalies and Regeneration Section

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

Research: Phenotypic and Mechanistic Characterization of Dental Anomalies in Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is a rare connective tissue disorder caused by mutations in the TGF- β signaling pathway (*TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2* and *SMAD3*). It is characterized by aortic aneurysms and craniofacial defects, including poorly-characterized dental defects.

Patients with LDS were enrolled in a study to characterize dental anomalies and assess oral health-related quality of life (OHRQoL). Additionally, a mouse model harboring a G357W allele in *TGFBR2* (*Tgfb2*^{G357W/+} mice) was used to recapitulate the effects of this LDS-causing

mutation on enamel development. Patients with LDS exhibited various degrees of enamel defects (rough, pitted, eroded, chipped) with *TGFBR2* mutations leading to the most severe phenotypes. Other oral manifestations included malocclusion, abnormal hard- and soft-palate, and gingivitis. Patients with LDS had worse OHRQoL compared with unaffected family members or the general population (measured by Oral Health Impact Profile-14 scores, $P < 0.01$). Worse OHRQoL was significantly associated with dental hypersensitivity and temporomandibular joint (TMJ) abnormalities.

Tgfb2^{G357W/+} mice were evaluated for enamel phenotype. Tooth enamel is the strongest tissue in the body with 96 percent mineral composition and is made of enamel rods arranged in an intricate decussation pattern. Enamel rod decussation involves a coordinated movement of ameloblasts during enamel secretion. Micro-computed tomography and scanning electron microscopy revealed that, although enamel rods were fully mineralized in *Tgfb2*^{G357W/+} mice, their decussation pattern was lost. RNA-seq analysis on the enamel organ of WT and *Tgfb2*^{G357W/+} mice revealed altered expression of G-protein coupled receptors known to regulate smooth muscle contraction through the modulation of myosin II activity, suggesting that these receptors may regulate a contractile machinery that drives ameloblast movement.

Our clinical data characterize the dental anomalies experienced by LDS patients, and provide an appreciation of the impact of these anomalies on OHRQoL. Our work also provides new insights into the cellular and molecular mechanisms that lead to enamel defects in LDS. Specific treatment guidelines are necessary to ensure optimal OHRQoL in LDS, with a particular focus on dental hypersensitivity and TMJ abnormalities.

Full Length Publications:

- **Nguyen QC**, Duverger O, Mitnik GL, Jani P, Mishra R, Guerrero P, Lee JS. Oral health-related quality of life in Loeys-Dietz Syndrome, a rare connective tissue disorder: A retrospective cohort study. *Orphanet J Rare Dis*. [Under Review]

Abstract Publications:

- Duverger O, **Nguyen QC**, Jani P, Mishra R, Monkash N, Curry NL, Guerrero P, Lee JS. New insights into enamel rod decussation: Lessons from Loeys-Dietz Syndrome. 13th International Conference on the Chemistry and Biology of Mineralized Tissues. Montreal, Quebec, Canada; Oct. 2019. [Podium presentation]
- Duverger O, **Nguyen QC**, Jani P, Mishra R, Monkash N, Curry NL, Guerrero P, Lee JS. Amelogenesis imperfecta associated with cardiac anomalies: Lessons from Loeys-Dietz-Syndrome. International Association for Dental Research. Vancouver, BC, Canada; Jun. 2019. [Podium presentation]
- **Nguyen QC**, Duverger O, Mishra R, Jani P, Lee JS. Oral health status in a rare disease, Loeys-Dietz Syndrome: An unmet need. 20th Annual National Oral Health Conference. Memphis, TN; Apr. 2019. [Poster presentation]

Travel to Professional Meetings:

- Colgate-Palmolive Clinical Research Innovation Day, Piscataway, NJ; Jun. 2019.
- International Association for Dental Research Annual Meeting, Vancouver, BC, Canada; Jun. 2019.
- 20th Annual National Oral Health Conference, Memphis, TN; Apr. 2019.
- Academy of Osteointegration Annual Meeting, Washington, DC; Mar. 2019.

Awards:

- American Association for Dental Research/Dentsply Sirona Student Competition for Advancing Dental Research: Second Place Award in Basic and Translational Science Research, Vancouver, BC, Canada.
- National Institute of Dental and Craniofacial Research Fellows' Scientific Training: Best Poster Design and Presentation Award, Washington, D.C.



Asmi Panigrahi

School: Rutgers New Jersey Medical School

Mentor: Eliseo Pérez-Stable, M.D., Director, National Institute of Minority Health and Health Disparities; Chief, Minority Health and Health Disparities Population Laboratory, NHLBI

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

Research: Influence of Individual-Level Neighborhood Factors on Health Promoting and Risk Behaviors in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

There is a consistent body of evidence showing that neighborhood context influences a range of health behaviors and outcomes, yet there remains a dearth of research investigating the impact of neighborhood environment on immigrant health, particularly among diverse Hispanic/Latino populations.

We evaluated the relationships between individual-level neighborhood factors and health behaviors in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Sociocultural

Ancillary Study, which includes 5313 foreign-born and US-born adults recruited from San Diego, Chicago, Miami, and New York City, from Mexican, Puerto Rican, Cuban, Central American, Dominican and South American background. All participants underwent a baseline clinical exam and sociocultural survey including measures of perceived neighborhood social cohesion (PNSC) and perceived neighborhood problems (PNP).

Participants had a mean age of 42.5 years (SD 0.38), 55 percent were women, and 73 percent were foreign-born. Mean PNP was greater in US-born vs foreign-born participants ($p < 0.01$). Health promoting behaviors were significantly less prevalent among foreign-born vs US-born participants including physical activity (62% vs 68%), colon cancer screening (51% vs 72%), pap smear (72% vs 81%), mammogram (74% vs 84%), and prostate cancer screening (52% vs 63%). Health risk factors including smoking (31% vs 16%), obesity (37% vs 50%), hypertension (71% vs 60%), and poor diet (37% vs 17%) were significantly more prevalent among U.S.-born vs foreign-born participants. Compared to participants with low PNP, foreign-born participants with moderate PNP were significantly more likely to be current smokers at visit one, and foreign-born participants with moderate and very high PNP were also significantly more likely to be current smokers at visit two ($p < 0.05$ for all comparisons).

Our findings demonstrate that perceived neighborhood problems may uniquely contribute to health behaviors of Latino immigrants versus U.S.-born Latinos, and that neighborhood environment is important for health systems to consider in prevention and treatment strategies that influence Hispanic/Latino health.

Abstract Publications:

- **Panigrahi A**, Rodriguez EJ, Bayly JE, Pérez-Stable EJ. Neighborhood environment as a social determinant of health among Hispanic/Latino immigrants: a longitudinal analysis of the HCHS/SOL Sociocultural Ancillary Study. Society for Behavioral Medicine Annual Meeting, Washington DC; Mar. 6–9, 2019. [Poster presentation]
- **Panigrahi A**, Rodriguez EJ, Bayly JE, Pérez-Stable EJ. Influence of individual-level neighborhood factors on health promoting and risk behaviors in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). American College of Physicians Annual Meeting, Philadelphia, PA; Apr. 11–13, 2019. [Oral presentation]

Travel to Professional Meetings:

- Society for Behavioral Medicine Annual Meeting, Washington DC; Mar. 6–9, 2019.
- American College of Physicians Annual Meeting, Philadelphia, PA; Apr. 11–13, 2019.
- Society for General Internal Medicine Annual Meeting, Washington DC; May 8–10, 2019.

Awards:

- American College of Physicians Annual Meeting, Student Oral Abstract Award, 2019.



Deeti J. Pithadia

School: Medical College of Georgia at Augusta University

Mentor: Thomas Darling, M.D., Ph.D., Chair, Department of Dermatology, Uniformed Services University; Joel Moss, M.D., Ph.D., Head, Translational Research Section and Lymphangioleiomyomatosis Research Program, Pulmonary Branch

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

Research: Molluscum Pendulum Necklace Sign: a Novel Cutaneous Marker of Pulmonary Disease Severity in Tuberous Sclerosis Complex

Acrochordons, or skin tags, are prevalent in the general population and may signify insulin resistance. Multiple acrochordons on the neck, known as the necklace sign, have been observed in tuberous sclerosis complex (TSC), a genetic disorder characterized by tumors in multiple organs, including angiofibromas, ungual fibromas, and fibrous cephalic plaques. Tumorigenesis in TSC involves activation of mechanistic target of rapamycin (mTOR) signaling with concomitant disruption of insulin sensitivity. We sought to determine if the necklace sign is associated with increased phenotypic severity of TSC, reasoning that presence of

acrochordons may indicate heightened susceptibility to mTOR activation. We performed a retrospective chart review of a cohort of 113 adult women with TSC enrolled in a protocol to study pulmonary lymphangioleiomyomatosis (LAM), a female-predominant manifestation of TSC. Twenty-four patients were excluded due to inadequate photos and seven due to presence of asymmetrically distributed facial angiofibromas, a marker for mosaicism and a milder disease phenotype. Of 82 patients analyzed, 20 (24%) showed the necklace sign, defined as two or more acrochordons on the neck. The frequency of LAM was greater in patients with the necklace sign (20/20, 100%) compared to those without (48/62, 77%) ($p=0.017$). LAM symptom onset age was earlier in patients with the necklace sign (30.3 years, $n=19$) than those without (35.6 years, $n=43$) ($p=0.023$). In patients with the necklace sign, pulmonary function measured by percent predicted forced expiratory volume in one second (80.5%, $n=20$) and percent predicted diffusing capacity for carbon monoxide (69.3%, $n=20$) were lower compared to those without the sign (89.7%, $p=0.12$, and 85.6%, $p=0.010$, respectively, $n=48$). Initial pulmonary cyst burden, determined computationally using chest CT scans, was higher in patients with the necklace sign (13%, $n=16$) versus those without (7.2%, $n=43$) ($p=0.044$). These results suggest that the necklace sign may aid in identification of TSC patients at risk for developing more severe LAM earlier in life and that interindividual variability in mTOR signaling may influence TSC-associated tumorigenesis.

Full Length Publications:

- **Pithadia DJ**, Treichel AM, Lee CR, Cowen EW, Linehan WM, Moss J, Darling TN. Birt-Hogg-Dubé syndrome initially diagnosed as tuberous sclerosis complex. *JAAD Case Rep.* 2019;5(4):368-371.
- **Pithadia DJ**, Treichel AM, Jones AM, Julien-Williams P, Machado T, Moss J, Darling TN. Dermatologic adverse events associated with oral mTOR inhibitor therapy in a cohort of individuals with tuberous sclerosis complex. *Br J Dermatol.* [Under review]
- Treichel AM, **Pithadia DJ**, Lee CR, Oyerinde O, Moss J, Darling TN. Histologic analysis of fibrous cephalic plaques in tuberous sclerosis complex. *J Am Acad Dermatol.* [Under review]

Abstract Publications:

- **Pithadia DJ**, Treichel AM, Gopalakrishnan V, Moss J, Darling TN. Necklace sign as a marker of pulmonary disease severity in tuberous sclerosis complex. Society for Investigative Dermatology 77th Annual Meeting, Chicago, IL, May 8–11 2019. [Poster presentation]
- **Pithadia DJ**, Roman J, Biesecker LG, Darling TN. Unilateral patchy hair growth is frequent in children with Proteus syndrome. 2019 Annual Southeastern Pediatric Research Conference, Atlanta, GA, June 10, 2019. [Poster presentation]
- **Pithadia DJ**, Treichel AM, Jones AM, Julien-Williams P, Machado T, Moss J, Darling TN. Dermatologic adverse events in adult patients with tuberous sclerosis complex treated with systemic mTOR inhibitors. 2019 International Tuberous Sclerosis Complex Research Conference, Toronto, ON, CA, June 20–22, 2019. [Poster presentation]
- **Pithadia DJ**, Roman J, Sapp J, Biesecker LG, Darling TN. Dermatologic findings in Proteus syndrome: a retrospective clinical review of 49 genetically-confirmed individuals. 2019 Society for Pediatric Dermatology Annual Meeting, Austin, TX, July 11–13, 2019. [Poster presentation]
- Treichel AM, **Pithadia DJ**, Lee CR, Moss J, Darling TN. Tumor of follicular infundibulum in tuberous sclerosis complex. American Society of Dermatopathology 56th Annual meeting, San Diego, CA, Oct. 17–20, 2019. [Poster presentation]

Travel to Professional Meetings:

- American Academy of Dermatology Annual Meeting, Washington, DC; Mar. 1–5, 2019.
- Society for Pediatric Dermatology 31st Annual Pre-AAD Meeting, Washington, DC; Feb. 28, 2019.
- Society for Investigative Dermatology 77th Annual Meeting, Chicago, IL; May 8–11, 2019.
- 2019 Annual Southeastern Pediatric Research Alliance Conference, Atlanta, GA; June 10, 2019.
- 2019 International Tuberous Sclerosis Alliance Research Conference, Toronto, ON, Canada; June 20–22, 2019.
- Society for Pediatric Dermatology 44th Annual Meeting, Austin, TX; July 11–14, 2019.

Awards:

- Society for Pediatric Dermatology Annual Meeting, Research Travel Award, 2019.



Madeline P. Pyle

School: Medical College of Wisconsin

Mentor: Michael Hoa, M.D., Otolaryngology Surgeon-Scientist, Auditory Development and Restoration Program; Andrew J. Griffith, M.D., Ph.D., NIDCD Scientific Director; Chief, Molecular Biology and Genetics Section

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

Research: Characterizing Transcriptional Differences between Aged and Aged Regenerated Microglia at the Single-cell Level

Tissue-resident macrophages in the retina, known as microglia, maintain immune and functional homeostasis; however, aberrant or prolonged microglial activation is implicated in several age-related retinal diseases. One way to modulate age-related microglial activation is to pharmacologically reset aged microglia by using a CSF1R small-molecule inhibitor drug to eliminate microglia and allow them to repopulate. While repopulated microglia are morphologically and functionally similar to young, homeostatic microglia, complete characterization of repopulated microglia, including how this process occurs in the retina, remains incomplete.

Using single-cell RNA sequencing of FACS-sorted retinal microglia from young, aged, and aged-repopulated (CSF1R inhibitor-treated and repopulated) mouse retinas, we were able to detect novel subpopulations of retinal microglia associated with aging and repopulation.

Unbiased clustering analysis revealed two subpopulations of retinal microglia with low expression of microglia signature genes: one with low *Csf1r* expression, suggesting that these cells are resistant to the effects of CSF1R blockade and become the source of repopulated microglia; and one with upregulated genes known to be expressed in repopulating microglia (*ApoE*, *Cybb*, *Ms4a7*), suggesting these cells are on the trajectory of repopulation but are not yet mature microglia. Cells from all three experimental groups were present in these subpopulations; however, the aged-repopulated microglia were most heavily represented in the low *Csf1r*-expressing subpopulation while both P90 and aged-repopulated cells were equally represented in the subpopulation expressing repopulation genes. Aged microglial cell transcriptomes were homogenous and downregulated expression of microglia signature genes (*Tmem119*, *Olfml3*, *P2ry12*, *Cx3cr1*), while aged-repopulated microglia were rejuvenated in their expression of these microglia-specific genes and were transcriptionally heterogeneous. With the high sensitivity of single-cell RNA sequencing, we were able to characterize novel heterogeneity within retinal microglia and transcriptional changes between young, aged, and aged-repopulated microglia, and hypothesize which cells may be responsible for retinal microglial repopulation.

Abstract Publications:

- Pyle M, Zheng L, Ma W, Martin D, Boger E, Morell R, Wong W, Hoa M. Characterizing transcriptional differences between aged and aged regenerated microglia at the single-cell level: a collaboration with NEI. NIDCD Division of Intramural Research Retreat, Washington, DC; Apr. 26, 2019. [Podium presentation]
- Korrapati S, Pyle M, Taukulis I, Boger E, Martin D, Morrel R, Hoa M. Gene regulatory network mapping and druggable genome target identification using stria vascularis single-cell/single-nucleus transcriptomics. Association for Research in Otolaryngology 42nd Annual MidWinter Meeting, Baltimore, MD; Feb. 9–13, 2019. [Podium presentation]
- Griffiths C, Taukulis I, Pyle M, Korrapati S, Olszewski R, Hoa M. Quantification of DNA and mRNA in single molecule fluorescent *in situ* hybridization (smFISH) image processing. NIH Summer Research Program Poster Day, Bethesda, MD; Aug. 9, 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Otolaryngology 42nd Annual MidWinter Meeting, Baltimore, MD; Feb. 9–13, 2019.

Awards:

- NIDCD Best Graduate Student Trainee Talk (Second place), 2019.



Jeannie G. Radoc

School: David Geffen School of Medicine at University of California, Los Angeles

Mentor: Enrique F. Schisterman, Ph.D., Division of Intramural Population Health Research, Epidemiology Branch

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

Research: Preconception Antidepressant Use and Pregnancy: A Secondary Analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) Trial

In the past two decades, antidepressant use in pregnant women in the U.S. rose from under one percent to seven percent. The purpose of our study was to examine the association between preconception antidepressant use and reproductive hormones, ovulation, fecundability, live birth, and pregnancy loss.

Within the EAGeR trial, women aged 18-40 years old (n=1212) were followed for up to six months while attempting pregnancy. Women were asked to report antidepressant use for 12 months prior to conception and were screened for urinary concentrations of fluoxetine, sertraline, escitalopram, citalopram, and tricyclic antidepressants at enrollment and at each preconception cycle via a biochip competitive chemiluminescent immunoassay. Reproductive hormone concentrations were collected for up to six preconception cycles. Cox proportional hazard regression was used to calculate fecundability odds ratios (FOR), and log-binomial regression to estimate risk ratios (RR) of live birth and pregnancy loss, adjusting for age, body mass index, smoking, alcohol use, and screened or self-reported marijuana and opioid use.

Two hundred thirty five women (19%) either screened positive (n=183) or self-reported antidepressant use (n=113). Women who screened positive/self-reported use had lower fecundability compared to those who did not use antidepressants (screen/self-report: FOR 0.80, 95% CI 0.64, 1.00), and had lower levels of urinary estrone-3-glucuronide ($\beta = -0.16$; 95% -0.28, -0.04), pregnanediol glucuronide ($\beta = -0.17$; 95% -0.31, -0.03), and progesterone ($\beta = -0.20$; 95% -0.30, -0.09) concentrations at enrollment. Antidepressant use was not associated with urinary estradiol, follicle-stimulating hormone, or luteinizing hormone concentrations. No difference was found in intercourse frequency between antidepressant users and non-users ($p = 0.44$). No associations were observed between antidepressant use and ovulation (RR 0.99; 95% CI 0.72, 1.36), live birth (RR 0.91; 95% CI 0.78, 1.05) or pregnancy loss (RR 1.04; 95% CI 0.76, 1.40).

Women who screened positive or self-reported antidepressant use during preconception had reduced fecundability, likely through hormonal pathways influencing implantation as no associations were observed with ovulation, live birth, or pregnancy loss. Further investigations are needed to determine how class, duration and dose of antidepressants impacts fecundability.

Full Length Publications:

- Flannagan KS, Sjaarda LA, Hill MJ, Connell MT, Zolton JR, Perkins NJ, Mumford SL, Plowden TC, Andriessen VC, **Radoc JG**, Schisterman EF. Pilot randomized trial of short-term changes in inflammation and lipid levels during and after aspirin and pravastatin therapy. *Reproductive Health*. [Under review]
- Connell MT, Kim K, White MV, **Radoc JG**, Sjaarda LA, Mumford SL, Plowden TC, Kuhr DL, Omosigbo UR, Holland TL, Pollack AZ, Silver RM, Schisterman EF. Occupational exposures in women and their relationship with time to pregnancy and pregnancy loss in a U.S. cohort. *Paediatr Perinat Epidemiol*. [Under review]
- Plowden TC, Zarek SM, DeVilbiss EA, **Radoc JG**, Kim K, Sjaarda LA, Schisterman EF, Silver RM, Kuhr DL, Omosigbo UR, Yeung EH, Mumford SL. Preconception leptin and fecundability, pregnancy, and live birth among women with a history of pregnancy loss. *J Clin Endocrinol Metab*. [Under review]
- Levine LD, Kim K, Purdue-Smithe A, Sundaram R, Schisterman EF, Connell MT, DeVilbiss EA, Alkhalaf Z, **Radoc JG**, Buck Louis GM, Mumford SL. Urinary phytoestrogens and menstrual cycle length and variability among healthy, eumenorrheic women. *J Clin Endocrinol Metab*. [Under review]
- Purdue-Smithe AC, Kim K, Nobles C, Schisterman EF, Schliep KC, Perkins NJ, Sjaarda LA, Freeman JR, Robinson SL, **Radoc JG**, Mills JL, Silver RM, Ye A, Mumford SL. The role of maternal preconception vitamin D status in human sex ratio aberration. [Under review]
- Flannagan K, Radoc JG, Mumford SL, Zolton J, Enrique F Schisterman EF. Preconception opioid use and pregnancy outcomes. [Under review]

- Mumford SL, Flannagan K, **Radoc JG**, Plowden TC, Kim K, Purdue-Smithe A, Zolton J, Lindsey Sjaarda, Perkins N, Freeman JF, Alkhalaf Z, Andriessen V, Silver RM, Enrique F Schisterman EF. Preconception marijuana use and pregnancy outcomes. [Under review]
- Sjaarda LA, Flannagan K, **Radoc JG**, Mumford SL, Perkins NJ, Silver RM, Schisterman EF. Antidepressant medication exposure and time to pregnancy and risk of pregnancy loss. [Under review]
- Eubanks AA, Nobles CJ, Mumford SL, Kim K, Hill MJ, DeCherney AH, Sjaarda LA, **Radoc JG**, Perkins NJ, Silver RM, Schisterman EF. The safety of low dose aspirin on the mode of delivery: secondary analysis of the Effect of Aspirin in Gestation and Reproduction (EAGeR) trial. [Under review]
- Robinson SL, Mumford SL, Guan W, Trinh MH, Flannagan K, Kim K, **Radoc JG**, Zeng X, Schisterman EF, Yeung EH. Maternal fatty acid concentrations and newborn DNA methylation. [Under review]
- Theilen LH, Campbell HD, Mumford SL, Purdue-Smithe AC, Sjaarda LA, Perkins NJ, **Radoc JG**, Silver RM, Schisterman EF. Platelet activation and placenta-mediated adverse pregnancy outcomes. [Under review]

Abstract Publications:

- Flannagan K, **Radoc JG**, Mumford SL, Zolton J, Enrique F Schisterman EF. Preconception opioid use and pregnancy outcomes. 32nd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Minneapolis, MN, June, 2019. [Poster presentation]

Continued on the Next Page

- Mumford SL, Flannagan K, **Radoc JG**, Plowden TC, Kim K, Purdue-Smithe A, Zolton J, Lindsey Sjaarda, Perkins N, Freeman JF, Alkhalaf Z, Andriessen V, Silver RM, Enrique F Schisterman EF. Preconception marijuana use and pregnancy outcomes. 32nd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Minneapolis, MN, June, 2019. [Podium presentation]
- Kim K, Nobles CJ, Purdue-Smithe A, Wactawski-Wende J, Pollack AZ, Freeman J, Alkhalaf Z, Andriessen V, **Radoc JG**, Mumford SL. Interaction between toxic metals, foods, and reproductive hormones among healthy premenopausal women. 32nd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Minneapolis, MN, June, 2019. [Poster presentation]
- Purdue-Smithe AC, Kim K, Nobles CJ, Schisterman EF, Schliep KC, Perkins NJ, Sjaarda LA, Freeman JR, Robinson SL, **Radoc JG**, Mills JL, Silver RM, Ye A, Mumford SL. Preconception vitamin D status and offspring sex ratio among women with history of pregnancy loss. 32nd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Minneapolis, MN, June, 2019. [Poster presentation]
- Purdue-Smithe AC, Kim K, Schisterman EF, Schliep KC, Perkins NJ, Sjaarda LA, Mills J, Silver RM, Andriessen V, Alkhalaf Z, **Radoc JG**, and Mumford SL. Caffeinated beverage intake and serum caffeine metabolites and risk of pregnancy loss. 52nd Annual Meeting of the Society for Epidemiologic Research, Minneapolis, MN, June, 2019. [Podium presentation]
- Alkhalaf Z, Kim K, Purdue-Smithe A, **Radoc JG**, Freeman JR, Yisahak SF, Kuhr D, Pollack A, Silver RM, Sjaarda LA, Perkins NJ, Schisterman EF, Mumford SL. Vitamin D and premenstrual syndrome and symptoms in healthy women with regular cycles. Annual Meeting of the Society for Nutrition, Baltimore, MD, June, 2019. [Poster presentation]
- Robinson SL, Mumford SL, Guan W, Trinh MH, Flannagan K, Kim K, **Radoc JG**, Zeng X, Schisterman EF, Yeung EH. Maternal fatty acid concentrations and newborn DNA methylation. Pediatric Academic Societies Meeting, Baltimore, MD, Apr. 2019. [Poster presentation]

Travel to Professional Meetings:

- Society for Reproductive Investigation. 66th Annual Meeting, Paris, France; Mar. 12–16, 2018.



Jonathan J. Sackett

School: Loma Linda University School of Medicine

Mentor: Peter L. Choyke, M.D., Director, Molecular Imaging Branch; Baris Turkbey, M.D., Associate Research Physician, Molecular Imaging Branch

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

Research: Quality Control in Multi-Parametric MRI of the Prostate: Analysis of Current Guidelines and Development of Automated Quality Control Methods

Multi-parametric prostate MRI has become a vital component in screening, assessing, and treating prostate cancer. The Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) established a set of minimum technical standards to improve image quality and reduce variability in acquisition. A multi-institutional multi-reader study was designed to determine whether adherence to PI-RADSv2 Minimum Technical Standards improves perceived image quality.

The study was a blinded study of adherent and non-adherent scans (n=62) from 62 different centers and utilized 6 different trained readers to score imaging as adequate or inadequate and rank images on a one-to-five scale for different quality metrics. The study results demonstrated that following the guidelines did not increase the chances of having a qualitatively adequate image. Following the guidelines, however, did have a weak (tau-b correlation = 0.22), but significant effect on subjective image quality in T2 imaging (p-value=0.01). No similar effect was found for diffusion weighted imaging (DWI). The study also demonstrated wide variability in quality with only 56 percent of acquired prostate MRIs adequate in both T2 and DW imaging.

Since current state of prostate MRI image quality is highly variable and the guidelines failed to achieve adequate quality control, two new methods of quality control are being developed. The first method utilizes radiomic features calculated from gray level co-occurrence matrices, k-space spectral analysis, and prostate morphology supplied to a support vector machine learning algorithm to create automated predictions of image quality. The second method bypasses measurement and directly improves image quality by using a deep learning technique to remove image artifacts and create super resolution images. Both methods are undergoing validation. While prostate MRI suffers from image quality variability, new technologies offer ways to improve quality and increase access to high quality prostate cancer care.

Full Length Publications:

- **Sackett J**, Choyke PL, Turkbey B. Prostate imaging reporting and data system version 2 for MRI of prostate cancer: Can we do better? *Am J Roentgenol*. 2019 Mar; 212(6):1244–1252.

Abstract Publications:

- **Sackett J**, Harmon S, Barrett T, Coskun M, Madariaga M, Marko J, Law YM, Turkbey E, Mehralivand S, Sanford T, Lay N, Brender J, Wood B, Choyke PL, Turkbey B. Does compliance equal quality? A multi-reader analysis of PI-RADSv2 technical requirements. Society of Abdominal Radiology Annual Meeting Orlando, FL; Mar. 17–22, 2019. [Poster Presentation]

Travel to Professional Meetings:

- Society of Abdominal Radiology, Orlando, FL; Mar. 17–22, 2019



Gurpreet K. Seehra

School: University of Missouri - Kansas City School of Medicine

Mentor: Ellen Sidransky, M.D., Chief, Section on Molecular Neurogenetics, Medical Genetics Branch

Institute: National Human Genome Research Institute (NHGRI)

Research: Five-parameter Evaluation of Dysphagia: a Novel Prognostic Scale for Assessing Neurological Decline in Gaucher Disease Type 2

Gaucher disease type 2 (GD2) is defined by acute neurological decline, failure to thrive, and early demise. Currently, there is no clear standard for evaluating, staging, and counseling regarding neurological decline in GD2. Due to the high prevalence of progressive dysphagia secondary to acute neurological involvement, we aimed to identify key components of swallow function which could serve as markers of disease progression in GD2.

A post-hoc analysis of modified barium swallow studies was performed. Six parameters of swallowing were scored in a retrospective chart review of eleven infants with GD2. Mixed effects regression, principal component analysis (PCA), and a transition analysis were used to evaluate swallow function and model disease progression.

All patients exhibited impaired swallow function. There was no association between any of the swallow parameters and age, indicating non-linear disease progression. PCA and transition analysis identified five parameters (American Speech-Language-Hearing Association National Outcome Measurement System swallowing level scale, aspiration/laryngeal penetration, oral phase dysphagia, head extension, and dyssynchronization of suck, swallow, and breathing) capturing multiple dimensions of swallowing which defined two distinct disease states. Transition analysis revealed transition points indicating higher probabilities of swallow dysfunction in state two, thus marking state two as a more severe disease state. Transition probabilities revealed a 100 percent probability of transition to state two from state one, with a zero percent probability of returning to state one. The directionality, of both the severity of scores and the transition probabilities between the two states, implies that all individuals will progress to state two and will not return to state one.

This five-parameter scoring system was sufficient to identify a clear delineation of stages of disease progression and model prospective outcomes. Establishing disease progression is important when counseling families and healthcare providers on treatment options. This multi-dimensional evaluation could also be a useful efficacy parameter for future therapeutic trials in GD2 and other neurodegenerative disorders of infancy.

Full Length Publications:

- Eghbali A, Hassan S, **Seehra G**, Fitzgibbon E, Sidransky E. Ophthalmological findings in Gaucher disease. *Mol Genet Metab*. 2019 May; 127(1):23-27.
- Ryan E, **Seehra G**, Sharma P, Sidransky E. GBA1-associated parkinsonism: new insights and therapeutic opportunities. *Current Opinion in Neurology*. 2019 Jun 10. doi: 10.1097/WCO.0000000000000715 [Epub ahead of print]
- **Seehra G**, Solomon B, Ryan E, Steward A, Roshan Lal T, Tanimia Y, Lopez G, Sidransky E. Five-parameter evaluation of dysphagia: a novel prognostic scale for assessing neurological decline in Gaucher disease type 2. *Mol Genet Metab*. [In press]
- **Seehra G***, Eghbali A*, Sidransky E, Fitzgibbon E. White vitreous opacities in five patients with Gaucher disease type 3. *Mol Genet Metab*. [Under review].

*Equal contribution

Abstract Publications:

- **Seehra G**, Solomon B, Ryan E, Steward A, Roshan Lal T, Tanimia Y, Lopez G, Sidransky E. Five-parameter evaluation of dysphagia: a novel prognostic scale for assessing neurological decline in Gaucher disease type 2. WORLD Symposium - Lysosomal Disease Research and Conference, Orlando, FL; Feb. 4-8, 2019. [Poster presentation].

Travel to Professional Meetings:

- WORLD Symposium, Lysosomal Disease Research and Conference, Orlando, FL; Feb. 4-8, 2019.

Awards:

- Scientific Poster Award, National Human Genome Research Institute Research Symposium, 2019.



Tiahna A.L. Spencer

School: University of Connecticut School of Medicine

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

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

Research: Dissecting the Pathogenetic Mechanism of Pain in Fibrous Dysplasia

Fibrous dysplasia (FD) is a disease caused by somatic activating GNAS mutations, resulting in replacement of normal bone with fibrous tissue, leading to fractures and disability. Pain in FD is common; however, its mechanisms are poorly understood. Studies have shown that FD pain relief is variable with treatment and does not correlate with disease burden.

Pain is conceptualized into two categories: nociceptive pain (tissue-damaging stimuli) and neuropathic pain (dysfunction of the somatosensory nervous system). Distinguishing pain types is important to inform treatments. We sought to characterize the types of pain and their outcomes in patients with FD, with a view toward developing effective treatment strategies and improving quality of life.

In this retrospective cross-sectional study, data were analyzed from two patient registries: the FD Foundation (FDF) (US) and the Rare and Undiagnosed Diseases (RUDY) study (UK). Subjects completed questionnaires to distinguish neuropathic from nociceptive pain (painDETECT), health-related quality of life (SF-36), sleep quality (Pittsburg Sleep Quality Index) and mental health (Hospital Anxiety and Depression Scale). Analyses by one-way ANOVA, Kruskal-Wallis multiple comparison tests, and Chi-squared tests were completed using Graphpad Prism.

Two hundred forty one subjects were analyzed: 173 FDF registry participants (mean age 40y, range 18-77, 85% women) and 68 RUDY participants (mean age 47y, range 18-77, 75% women). Distribution of pain types for nociceptive pain (45.2%), neuropathic pain (31.5%), and unclear pain (23.2%) varied by severity of pain. Compared to subjects with nociceptive pain, those with neuropathic pain scored significantly worse in all quality of life scales ($p < 0.05$), reported increased anxiety and depression ($p < 0.01$), had higher percentages of severe anxiety and depression ($p < 0.01$), and poorer sleep quality ($p < 0.01$).

These findings demonstrate that FD pain includes both nociceptive and neuropathic elements. Those with neuropathic pain reported diminished quality of life and mental health. Evaluation of patients with FD should include assessment of neuropathic pain to practice effective management strategies.

Full Length Publications:

- Boden BP, Fine KM, **Spencer TA**, Breit I, Anderson SA. Non-traumatic exertional fatalities in football: excess in conditioning kills, Part II. *Am J Sports Med*. [In review]

Abstract Publications:

- **Spencer TA**, Soni A, Pinedo-Villanueva R, Boyce AM, Javaid MK. Characterization of pain in patients with fibrous dysplasia. International Consortium for Children's Bone Health, Salzburg, Austria; June 22–25, 2019. [e-Poster presentation]

Travel to Professional Meetings:

- American Society for Bone and Mineral Research, Montreal, Canada; Sep. 26–Oct. 1, 2018.
- Orthopaedic Research Society Annual Meeting, Austin, Texas; Feb. 2–5, 2019
- Student National Medical Association Annual Medical Education Conference, Philadelphia, PA; Apr. 18–21, 2019.
- International Consortium for Children's Bone Health, Salzburg, Austria; June 22–25, 2019.



Sydney R. Stein

School: University of Missouri College of Veterinary Medicine

Mentor: Daniel S. Chertow, M.D., M.P.H., Head, Emerging Pathogens Section, Critical Care Medicine Department

Institute: NIH Clinical Center (CC)

Research: *In utero* Zika Virus Exposure and Postnatal Protection Against Zika Re-Challenge in a Rhesus Macaque Model.

An estimated one in seven infants born to pregnant women infected with Zika virus (ZIKV) develop Congenital Zika Syndrome (CZS), a spectrum of birth defects that can include severe brain abnormalities. To date, nonhuman primate (NHP) studies of CZS have focused solely on gestation. We report the first longitudinal study of NHPs exposed to ZIKV in utero during the postnatal period with subsequent infection after a year of age.

We infected pregnant rhesus macaques with 1×10^6 PFU of ZIKV during early ($n=3$) or late ($n=3$) gestation. Infected dams developed viremia by three days post-infection and produced ZIKV-specific neutralizing antibodies. We detected ZIKV RNA in amniotic fluid of half the fetuses. One early and one late maternal-fetal pair were sacrificed at term. Histologic examination did not reveal pathology; however, ZIKV RNA was detected in brain tissue of the late infected fetus. We used ultrasonography and MRI to assess growth and neurodevelopment of animals during gestation and through six months of age in the surviving infants. We observed no developmental abnormalities for >12 months postpartum.

At 13-15 months postpartum, we infected previously exposed infants ($n=4$) with the same dose of ZIKV alongside a group of age-matched naïve control animals ($n=3$). Similar levels of ZIKV RNA and ZIKV-specific neutralizing antibodies were detected in the serum of both groups. We detected ZIKV RNA three days post-infection in CSF from two previously exposed infants and a control infant. The concentration and distribution of ZIKV RNA in tissues did not differ between the groups at necropsy two weeks after re-challenge. On histologic examination, we observed inflammation in the spinal cord of animals previously exposed to ZIKV in utero, but not in control animals.

Despite literature supporting fetal pathogen-specific immune cell development during gestation, our data indicate that previously-exposed NHP fetuses had insufficient immunological memory to protect against postnatal ZIKV infection. This observation has clinical and epidemiologically relevance to understanding infant susceptibility to ZIKV infection.

Abstract Publications:

- **Stein S**, Vannella K, Connelly M, Amaro-Carambot E, Whitehead S, Winkler C, Peterson K, Babyak A, Hammound D, Kindrachuk J, Swerczek J, Herbert R, Chertow DS. Rhesus macaque infants exposed to Zika virus in utero display no neurologic abnormalities through one year postpartum. American Society for Virology Annual Meeting, Minneapolis, MN; July 20–24, 2019. [Podium presentation]

Travel to Professional Meetings:

- 68th Annual Epidemic Intelligence Service Conference, Atlanta, GA; Apr. 29–May 2, 2019.
- 38th Annual American Society for Virology Meeting, Minneapolis, MN; July 20–24, 2019.



Nick F. Thoreson

School: Boston University School of Medicine

Mentor: Bradford Wood, M.D., Senior Investigator, Center for Interventional Oncology

Institute: NIH Clinical Center (CC)

Research: Long-Term Outcomes in Patients with Hereditary Renal Cell Carcinoma treated with Radiofrequency Ablation

Patients with hereditary renal cell carcinoma (RCC) are difficult to treat due to recurrent bilateral, multifocal tumors developing over time, requiring a balance between prevention of metastatic disease and preservation of renal function. Radiofrequency ablation (RFA) may be an effective means of treating hereditary RCC for tumors less than four cm in diameter while still preserving renal function, as RFA involves a smaller area of tissue damage compared to surgical procedures. This study sought to determine the long-term clinical impact of treating patients with hereditary RCC with RFA.

Forty six patients were enrolled in the study from 1999 to 2004, during which a total of 86 lesions were treated with RFA. Follow-up exam, history, imaging, serum and urine assessments were performed preoperatively, at two-months, six-months, one-year, and annually thereafter. We quantitated the number of subsequent interventions on the ipsilateral kidney over the course of each patient's lifetime, following the first ablation performed during the study period. All-cause lifetime mortality rates, RCC-specific mortality rates, and lifetime RCC metastasis rates (defined as any new extra-renal RCC lesion) were also calculated.

There was a local success rate of 97 percent. Long-term outcomes revealed an all-cause mortality rate of 14.9 percent, an RCC-specific mortality of 6.4 percent, and an RCC metastatic rate of 8.5 percent over a mean follow-up period of 91 ± 51 (SD) months per patient. The median number of subsequent ipsilateral interventions was one per patient (range 0-7), for a total of 66 interventions in the entire patient population. There was a 10 percent mean decline in eGFR during the follow-up period, consistent with prior studies of patients with von Hippel Lindau syndrome undergoing RFA, which showed a 7.6-12.8 percent mean reduction in eGFR. RFA is a safe, feasible treatment for patients with hereditary RCC syndromes and should be considered in all patients with tumors <4 cm in diameter, due to minimal effects on renal function and low rates of metastasis and RCC-specific mortality.



Durin Y. Uddin

School: University of Nevada, Reno School of Medicine

Mentor: Catherine A. Cukras, M.D., Ph.D., Lasker clinical Research Scholar; Director, Medical Retina Fellowship Program; Head, Unit on Clinical Investigation of Retinal Disease; Brett G. Jeffrey, Ph.D., Head, Human Visual Function Core, Ophthalmic Genetics and Visual Function Branch

Institute: National Eye Institute (NEI)

Research: Comparative Assessment of Dark Adaptation in Age-related Macular Degeneration and Reproducibility of Results using the Medmont DAC Perimeter versus the AdaptDx Dark Adaptometer

Functional studies of dark adaptation (DA) in age-related macular degeneration (AMD) using the Medmont Dark-Adapted Chromatic Perimeter (DACP) and the AdaptDx dark adaptometer have demonstrated impairments in rod-mediated kinetics. We investigated the repeatability of static scotopic thresholds, rod intercept time (RIT) measures, and other DA curve-derived parameters for the Medmont DACP. We also compared the RITs obtained at two retinal loci on the AdaptDx with RITs obtained using the Medmont DACP.

Forty-five participants >50 years of age with a range of AMD severity underwent dark adaptation testing on two instruments, the Medmont DACP and AdaptDx, less than 16 days apart. The Medmont DACP was used to measure DA kinetics at eight loci (4°, 6°, 8°, 12° superior and inferior) along the vertical meridian after a 30 percent rhodopsin photobleach. DA was measured using the AdaptDx protocol at 5° superior to the fovea. Rod intercept time (RIT), defined as the time to detect a 3.1 log cd/m² green stimulus (500/505 nm), was obtained on both instruments. Bland-Altman plots were used to compare RITs measured at 4° and 6° superior on the Medmont DACP to RITs measured at 5° on the AdaptDx. Twelve patients underwent repeat testing on the Medmont DACP within 50 days of each other.

Longer RITs were observed on the AdaptDx 5° than either the Medmont 4° (mean difference \pm SD = -2.4 ± 4.1 min) or 6° (-3.5 ± 4.2 min). Repeatability coefficients (RC) for static red and green thresholds were 5.9 dB and 7.2 dB, respectively. Curve-derived cone threshold RC was 3.9 dB and final threshold RC was 5.3 dB. Medmont RIT and RIT slope RCs were 7.6 minutes and 0.535 min/deg, respectively.

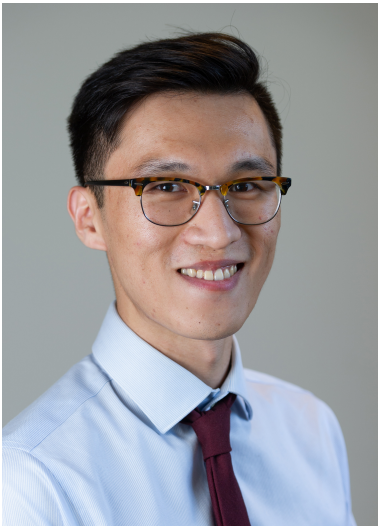
The mean differences in RIT between the instruments indicate a systematic bias which could be attributed to different methodologies, such as bleach delivery and/or different curve fitting methods.

Abstract Publications:

- **Uddin D**, Jeffrey B, Wong, W, Wiley H, Keenan T, Flynn O, Chew E, Cukras C. Repeatability and comparison of dark adaptation using the Medmont DAC Perimeter and AdaptDx Dark Adaptometer. Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, Canada; Apr. 27–May 2. [Poster presentation]
- **Uddin D**, Jeffrey B, Wong, W, Wiley H, Keenan T, Flynn O, Chew E, Cukras C. Repeatability and comparison of dark adaptation in AMD using the Medmont DAC Perimeter and AdaptDx Dark Adaptometer. 60th Annual National Student Research Forum, Galveston, TX; Apr. 18–19, 2019. [Podium presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, Canada; Apr. 27–May 2, 2019.
- 60th Annual National Student Research Forum, Galveston, TX; Apr. 18–19, 2019.



Wen Da Ye

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Mentor: Nicole Schmitt, M.D., Principal Investigator, Otolaryngology Surgeon-Scientist, Integrative Therapeutics Program; Carter Van Waes, M.D., Ph.D., Clinical Director, NIDCD; Chief, Tumor Biology Section, Head and Neck Surgery Branch
Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)
Research: Antagonist of cIAP1/2 and XIAP Promotes Immunogenic Cell Death and Increases Antigen Processing Machinery in Preclinical Models of Head and Neck Cancer

Inhibitor of apoptosis protein (IAP) antagonists have shown immune stimulatory activity in pre-clinical models of head and neck squamous cell cancer (HNSCC) and other cancer types. However, tumor-cell intrinsic mechanisms for this immune upregulation have been largely unexplored. In this study, we show that ASTX660, a dual antagonist of cIAP1/2 and XIAP, when combined with TNF α , induces expression of immunogenic cell death (ICD) markers calreticulin, heat shock protein 70, and high mobility group box one in sensitive human HNSCC cell lines *in vitro*. In *in vivo* vaccination experiments, mice were inoculated in the left flank with murine

oral cancer 1 (MOC1) cells treated with XRT, mitoxantrone (MTX), ASTX660 + TNF α , or the combination of XRT + ASTX660 + TNF α . One week later, mice were re-challenged in the right flank with live MOC1 cells and monitored for subsequent tumor formation/growth. Known ICD inducers XRT and MTX resulted in tumor rejection rates (right flank) of 50 percent and 60 percent, respectively. Cells treated with ASTX660 + TNF α demonstrated vaccination site tumor growth on the left, and 40 percent rejection when re-challenged with viable cells on the right. Combination vaccination group XRT + ASTX660 + TNF α showed 73 percent tumor rejection with no vaccination site growth. Similar results were obtained with the MEER (HPV-positive) mouse tumor model. ASTX660 also enhanced killing of multiple murine cell lines by cytotoxic tumor-infiltrating lymphocytes, and when combined with XRT, stimulated clonal expansion of antigen-specific T lymphocytes and expression of MHC class I on the surface of tumor cells. Flow cytometry experiments in several human HNSCC cell lines showed that HLA-A,B,C was reliably upregulated in response to ASTX660 + TNF α , while increases in other antigen processing machinery components were variable. These findings suggest that ASTX660 may enhance anti-tumor immunity both by promoting ICD in sensitive tumor cells and by enhancing antigen processing/presentation.

Full Length Publications:

- **Ye W**, Schmitt N. Pembrolizumab for recurrent/metastatic head and neck cancer: equally promising for Asian patients? *Ann Transl Med*. 2019 Mar 7. doi: 10.21037/atm.2019.01.46. [Epub ahead of print]
- Park S, **Ye W**, Xiao R, Silvin C, Padgett M, Hodge J, Van Waes C, Schmitt N. Cisplatin and oxaliplatin induce similar immunogenic changes in preclinical models of head and neck cancer. *Oral Oncol*. [In press]
- Xiao R, An Y, **Ye W**, Derakhshan A, Cheng H, Yang X, Allen C, Chen Z, Schmitt N, Van Waes C. Dual antagonist of cIAP/XIAP ASTX660 sensitizes HPV(-) and HPV(+) head and neck cancers to TNF α , TRAIL, and radiation therapy. *Clin Cancer Res*. [In press]
- **Ye W**, Schmitt N, Ferris R, Allen C. Improving the therapeutic ratio in head and neck cancer. R. Kimple (Ed.), Improving responses to immunotherapy in head and neck squamous cell carcinoma. Philadelphia: Elsevier; 2019. [In press]

Abstract Publications:

- **Ye W**, Allen C, Hong Y, Gunti S, Van Waes C, Schmitt N. Antagonist of cIAP1/2 and XIAP induces immunogenic cell death and alters antigen processing machinery in preclinical head and neck cancer models. American Association for Cancer Research: American Head and Neck Society Head and Neck Cancer Conference, Austin, TX; Apr. 29–30, 2019. [Poster presentation]

Travel to Professional Meetings:

- American Association for Cancer Research: American Head and Neck Society Head and Neck Cancer Conference, Austin, TX; Apr. 29–30, 2019.

Index of Scholars by NIH Institutes and Centers

Clinical Center (CC)

Cameron N. Fick

Georgetown University School of Medicine
Frances T. Sheehan-Gavelli, Ph.D., Senior Investigator; Functional and Applied Biomechanics Section, Rehabilitation Medicine Department

Jenny J. Kim

Stony Brook University School of Medicine
Andrew J. Mannes M.D., Chief, Department of Perioperative Medicine
Michael J. Iadarola, Ph.D., Senior Scientist, Department of Perioperative Medicine

Mengyun Lu

University of North Carolina School of Medicine
Michael Solomon, M.D., Head, Cardiology Section, Critical Care Medicine Department, NIH Clinical Center
Jason Elinoff, M.D., Head, Pulmonary Vascular Biology Section, Critical Care Medicine Department, NIH Clinical Center

Sydney R. Stein

University of Missouri College of Veterinary Medicine
Daniel S. Chertow, M.D., M.P.H., Head, Emerging Pathogens Section, Critical Care Medicine Department

Nick F. Thoreson

Boston University School of Medicine
Bradford Wood, M.D., Senior Investigator, Center for Interventional Oncology

National Cancer Institute (NCI)

Nicole H. Dalal

Duke University School of Medicine
Lindsay M. Morton, Ph.D., Senior Investigator, Radiation Epidemiology Branch

Timothy R. Donahoe

Weill Medical College of Cornell University
Amy Berrington de Gonzalez, Ph.D., Chief, Radiation Epidemiology Branch

Erika J. Lampert

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Jung-Min Lee, M.D., Lasker Clinical Research Scholar, Women's Malignancies Branch

Diane M. Libert

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Jack Shern, M.D., and Nirali Shah, M.D.; Pediatric Oncology Branch

Katherine E. Masih

University of Miami Leonard M. Miller School of Medicine
Javed Khan, M.D., Deputy Chief, Genetics Branch; Head, Oncogenomics Section

Grace B. McKay-Corkum

University of Massachusetts Medical School
Christine Heske, M.D., Head, Translational Sarcoma Biology Group, Pediatric Oncology Branch

Rogelio Medina

David Geffen School of Medicine at University of California, Los Angeles
Zhengping Zhuang, M.D., Ph.D., Senior Investigator, Neuro-Oncology Branch

Jonathan J. Sackett

Loma Linda University School of Medicine
Peter L. Choyke, M.D., Director, Molecular Imaging Branch; Baris Turkbey, M.D., Associate Research Physician, Molecular Imaging Branch

National Eye Institute (NEI)

Trent TsunKang Chiang

Case Western Reserve University School of Medicine
Wai T. Wong, M.D., Ph.D., Chief, Section on Neuron-Glia Interaction in Retinal Diseases, Laboratory of Retinal Cell and Molecular Biology

Natasha Kesav

Northeast Ohio Medical University
H. Nida Sen, M.D., Lasker Clinical Research Scholar, Head, Unit on Clinical Translational Immunology, Laboratory of Immunology

Debora H. Lee

University of California, Irvine School of Medicine
Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications
Tiarnan D. Keenan, B.M. B.Ch., Ph.D., Staff Clinician, Division of Epidemiology and Clinical Applications

Durin Y. Uddin

University of Nevada, Reno School of Medicine
Catherine A. Cukras, M.D., Ph.D., Lasker clinical Research Scholar; Director, Medical Retina Fellowship Program; Head, Unit on Clinical Investigation of Retinal Disease
Brett G. Jeffrey, Ph.D., Head, Human Visual Function Core, Ophthalmic Genetics and Visual Function Branch

National Human Genome Research Institute (NHGRI)

Gurpreet K. Seehra

University of Missouri - Kansas City School of Medicine
Ellen Sidransky, M.D., Chief, Section on Molecular Neurogenetics, Medical Genetics Branch

National Heart, Lung, and Blood Institute (NHLBI)

Tyler M. Bauer

Sidney Kimmel Medical College at Thomas Jefferson University
Elizabeth Murphy, Ph.D., Senior Investigator, Laboratory of Cardiac Physiology

Harry Choi

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Nehal N. Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases

Leah M. Gober

Mercer University School of Medicine
Beth A. Kozel, M.D., Ph.D. Lasker Clinical Research Scholar, Laboratory of Vascular and Matrix Genetics, Translational Vascular Medicine

Nikhil Gupta

Cleveland Clinic Lerner College of Medicine of the Case Western Reserve University
Haiming Cao, Ph.D., Stadtman Investigator, Laboratory of Obesity and Metabolic Diseases

Steven D. Langerman

George Washington University School of Medicine & Health Sciences
Tiffany M. Powell-Wiley, M.D., M.P.H., Chief, Social Determinants of Obesity and Cardiovascular Risk Laboratory

Asmi Panigrahi

Rutgers New Jersey Medical School
Eliseo Pérez-Stable, M.D., Director, National Institute of Minority Health and Health Disparities; Chief, Minority Health and Health Disparities Population Laboratory, NHLBI

Deeti J. Pithadia

Medical College of Georgia at Augusta University
Thomas Darling, M.D., Ph.D., Chair, Department of Dermatology, Uniformed Services University; Joel Moss, M.D., Ph.D., Head, Translational Research Section and Lymphangioleiomyomatosis Research Program, Pulmonary Branch

National Institute of Allergy and Infectious Diseases (NIAID)**Gloria H. Hong**

Johns Hopkins University School of Medicine
Steven M. Holland, M.D., Director, Division of Intramural Research

Anthony J. Lee

University of Miami Miller School of Medicine
Clifton Barry, Ph.D., Chief, Tuberculosis Research Section

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)**Jeannie G. Radoc**

David Geffen School of Medicine at University of California, Los Angeles
Enrique F. Schisterman, Ph.D., Division of Intramural Population Health Research, Epidemiology Branch

National Institute on Deafness and Other Communication Disorders (NIDCD)**Sarah E. Greene**

Duke University School of Medicine
Clint T. Allen, M.D., Principal Investigator, Translational Tumor Immunology Program; Carter Van Waes, M.D., Ph.D., Chief, Tumor Biology Section, Head and Neck Surgery Branch

Madeline P. Pyle

Medical College of Wisconsin
Michael Hoa, M.D., Otolaryngology Surgeon-Scientist, Auditory Development and Restoration Program
Andrew J. Griffith, M.D., Ph.D., NIDCD Scientific Director; Chief, Molecular Biology and Genetics Section

Wen Da Ye

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Nicole Schmitt, M.D., Principal Investigator, Otolaryngology Surgeon-Scientist, Integrative Therapeutics Program
Carter Van Waes, M.D., Ph.D., Clinical Director, NIDCD; Chief, Tumor Biology Section, Head and Neck Surgery Branch

National Institute of Dental and Craniofacial Research (NIDCR)**David A. Cruz Walma**

University of Alabama at Birmingham School of Dentistry
Kenneth Yamada, M.D., Ph.D., NIH Distinguished Investigator

Quynh C. Nguyen

University of Mississippi Medical Center School of Dentistry
Janice S. Lee, D.D.S., M.D., Clinical Director
Olivier Duverger, Ph.D., Staff Scientist, Craniofacial Anomalies and Regeneration Section

Tiahna A.L. Spencer

University of Connecticut School of Medicine
Michael T. Collins, M.D., Chief, Skeletal Disorders and Mineral Homeostasis Section

National Institute of Mental Health (NIMH)**Katharina R. Clore-Gronenborn**

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Kathleen R. Merikangas, Ph.D., Chief, Genetic Epidemiology Research Branch

Rebecca Hu

University of California, San Diego School of Medicine
Ellen Leibenluft, M.D., Chief, Section on Mood Dysregulation and Neuroscience, Emotion and Development Branch
Daniel S. Pine, M.D., Chief, Section on Development and Affective Neuroscience, Emotion and Development Branch

National Institute of Neurological Disorders and Stroke (NINDS)**Saadia Hasan**

Medical College of Georgia at Augusta University
Michael Ward, M.D., Ph.D., Investigator, Inherited Neurodegenerative Diseases Unit, Neurogenetics Branch



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