FNIH
Foundation for the
National Institutes of Health

The National Institutes of Health's Medical Research Scholars Program

2017-2018 Scholars & Abstracts

Table of Contents

Table of Contents 1

About the MRSP 2

Research Achievements 3-5

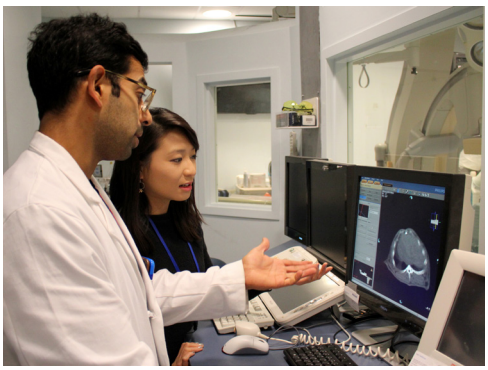
Scholar Profiles

- Mairead R. Baker 6
- Fatima Barragan 7
- Jennifer E. Bayly 8
- Jacqueline N. Boyle 9
- Rebecca O. Breese 10
- Sonny Caplash 11
- Katherine G. Chen 12
- Sophie E. Claudel 13
- Shavonne M. Collins 14
- Shazia Dharssi 15
- Joshua M. Diamond 16
- Youssef A. Elnabawi 17-18
- Joseph Featherall 19
- Kathleen E. Fenerty 20
- Samuel A. Gold 21-22
- Morgan C. Graves 23
- Jacob W. Groenendyk 24
- Russ M. Guidry 25
- Graham R. Hale 26
- Christopher K. Hampton 27
- Belen G. Hernandez 28
- Christopher T. Hogden 29
- Tommy Y. Hu 30
- Eileen Hu-Wang 31
- Sahar Q. Khan 32
- Alyssa K. Kosturakis 33
- Jason J. Lau 34
- Michelle M. Lee 35
- Andrew G. Lum 36
- Uchenna C. Okoro 37
- Kristen S. Pan 38
- Priya K. Patel 39
- Grant J. Randall 40
- Corinne E. Rauck 41
- Kareem N. Rayn 42
- Aakash V. Sathappan 43
- Clayton P. Smith 44-45
- Dattanand M. Sudarshana 46
- Enock B. Teefe 47
- Alison M. Treichel 48
- Fernando A. Vazquez 49
- Jeannette J. Yu 50

Scholars by Institutes and Centers 51-53

About the FNIH 54

MRSP Donors 54



"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 2017-2018 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-envisions 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.

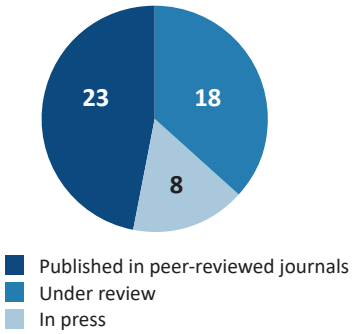
Recognizing that successful biomedical research depends on the talent and dedication of the scientific workforce, the NIH supports innovative training programs like the MRSP that foster scientific creativity and exploration. The NIH's goal is to strengthen our nation's research capacity, broaden our 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@fnih.org*.

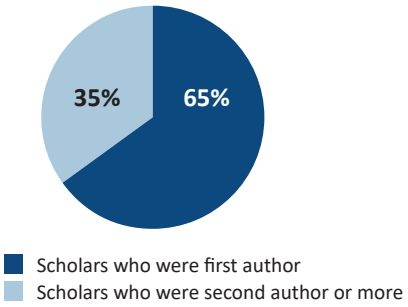
Research Achievements and Scholarly Output
MRSP Class of 2017-2018

During the 2017-2018 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, 26 scholars (62 percent) produced a total of 49 manuscripts for peer-reviewed publication; 38 scholars (90 percent) attended 78 professional meetings where they presented a total of 102 abstracts; and 14 scholars (33 percent) received a **total of 19 awards**.

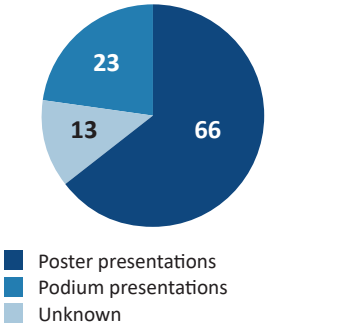
Graph 1. Completion of 49 MRSP Manuscripts



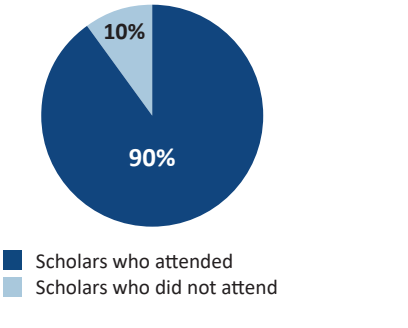
Graph 2. Authorhip of MRSP Publications



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

- **Baker M**, Cordes L, Brownell I. Avelumab: a new standard for treating metastatic Merkel cell carcinoma. *Expert Rev Anticancer Ther. 2018;4: 319-326.*
- **Bayly JE,** Bernat D, Porter L, O'Dare K, Choi K. Prevalence and characteristics of secondhand smoke and secondhand vapor exposure among youth. *Tob Control.* 2018 Jul 18. DOI: 10.1136/tobaccocontrol-2018-054265. [Epub ahead of print]
- **Caplash S**, Gangaputra S, Kodati S, Tuchman S, Srinivasalu H, Sen HN. Treatment challenges in an atypical presentation of tubulointerstitial nephritis and uveitis (TINU). *Am J Ophthalmol Case Rep*. 2018 Mar 8;10:253-256.
- **Gold SA**, **Hale GR**, Bloom JB, Smith CP, Rayn KN, Valera V, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Follow-up of negative MRI-targeted prostate biopsy: when are we missing cancer? *World J Urol.* 2018 May 21. doi: 10.1007/s00345-018-2337-0. [Epub ahead of print]
- Bloom JB, **Gold SA**, **Hale GR**, **Rayn KN**, Sabarwal V, Bakhutashvili I, Turkbey B, Pinto PA, Wood BJ. "Super-active surveillance": MRI ultrasound fusion biopsy and ablation for less invasive management of prostate cancer. *Gland Surg* 2018 Apr;7(2):166-187. Review.

- **Gold SA**, **Hale GR**, **Rayn KN**, Valera V, Bloom JB, Pinto PA. MRI imaging of seminal vesicle invasion in prostate adenocarcinoma. *Prostate Cancer Imaging: An Engineering and Clinical Perspective.* Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.
- **Groenendyk JW**, Mehta NN. Applying the ordinal model of atherosclerosis to imaging science: a brief review. Open Heart. 2018 Jul 30;5(2):e000861. doi: 10.1136/openhrt-2018-000861. eCollection 2018. Review. PubMed PMID: 30094037; PubMed Central PMCID: PMC6074639.
- **Hale GR**, Czarniecki M, Cheng A, Bloom JB, Seifabadi R, **Gold SA**, **Rayn KN**, Sabarwal V, Mehrivaland S, Choyke PL, Turkbey B, Wood BJ, Pinto PA. Comparison of elastic and rigid registration during magnetic resonance imaging/ultrasound fusion-guided prostate biopsy: A multi-operator phantom study. *J Urol.* 2018 Jun 22. doi: 10.1016/j.juro.2018.06.028. [Epub ahead of print]
- **Hernandez B**, Adissu HA, Wei BR, Michael HT, Merlino G, Simpson RM. Naturally occurring canine melanoma as a predictive comparative oncology model for human mucosal and other triple wild-type melanomas. *Int J Mol Sci.* 2018 Jan 30;19(2). Review.
- Kruszka P, Porras AR, de Souza DH, Moresco A, Huckstadt V, Gill AD, Boyle AP, **Hu T**, Addissie YA, Mok GTK, Tekendo-Ngongang C, Fieggen K, Prijoles EJ, Tanpaiboon P, Honey E, Luk HM, Lo IFM, Thong MK, Muthukumarasamy P, Jones KL, Belhassan K, Ouldim K, El Bouchikhi I, Shukla A, Girisha KM, Sirisena ND, Dissanayake VHW, Paththinige CS, Mishra R, Kisling MS, Ferreira CR, de Herreros MB, Lee NC, Jamuar SS, Lai A, Tan ES, Ying Lim J, Wen-Min CB, Gupta N, Lotz-Esquivel S, Badilla-Porras R, Hussen DF, El Ruby MO, Ashaat EA, Patil SJ, Dowsett L, Eaton A, Innes AM, Shotelersuk V, Badoe Ë, Wonkam A, Obregon MG, Chung BHY, La Serna J, Gallardo Jugo BE, Chávez Pastor M, Abarca Barriga HH, Megarbane A, Kozel BA, van Haelst MM, Stevenson RE, Summar M, Adeyemo AA, Morris CA, Moretti-Ferreira D, Linguraru MG, Muenke M. Williams-Beuren syndrome in diverse populations. *Am J Med Genet A.* 2018 May;176(5):1128-1136.
- Hong S, Hu P, Roessler E, **Hu T**, Muenke M. Loss-of-function mutations in FGF8 can be independent risk factors for holoprosencephaly. *Hum Mol Genet.* 2018 Jun;27(11):1989-1998.
- **Pan KS**, FitzGibbon EJ, Lee JS, Collins MT, Boyce AM. Optical coherence tomography in the management of skull base fibrous dysplasia with optic nerve involvement. *World Neurosurg.* 2018 Jun;114:427-428. Letter.
- **Pan KS**, Heiss JD, Brown SM, Collins MT, Boyce AM. Chiari I malformation and basilar invagination in fibrous dysplasia: prevalence, mechanisms, and clinical implications. *J Bone Miner Res.* 2018 Jun 20. doi: 10.1002/jbmr.3531 [Epub ahead of print]
- Xiao R, Allen C T, Tran L, **Patel P**, Park S, Chen Z, Van Waes, C, Schmitt NC. (2018). Antagonist of cIAP1/2 and XIAP enhances anti-tumor immunity when combined with radiation and PD-1 blockade in a syngeneic model of head and neck cancer. *OncoImmunology. doi*: 10.1080/2162402X.2018.1471440 (Epub ahead of print)
- **Rayn KN**, Ritchie C, Folio LR, Stamatakis L, Verghesel MM, Agarwal PK. Bilateral ureteroenteric strictures: a case of the "Reverse 7." *Urol.* 2018 May. doi: 10.1016/j.urology.2018.04.022. [Epub ahead of print]
- **Rayn KN**, Bloom JB, Gold SA, Hale GR, Baiocco JA, Mehralivand S, et al. Added value of multiparametric magnetic resonance imaging to clinical nomograms in predicting adverse pathology in prostate cancer. *J Urol.* 2018 May 28. doi: 10.1016/j.juro.2018.05.094. [Epub ahead of print]
- Sabarwal VK, Ritchie C, **Rayn KN**, Turkbey B, Pinto P. The disappearing PI-RADS 5 prostate lesion. *Can J Urol.* 2018;Apr 25(2): 9281-9283.
- **Rayn KN**, Bloom JB, **Gold SA**, **Hale GR**, Baiocco JA, Merhlivand S, Czarniecki M, Sabarwal VK, Valera V, Wood BJ, Merino MJ, Choyke P, Turkbey B, Pinto PA. Added value of multiparametric magnetic resonance imaging to clinical nomograms in predicting adverse pathology in prostate cancer. *J Urol.* 2018 May 28. doi: 10.1016/j.juro.2018.05.094. [Epub ahead of print]
- **Smith CP**, Czarniecki M, Mehralivand S, Stoyanova R, Choyke PL, Harmon S, Turkbey B. Radiomics and radiogenomics of prostate cancer. *Abdom Radiol.* 2018 Jun 20, doi: 10.1007/s00261-018-1660-7. [Epub ahead of print]
- **Smith CP**, Türkbey B. PI-RADS v2: Current standing and future outlook. *Turk J Urol.* 2018;44(3):189-194. Review.
- An JY, Harmon SA, Mehralivand S, Czarniecki M, **Smith CP**, Peretti JA, Wood BJ, Pinto PA, Choyke PL, Shih J, Turkbey B. Evaluating the size criterion for PI-RADSv2 category 5 upgrade: is 15 mm the best threshold? *Abdom Radiol.* 2018 May 11, doi: 10.1007/s00261-018-1631-z. [Epub ahead of print]
- Oyerinde O, Buccine D, **Treichel A**, Hong C, Lee CR, Moss J, Darling T. Fibrous cephalic plaques in tuberous sclerosis complex. *J Am Acad Dermatol.* 2018 Apr;78(4):717-724.
- **Yu JJ**, Agron E, Clemons TE, Domalpally A, van Asten F, Keenan TD, Cukras C, Chew EY; Age-Related Eye Disease Study 2 (AREDS2 Report No. 17). The natural history and genetics of drusenoid pigment epithelial detachments associated with age-related macular degeneration. Ophthalmology 2018 Aug 21. pii: S0161-6420(18)31752-4. doi: 10.1016/j.ophtha.2018.08.017. [Epub ahead of print]

In Press

- Trad C, **Bayly J**, Saint-Fort L, Andrews M, Patel M, Sabado-Liwag M, Haynie D, Simons-Morton B, Choi K. Adoption of tobacco-free and smoke-free policies in a U.S. national sample of postsecondary education institutions. *Am J Publ Health.*
- **Claudel SE**,* Adu-Brimpong J,* Banks A, Ayers C, Albert A, Das SR, de Lemos JA, Leonard T, Neeland IJ, Rivers JP, Powell-Wiley TM. Association between neighborhood-level socioeconomic deprivation and incident hypertension: a longitudinal analysis of data from the Dallas Heart Study. *Am Heart J.*
- **Claudel SE**,* Ceasar JN,* Andrews MR, Tamura K, Mitchell V, Brooks A, Dodge T, El-Toukhy S, Farmer N, Middleton K, Sabado-Liwag M, Troncoso M, Wallen G, Powell-Wiley TM. Step it up: community member engagement in the development of a mobile health technology-enabled physical activity and cardiovascular health intervention. *JMIR Formativ Res*.
- Goyal A, Dey AK, Chaturvedi A, **Elnabawi YA**, Aberra TM, Chung JH, Belur AD, **Groenendyk JW**, Lerman JB, Rivers JP, Rodante JA, Harrington CL, Varghese NJ, Sanda GE, Baumer Y, Sorokin AV, Teague HL, Genovese LB, Natarajan B, Joshi AJ, Playford MP, Bluemke DA, Chen MY, Alavi A, Pitman RK, Tawakol A, Powell-Wiley TM, Gelfand JM, Mehta NN. Chronic stress-related neural activity associates with subclinical cardiovascular disease in psoriasis – a prospective cohort study. *JACC Cardiovasc Imaging.*

*Equal contribution

- Joshi AA, Lerman JB, Dey AK, Belur AD, Sajja AA, **Elnabawi YA**, Rodante JA, Aberra TM, Chung JH, Goyal A, Rivers JP, Salahuddin T, Natarajan B, Dave J, Teague HL, Playford MP, Bluemke DA, Ahlman MA, Chen MY, Gelfand JM, Mehta NN. Association between aortic vascular inflammation and quantitative burden of coronary artery disease. *JAMA Cardiology.*
- **Hu T**, Kruszka P, Martinez AF, Ming JE, Shabason EK, Raam MS, Shaikh TH, Pineda-Alvarez DE, Muenke M. Cytogenetics and holoprosencephaly: A chromosomal microarray study of 222 individuals with holoprosencephaly. *Am J Med Genet C Semin Med Genet.*
- **Randall GJ**, Kraemer KH, Pugh J, Tamura D, DiGiovanna JJ, Khan SG, Oetjen KA. Mortality associated abnormalities in trichothiodystrophy: correlation of reduced levels of immunoglobulin and neutrophils with poor patient survival. *Brit J Hematol.*
- Lay N, Tsehay Y, Sumathipala Y, Cheng R, Gaur S, **Smith CP**, Barbu A, Lu L, Turkbey B, Choyke PL, Pinto P, Summers RM. A decomposable model for the detection of prostate cancer in multi-parametric MRI. *Med Image Comput Comput Assist Interv.*

Under Review

- **Bayly J**, Trad C, Saint-Fort L, Andrews A, Patel M, Haynie D, Simons-Morton B, Choi K. Adoption of electronic-cigarette-free, hookah-free and American College Health Association recommended tobacco-free policies among a national sample of postsecondary educational institutions. *J Am Coll Health.*
- **Boyle J**, Patronas NJ, Smirniotopoulos J, Herscovitch P, Dieckman W, Millo C, Maric D, Chatain G, Hayes CP, Benzo S, Scott G, Edwards N, Ray-Chaudhury A, Lodish MB, Sharma S, Nieman L, Stratakis C, Lonser RR, Chittiboina P. CRH stimulation to improve 18F-FDG-PET detection of pituitary adenomas in Cushing's disease.
- **Chen KG**, Alvarez JA, Yazdanie M, Papudesu C, Wong WT, Wiley HE, Chew EY, Ferris FL, Cukras CA. Longitudinal study of dark adaptation as a functional outcome measure for age-related macular degeneration. *Ophthalmology.*
- **Claudel SE**, Powell-Wiley TM, Andrews MR, Ceasar JN, Mitchell V, Tamura K. Using wearable technology to develop effective motivational messaging strategies to promote physical activity among overweight/obese African American women. *Front Public Health.*
- Peng Y*, **Dharssi S***, Chen C, Wong W, Chew E, Lu Z. EyesNet: A deep learning framework for classifying patient-based age-related macular degeneration severity in retinal color fundus photographs.
- Zheng S*, **Dharssi S***, Wu M, Li J, Lu Z. Text mining for drug discovery.
- **Diamond JM**, Chapeton JI, Theodore WH, Inati SK, Zaghloul KA. The seizure onset zone drives state-dependent epileptiform activity in susceptible brain regions. *Epilepsia.*
- **Elnabawi YA**, Dey AK, Goyal A, **Groenendyk JW**, Chung JH, Belur AD, Genovese, LD, Rodante J, Harrington CL, Teague HL, Baumer Y, Playford MP, Chen MY, Bluemke DA, Gelfand JM, Mehta NN. Effect of anti-interleukin-17 monoclonal antibody therapy on coronary plaque characteristics in psoriasis. *Circulation.*
- Sorokin AV, Kotani K, **Elnabawi YA**, Dey AK, Yamada S, Ueda M, Harrington CL, Baumer YA, Rodante J, Gelfand JM, Joshi AJ, Playford MP, Remaley AT, Mehta NN. The association of oxidation-dodified lipoproteins and coronary plaque in psoriasis: an observational cohort study. *JCI Insight.*
- Baumer Y, Harrington CL, **Elnabawi YA**, Ng Q, Sanda GE, Teague HL, Sorokin AV, Varghese NJ, **Groenendyk JW**, Rodante JA, Yu Z, Powell-Wiley TM, Playford MP, Dey AK, Mehta NN. Exploratory characterization of PCSK9 in psoriasis. *J Invest Dermatol.*
- **Groenendyk JW**, Shukla P, Elnabawi YA, Dey A, Genovese LD, Harrington CL, Goyal A, Belur A, Rodante J, Playford MP, Bluemke DA, Gelfand HM, Mehta NN. Aortic wall thickness by MRI in psoriasis: A prospective observational study. *Atherosclerosis.*
- **Hu-Wang E**, Schuzer JL, Rollison S, Leifer ES, Steveson C, Gopalakrishnan V, Yao J, Machado T, Jones AM, Julien-Williams P, Moss J, Chen MY. Chest computed tomography at radiation dose of a single chest x-ray: a proof of principle in patients with lymphangioleiomyomatosis.
- **Hu-Wang E**, Kureshi F, Leifer ES, Acharya T, Sathya B, Yu JH, Groves DW, Bandettini WP, Shanbhag SM, Chen MY. Calcium scoring improves pretest probability estimation of obstructive coronary artery disease in a real world population.
- **Khan SQ**, Berrington de Gonzalez A, Best AF, Chen Y, Haozous EA, Rodriquez E, Spillane S, Thomas D, Withrow D, Freedman ND, Shiels MS. Trends in infant and youth mortality in the United States by racial/ethnic group and cause of death.
- Shiels MS, Berrington de Gonzales A, Best AF, Chen Y, Chernyavskiy P, Hartge P, **Khan SQ**, Perez Stable E, Rodriquez E, Spillane S, Thomas D, Withrow D, Freedman ND. Premature mortality from all causes and drug poisonings in the United States according to socioeconomic status and rurality: an analysis of death certificate date by county from 2000-2015.
- **Lau JJ**, Gayen S, Ben Abacha A, Demner-Fushmen D. A dataset of clinically generated visual questions and answers about radiology images. *Scientific Data.*
- Michael H, Graff-Cherry C, Chin S, **Rauck CE**, Habtemichael A, Bunda P, Smith T, Bharti K, Arnheiter H, Merlino G, Day C. Partial rescue of ocular pigment cells and structure by inducible expression of Mitf-M in Mitf-deficient mice.
- **Smith CP**, Harmon, SA, Barrett T, Bittencourt LK, Law YM, Shebel H, An JY, Czarniecki M, Mehralivand S, Wood BJ, Pinto PA, Shih JH, Choyke PL, Turkbey B. Intra and inter-reader reproducibility of PI-RADSv2: A multi-reader study. *Abdol Radiol.*

Awards and Honors

- Eight best or outstanding abstract awards from professional societies.
- Seven student/scholar travel grants from professional societies.
- One Doris Duke Clinical Research Mentorship Award.
- One American Osteopathic Association Student Research Fellowship Award.
- One National Institute of Arthitis and Musculoskeletal and Skins Diseases (NIAMS) Best Presentation Award.
- One National Heart, Lung, and Blood Institute (NHLBI) Best Pre-doctoral Fellow Pitch Award.

*Equal contribution

Mairead R. Baker

School: Loyola University Stritch School of Medicine
Mentor: Isaac Brownell, M.D., Ph.D., Investigator, Dermatology Branch
Institute: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Research: Targeting CD200 as an Immune Checkpoint in Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer that predominantly affects fair-skinned, elderly, and immunocompromised populations. A highly immunogenic tumor, MCC responds well to PD-(L)1 blockade. However, not all patients respond to avelumab, the FDA-approved anti-PD-L1 inhibitor for the treatment of MCC. Thus, new MCC treatments are needed.

Recent studies have implicated the membrane glycoprotein CD200 as a tumor-promoting immune checkpoint. CD200 is the ligand for CD200R, a myeloid-expressed anti-inflammatory effector. Blocking antibodies against CD200 are under clinical investigation for hematologic malignancies. More than 95% of MCC tumors express CD200. Moreover, the tumor microenvironment attracts and induces an immunosuppressive myeloid population, including CD200R-positive myeloid cells. Little is known about the functional impact of CD200 in immune responses to solid tumors. Here we investigated the role of CD200-expressing MCC cells in modulating pro-inflammatory (M1) and anti-inflammatory (M2) macrophage phenotypes.

MCC cells were co-cultured with elutriated human monocytes for three days under three macrophage-stimulating conditions: M0 (M-CSF), M1 (M-CSF + IFNy), and M2 (M-CSF + IL-4). Flow cytometric analysis revealed that co-culture with CD200+ MKL-1 MCC cells enhanced the M2 polarization of IL-4 stimulated macrophages, as indicated by increased induction of CD200R, CD163, and CD206. Furthermore, co-culture led to increased production of the anti-inflammatory cytokine, IL-10, by M2 cells. This enhanced M2 polarization was dependent on physical MCC-macrophage interaction as MCC media failed to enhance polarization. Additionally, treatment with a CD200-blocking monoclonal antibody abrogated co-culture enhanced M2 polarization. This observation suggests that CD200 expressed on MCC cells promotes the differentiation and maturation of anti-inflammatory M2 macrophages, and this mechanism of tumor immune evasion can be blocked with anti-CD200 antibodies. Ongoing studies are needed to further characterize the overall immune impact of CD200 as well as to investigate the potential of combining CD200 inhibition with PD-(L)1 blockade.

Full Length Publications:

- **Baker M**, Cordes L, Brownell I. Avelumab: a new standard for treating metastatic Merkel cell carcinoma. *Expert Rev Anticancer Ther. 2018;4: 319-326.*

Abstract Publications:

- **Baker M**, Jiang H, Strauss J, Gulley J, Brownell I. Cancer treatment with a novel fusion protein targeting PD-L1 and TGF-beta results in keratoacanthoma formation. American Academy of Dermatology Annual Meeting, San Diego, CA; Feb. 16–20, 2018. [Podium presentation]
- **Baker M**, Roman JW, Reuben A, Hill N, Hudgens CW, Tetzlaff MT, Logemann NF, Brownell I. Spontaneous regression of Merkel cell carcinoma is driven by adaptive immune activation and clonal T cell expansion. American Association of Cancer Research Annual Meeting, Chicago, IL; Apr. 14–18, 2018. [Poster presentation]

Travel to Professional Meetings:

- American Academy of Dermatology Annual Meeting, San Diego, CA; Feb. 16–20, 2018.
- American Association of Cancer Research Annual Meeting, Chicago, IL; Apr. 14–18, 2018.

Awards:

- Finalist in NIAMS Three Minute Talk competition (3rd place)

Fatima Barragan

School: Michigan State University College of Human Medicine
Mentor: Carol J. Thiele, Ph.D., Deputy Chief, Pediatric Oncology Branch
Institute: National Cancer Research (NCI), Center for Cancer Research (CCR)
Research: Targeting *MYCN* Transcription using Bromodomain Inhibitors in Combination with Topoisomerase I Inhibitors

Children with high-risk, *MYCN*-driven neuroblastoma (NB) have poor long-term survival and significant therapy-related comorbidities with current intensive multidisciplinary treatments. More effective, less toxic therapies are needed. Bromodomain 4 (BRD4)-dependent phosphorylation of RNA Polymerase II (RNAPII) stimulates topoisomerase I (TOPI) activity. Recent studies indicate that C-myc-driven RNAPII-mediated transcription requires TOPI to relieve DNA torsional stress. We hypothesized that a similar mechanism operates in N-myc-driven NB tumors and renders these tumors sensitive to inhibitors targeting BRD4 and TOPI.

Six NB cell lines (3 *MYCN*-amp and 3 *MYCN*-wt) were treated with varying concentrations of the BRD4 inhibitor JQ1 alone or in combination with TOPI (topotecan or camptothecin) or TOPII (etoposide) inhibitors. The Bliss Independence Model was used to evaluate synergy of drug combinations. DNA damage was assessed by western blot analysis for P-γH2AX and P-ATM protein lysates from cells treated with synergistic drug combinations and single agents.

Synergistic concentrations of JQ1 and topotecan, but not JQ1 and etoposide, were found to block cell growth and decrease proliferation. In NGP *MYCN*-amp NB cells, a similar cell kill effect was achieved with a 4-fold lower dose of topotecan (7.5 nM) when combined with JQ1 (310 nM) compared to topotecan (30 nM) alone. Single drug agents induced detectable expression of P-γH2AX while the combination of a BRD4 inhibitor with a TOPI inhibitor produced a >3-log increase in the levels of P-γH2AX. Levels of P-ATM followed a similar pattern.

At the low dosages selected, single agents alone were not sufficient to cause significant DNA damage in NB cell lines. Our data suggest that a synergistic drug dose that reduces cell growth and induces DNA damage can be attained, and the combination of BRD4 inhibitor with TOPI inhibitor may be more effective than with TOPII inhibitors. Understanding the operational features and pathways affected by these drugs at low dosages may enable a new strategy to selectively target *MYCN*-driven NB.

Abstract Publications:

- **Barragan F**, Lam N, Yockey O, Shern J, Thiele CJ. Targeting *MYCN* transcription using BRD inhibitors in combination with TOPI inhibitors. 2nd Pediatric Precision Oncology Conference, Scottsdale, AZ; Mar. 4–7, 2018.
- **Barragan F**, Lam N, Yockey O, Shern J, Thiele CJ. Drugging *MYCN* transcription using BRD inhibitors in combination with TOPI inhibitors. Advances in Neuroblastoma Research Conference, San Francisco, CA; May 9–12, 2018.

Travel to Professional Meetings:

- 2nd Pediatric Precision Oncology Conference, Scottsdale, AZ, Mar. 4–7, 2018.
- Latino Medical Student Association National Conference, Miami, FL; Apr. 13–15, 2018.
- Advances in Neuroblastoma Research Conference, San Francisco, CA; May 9–12, 2018.

Jennifer E. Bayly

School: Rutgers Robert Wood Johnson Medical School
Mentor: Kelvin Choi, Ph.D., M.P.H., Stadtman Investigator, Social and Behavioral Group
Institute: National Institute on Minority Health and Health Disparities (NIMHD)
Research: Prevalence and Characteristics of Secondhand Smoke and Secondhand Vapor Exposure Among Youth

It is well-established that secondhand smoke (SHS) is harmful, and concern about the potential dangers associated with secondhand vapor (SHV) (i.e., vapor from electronic vapor products, EVP) is growing. This study examines the prevalence and characteristics associated with SHS and SHV exposure. Data from youth aged 11-17 who completed the 2016 Florida Youth Tobacco Survey (n= 58,616) were analyzed. Demographics, past 30-day SHS and SHV exposure, environmental factors, cigarette and EVP use status, SHS and SHV harm perceptions, and tobacco susceptibility were assessed. Weighted multivariable logistic regressions were performed to examine characteristics associated with SHS and SHV exposure, and SHS and SHV exposure with tobacco susceptibility. Overall, 42% of Florida youth reported SHS exposure and 29% reported SHV exposure during the past 30 days. SHS and SHV exposure were most common among non-Hispanic white youth (48% and 37%, respectively), followed by non-Hispanic American Indian/Alaskan Native youth (43% and 36%, respectively). Living in a home where tobacco use was permitted (vs. not permitted) was positively associated with SHS (AOR 2.57, 95% CI 2.35-2.81) and SHV exposure (AOR 1.56, 95% CI 1.44-1.70). Perceived SHS as harmful (vs. not harmful) was positively associated with SHS (AOR 1.73, 95% CI 1.54-1.93) and SHV exposure (AOR 1.97, 95% CI 1.76-2.21), while perceived SHV as harmful was negatively associated with SHS (AOR 0.86, 95% CI 0.81-0.92) and SHV exposure (AOR 0.56, 95% CI 0.53-0.59). SHS exposure (AOR 1.18, 95% CI 1.06-1.31) and SHV exposure (AOR 2.09, 95% CI 1.82-2.40) were both significantly associated with susceptibility to EVP use. Almost one-third of Florida youth reported SHV exposure. Factors associated with SHS and SHV exposure are somewhat similar, and exposure to SHS and SHV was associated with tobacco susceptibility in youth. Promoting tobacco-free homes is needed to protect youth from SHS and SHV exposure.

Full Length Publications:

- **Bayly JE,** Bernat D, Porter L, O'Dare K, Choi K. Prevalence and characteristics of secondhand smoke and secondhand vapor exposure among youth. *Tob Control.* 2018 Jul 18. DOI: 10.1136/tobaccocontrol-2018-054265. [Epub ahead of print]
- Trad C, **Bayly JE**, Saint-Fort L, Andrews M, Patel M, Sabado-Liwag M, Haynie D, Simons-Morton B, Choi K. Adoption of tobacco-free and smoke-free policies in a U.S. national sample of postsecondary education institutions. *Am J Public Health*. [In press]
- **Bayly JE**, Trad C, Saint-Fort L, Andrews A, Patel M, Haynie D, Simons-Morton B, Choi K. Adoption of electronic-cigarette-free, hookah-free and American College Health Association recommended tobacco-free policies among a national sample of postsecondary educational institutions. *J Am Coll Health*. [Under review]

Abstract Publications:

- **Bayly JE**, Bernat D, Porter L, O'Dare K, Choi K. Prevalence and characteristics of secondhand smoke and secondhand vapor exposure among youth in Florida. Society for Behavioral Medicine 39th Annual Meeting and Scientific Sessions, New Orleans, LA; Apr. 11–14, 2018. [Poster presentation]

Travel to Professional Meetings:

- Society for Research on Nicotine and Tobacco 2018 Annual Meeting, Baltimore, MD; Feb. 21–24, 2018.
- Society for Behavioral Medicine 39th Annual Meeting and Scientific Sessions, New Orleans, LA; Apr. 11–14, 2018.
- Society for Epidemiologic Research 2018 Meeting, Baltimore, MD; June 19–22, 2018.

Jacqueline N. Boyle

School: University of Illinois College of Medicine at Peoria
Mentor: Prashant Chittiboina, M.D., M.P.H., Assistant Clinical Investigator, Surgical Neurology Branch
Institute: National Institute of Neurological Diseases and Stroke (NINDS)
Research: (1) Metabolic Reprogramming in Cushing's Disease; (2) CRH Stimulation to Improve 18F-FDG-PET Detection of Pituitary Adenomas in Cushing's Disease

Project 1:

Having found evidence of metabolic reprogramming in adrenocorticotrophic hormone (ACTH)-secreting adenomas (corticotropinomas) causing Cushing's Disease (CD), we investigated the role of isozyme switching in key glycolytic pathway enzymes [hexokinase (HK) and lactate dehydrogenase (LDH)].

Multiplex Immunohistochemistry revealed remarkable overexpression of HK-2 (n=9/14) and LDH-A (n=10/16) in a majority of corticotropinomas compared to the adjacent normal gland. HK-2 overexpression (but not HK-1) was detected in corticotropinomas (n=4) compared to adjacent normal gland, suggesting isozyme switching. Seahorse analysis suggested increased glycolytic potential in human corticotropinomas (n=2) and AtT20 compared to matched normal counterparts. Treatment with 3-BP resulted in decreased glycolytic flux (60% decrease) and caused increased cell death (77% v. 41%) in corticotropinomas compared to matched normal tissue. Overall, these findings suggest selective metabolic dependence and survival on HK-2, and the potential for utilizing HK2 as a targeted anti-tumor strategy.

Project 2:

Modern MRI techniques can reliably detect corticotropinomas in only 50 - 80% cases of CD. Our lab's previous work demonstrated corticotropin-releasing hormone (CRH) stimulation leads to selective delay of glucose uptake in corticotropinomas. Therefore, we prospectively evaluated the utility of CRH stimulation in improving ^{18}F-FDG-PET detection of CD adenomas in patients.

The subjects (n = 30) served as their own controls, each receiving two ^{18}F-FDG-PET studies (one with ovine CRH) on PET platform. The mean SUV of adenomas was significantly increased from baseline FDG-PET (3.6 ± 1.5) with CRH administration (3.9 ± 1.7; $p = 0.003$). The neuroradiologists detected additional adenomas (3 and 6, respectively) correctly on CRH-stimulated PET images. No false positive reads were made during this study. Delay in PET imaging following CRH stimulation did not result in increased detection rates. The results of the current study suggest that CRH stimulation may lead to increased ^{18}F-FDG uptake and, if validated, could complement MRI to improve pre-surgical visualization of corticotropinomas.

Full Length Publications:

- **Boyle J**, Patronas NJ, Smirniotopoulos J, Herscovitch P, Dieckman W, Millo C, Maric D, Chatain G, Hayes CP, Benzo S, Scott G, Edwards N, Ray-Chaudhury A, Lodish MB, Sharma S, Nieman L, Stratakis C, Lonser RR, Chittiboina P. CRH stimulation to improve ^{18}F-FDG-PET detection of pituitary adenomas in Cushing's disease. [Under review]

Abstract Publications:

- **Boyle J**, Lu J, Chatain G, Maric D, Ray-Chaudhury A, Chittiboina P. Activation of canonical EGFR pathway in Cushing's Disease. 2018 Annual Meeting, American Association of Neurological Surgeons, New Orleans, LA; May, 2018. [Podium presentation]
- **Boyle J**, Kostantinos FV, Lu J, Chatain G, Maric D, Ray-Chaudhury A, Chittiboina P. Metabolic isozyme switching offers a targeted treatment strategy in Cushing's Disease. National Institute of Neurological Disorders and Stroke (NINDS) Intramural Science Retreat, Potomac, MD; June 2018. [Poster presentation]

Travel to Professional Meetings:

- American Association of Neurological Surgeons 2018 Annual Meeting, New Orleans, LA; Apr. 28–May 2, 2018.

Rebecca O. Breese

School: University of North Carolina Chapel Hill School of Medicine
Mentor: Zhengping Zhuang, M.D., Ph.D., Senior Investigator, Neuro-Oncology Branch
Institute: National Cancer Institute (NCI)
Research: Combination of PP2A Inhibition & PD-1 Blockade Synergistically Induces Regression of Murine Intracranial Glioblastoma

Checkpoint inhibition using monoclonal antibodies against programmed cell death protein 1 (PD-1) is currently under evaluation for treatment of glioblastoma (GBM). Inhibition of protein phosphatase 2A (PP2a) was recently identified as a novel strategy to enhance cancer immunity. We hypothesized that pharmacologic inhibition of PP2a utilizing the small-molecule inhibitor, LB-100, could enhance the therapeutic effect of anti-PD-1 checkpoint inhibition in a syngeneic murine GBM model.

C57BL/6 mice were inoculated with 130,000 GL261 cells in their right striatum. After eight days, mice were randomized into four treatment groups: control (PBS) (n=16), anti-PD-1 (n=15), LB100 (n=16), and combination (n=16). In a second cohort (n=20 per group), CD8-depleting antibodies were given prior to and during combination treatment. A third cohort (n=10 per group) had tumors collected and stained for FACS analysis 15 days after inoculation.

Mice treated with combination therapy demonstrated a significant increase in median survival (26 days) compared to monotherapy (19 days for anti-PD-1 and 18.5 days for LB100) or control (19 days) ($p<0.001$ for all comparisons with combination treatment). Complete regression (CR) occurred in 25% of combination treated mice. No CR was seen in any other group. When mice treated with combination therapy were concurrently given CD8 depleting antibodies, survival benefit was lost. FACS analysis of tumors demonstrated an increased infiltration of cytotoxic CD8 cells ($p<0.005$) and memory CD8 cells ($p<0.005$). Mice that experienced CR were re-challenged with either GL261 cells or unrelated B16 melanoma cells. Mice re-challenged with GL261 cells did not demonstrate tumor growth, whereas mice re-challenged with B16 cells lived an average of 13 days ($p<0.005$). Glial scar formation was found in GL261 re-challenged mice when examined with immunohistochemistry.

The data suggest that PP2a inhibition and PD-1 monoclonal antibody checkpoint inhibition act synergistically against intracranial GBM, inducing a long-term durable cure in 25% of mice. This finding appears to be at least partly attributed to increased intratumoral infiltration of cytotoxic and memory CD8+ T cells. This report supports further clinical investigation of combining LB-100 with checkpoint immunotherapy.

Abstract Publications:

- Maggio D, **Breese RO**, Ho WS, Wang H, Lu R, Heiss JD, Gilbert MR, Zhuang Z. Combination of protein phosphatase 2A inhibition and PD-1 blockade synergistically induce regression of murine intracranial glioblastoma. American Association of Neurological Surgeons 2018 Annual Meeting, New Orleans, LA; May 2018. [Podium presentation]
- Maggio D, **Breese RO**, Ho WS, Wang H, Lu R, Heiss JD, Gilbert MR, Zhuang Z. Combination of protein phosphatase 2A inhibition and PD-1 blockade synergistically induce regression of murine intracranial glioblastoma. Society for Neuro Oncology Annual Meeting, San Francisco, CA; Nov. 2017. [Poster presentation]

Travel to Professional Meetings:

- American Association of Neurological Surgeons 2018 Annual Meeting, New Orleans, LA; Apr. 28–May 2, 2018.

Awards:

- American Association of Neurological Surgeons, Young Neurosurgeons Research Forum, Best Basic Science Abstract for a Resident.
- Society for Neuro-Oncology Annual Meeting, Best Research Project.

Sonny Caplash

School: University of Connecticut School of Medicine
Mentor: H. Nida Sen, M.D., Director, Uveitis and Ocular Immunology Fellowship Program
Institute: National Eye Institute (NEI)
Research: Assessing the Variability and Repeatability of Optical Coherence Tomogaphy-Angiography in Uveitis Patients

Optical Coherence Tomogaphy-Angiography (OCT-A) is an imaging modality used for assessment of ocular disease. However, its variability and repeatability have been poorly characterized. We performed a retrospective clinical study to characterize both intra-visit and inter-operator variability of OCT-A. Sixty-nine uveitis patients were evaluated with 2 OCT-A scans per eye, per visit in a standardized clinical research protocol. Consecutive OCT-A scans were recorded by the same technician, separated by several minutes. Two separate operators retrospectively analyzed images using an algorithm developed by investigators to generate: total vessel area (TVA) and foveal avascular zone (FAZ) area of both the superficial and deep capillary plexus (SCP and DCP), and the total flow-void area of the choriocapillaris (CC). The right eye of each patient was chosen from the earliest available OCT-A scans for variability analyses, with poor images excluded. Bland-Altman modeling of averages vs differences was used to generate a coefficient of repeatability.

Intra-visit variability of total flow-void areas in patients with CC pathology was 0.243 ± .05 mm^2 with an average flow void area of .585 mm^2 across all tested eyes (n=18). Inter-operator variability in these patients was .141 ± .07 mm^2 with an average flow void area of .468 mm^2 across all tested eyes (n=24). Among panuveitis patients, intra-visit variability was .286 ±.050 mm^2 (SCP FAZ), .439 ± .059 mm^2 (DCP FAZ), .553 ± .106 mm^2 (SCP TVA) and .755 ± .171 mm^2 (DCP TVA). Inter-operator variability was .349±.056 (SCP FAZ), .586± .0946 mm^2 (DCP FAZ), $5.8x10^{-5}$± $1x10^{-5}$ (SCP TVA), and $2.47x10^{-4}$± $4x10^{-5}$ (DCP TVA). Average values for measured eyes were .609 (SCP FAZ), .936 (DCP FAZ), 2.83 (SCP TVA) and 3.55 (DCP TVA) mm^2 (n=30). Bland-Altman models showed no bias and nearly all data points falling within the limits of agreement. Preliminary data indicates that while OCT-A reasonably fulfills Bland-Altman models of repeatability, with minimal exclusion criteria, it may not be sensitive enough to detect subtle changes within disease as shown by the high coefficients of repeatability relative to average measurements, a finding attributed to the presence of outliers. Further analysis is underway to determine specific criteria for high reproducibility.

Full Length Publications:

- **Caplash S**, Gangaputra S, Kodati S, Tuchman S, Srinivasalu H, Sen HN. Treatment challenges in an atypical presentation of tubulointerstitial nephritis and uveitis (TINU). *Am J Ophthalmol Case Rep*. 2018 Mar 8;10:253-256.

Abstract Publications:

- **Caplash S**, Knickelbein JE, Tucker W, Kodati S, Sen HN. Assessing the variability and repeatability of optical coherence tomogaphy-angiography in uveitis patients. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, Hawaii; Apr. 30–May 5, 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, Hawaii; Apr. 8–May 3, 2018.

Awards:

- Association for Research in Vision and Ophthalmology Annual Meeting Travel Grant.

Katherine G. Chen

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; Catherine Cukras, M.D., Ph.D., Staff Clinician, Division of Epidemiology and Clinical Applications
Institute: National Eye Institute (NEI)
Research: Longitudinal Study of Dark Adaptation as a Functional Outcome Measure for Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly worldwide. While visual acuity is generally stable in early stages, night vision has been shown to be affected. The purpose of our study was to assess for correlation of changes in dark adaptation (DA) with AMD severity and presence of subretinal drusenoid deposits (SDD) over 4 years.

77 participants ≥50 years of age each contributing a single study eye were assigned into person-based AMD severity groups based on fundus characteristics (drusen, pigmentary changes, late AMD, and SDD). DA function was assessed at baseline, 3, 6, 12, 18, 24, 36, and 48 months, and the slope of the rod intercept time (RIT), or the rate of change in RIT (time for recovery to a stimulus intensity of 5×10^{-3} cd/m^2), was calculated by linear regression fits for each individual's RIT data. Patient-reported responses on a low luminance questionnaire (LLQ) were also obtained.

Longitudinal analysis of 65 eyes followed on the standard protocol revealed that higher rates of RIT prolongation were correlated with AMD severity group assignment at baseline ($p=0.026$) and at year 4 ($p=0.0011$). Study eyes that developed SDD during follow-up demonstrated higher rates of RIT prolongation relative to those that did not ($p<0.0001$). An additional 12 eyes, the majority of which had SDD, were followed on a modified protocol and also demonstrated a high rate of RIT prolongation. Overall, higher rates of RIT prolongation were significantly correlated with greater 4-year decreases in LLQ scores (total mean score, $p=0.0032$).

Our study demonstrated that longitudinal decline in DA function, which correlated with patient-reported functional deficits, was accelerated in eyes with greater AMD severity and especially in eyes with SDD. RIT prolongation as a measure of changing DA function may be a functional outcome measure in AMD clinical studies.

Full Length Publications:

- **Chen KG**, Alvarez JA, Yazdanie M, Papudesu C, Wong WT, Wiley HE, Chew EY, Ferris FL, Cukras CA. Longitudinal study of dark adaptation as a functional outcome measure for age-related macular degeneration. *Ophthalmology.* [In review]

Abstract Publications:

- **Chen KG**, Alvarez J, Wong WT, Wiley HE, Chew EY, Ferris FL, Cukras CA. Longitudinal study of dark adaptation as a functional outcome measure for age-related macular degeneration. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; May 2018. [Poster presentation]
- Allahdina A, **Chen KG**, Alvarez J, Wong WT, Chew EY, Cukras CA. Longitudinal changes in eyes with hydroxychloroquine retinal toxicity. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; May 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, Hawaii; Apr. 28–May 3, 2018.

Awards:

- Knights Templar Eye Foundation Travel Grant Award, Association for Research in Vision and Ophthalmology Annual Meeting, 2018.

Sophie E. Claudel

School: Wake Forest School of Medicine
Mentor: Tiffany M. Powell-Wiley, M.D., M.P.H., Chief of the Social Determinants of Obesity & Cardiovascular Risk Laboratory, Cardiovascular & Pulmonary Branch
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research: The Relationship Between Neighborhood Socioeconomic Deprivation and Telomere Length: NHANES 1999-2002

Socioeconomically disadvantaged neighborhoods have been associated with poor health outcomes. Little is known about the mechanism by which deprived neighborhood conditions exert negative influences on health.

Data from the 1999-2002 National Health and Nutrition Examination Surveys (NHANES) were used to assess the relationship between neighborhood deprivation index (NDI) and log-transformed leukocyte telomere length (LTL) via multilevel modeling to control for census tract level clustering. NDI was calculated using census tract level socioeconomic indicators from the 2000 US Census.

The sample (n=5,106 adults) was 47.5% female and consisted of 56.0% non-Hispanic whites, 17.7% non-Hispanic blacks, and 26.3% Mexican Americans. Mean age was 45.8 years. Residents of neighborhoods with higher NDI were younger, non-white, had lower educational attainment, and had a lower poverty to income ratio (all p <0.0001). Neighborhood deprivation was inversely associated with LTL among individuals living in neighborhoods with medium NDI (β=-0.04, SE=0.01, p=0.0005) and high NDI (β=-0.04, SE=0.01, p=0.003). Among men, both medium (β=-0.04, SE=0.01, p=0.002) and high (β=-0.04, SE=0.02, p=0.001) NDI were associated with shorter LTL. Among women, only medium NDI (β=-0.02, SE=0.02, p=0.009) was associated with shorter LTL.

After controlling for individual characteristics, increasing neighborhood socioeconomic deprivation is associated with shorter LTL among a nationally representative sample of US adults. This suggests that telomere shortening may be a mechanism through which neighborhood deprivation results in poor health outcomes.

Full Length Publications:

- **Claudel SE**,* Adu-Brimpong J,* Banks A, Ayers C, Albert A, Das SR, de Lemos JA, Leonard T, Neeland IJ, Rivers JP, Powell-Wiley TM. Association between neighborhood-level socioeconomic deprivation and incident hypertension: a longitudinal analysis of data from the Dallas Heart Study. *Am Heart J.* [In press]
- **Claudel SE**,* Ceasar JN,* Andrews MR, Tamura K, Mitchell V, Brooks A, Dodge T, El-Toukhy S, Farmer N, Middleton K, Sabado-Liwag M, Troncoso M, Wallen G, Powell-Wiley TM. Step it up: community member engagement in the development of a mobile health technology-enabled physical activity and cardiovascular health intervention. *JMIR Formativ Res.* [Under review]
- **Claudel SE**, Powell-Wiley TM, Andrews MR, Ceasar JN, Mitchell V, Tamura K. Using wearable technology to develop effective motivational messaging strategies to promote physical activity among overweight/obese African American women. *Front Public Health.* [Under review]

Abstract Publications:

- **Claudel SE**, Powell-Wiley TM, Andrews MR, Ceasar JN, Mitchell V, Tamura K. Using wearable technology to develop effective motivational messaging strategies to promote physical activity among overweight/obese African American women. American Public Health Association, San Diego, CA; Nov. 2018. [Podium presentation]
- Ceasar JN, **Claudel SE**, Andrews MR, Tamura K, Mitchel VM, Brooks A, Dodge T, El-Toukhy S, Farmer N, Middleton K, Sabado-Liwag M, Troncoso M, Wallen G, Powell-Wiley TM. Community member engagement for user-centered design of a physical activity promoting mobile health application. American Public Health Association, San Diego, CA; Nov. 2018. [Podium presentation]

*Equal contribution

- **Claudel SE**, Shiroma EJ, Harris TB, Mode NA, Ahuja C, Zonderman AB, Evans MK, Powell-Wiley TM. Association of neighborhood perception and physical activity in the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) cohort study. American Heart Association Epidemiology Lifestyle Sessions, New Orleans, LA; Mar. 2018. [Poster presentation]
- Andrews MR, Ayers C, Ceasar JN, **Claudel SE**, Das SR, Neeland IJ, Tamura K, Powell-Wiley TM. The relationship between neighborhood food environment and adiposity measures: Data from the Dallas Heart Study. American Heart Association Epidemiology Lifestyle Scientific Sessions, New Orleans, LA; Mar. 2018. [Poster presentation]
- Andrews MR, Ayers C, Ceasar JN, Das SR, Neeland IJ, Tamura K, **Claudel SE**, de Lemos JA, Powell-Wiley TM. Relationship between changes in perceptions about neighborhood environment and changes in blood pressure: Data from the Dallas Heart Study. Society of Behavioral Medicine; New Orleans, LA; Apr. 2018. [Poster presentation]
- Ceasar JN, Ayers C, Andrews MR, **Claudel SE**, Tamura K, Das SR, de Lemos JA, Neeland IJ, Powell-Wiley TM. Unfavorable perceived neighborhood environment associates with less routine healthcare utilization: Data from the Dallas Heart Study, 2007-2009. American Heart Association Epidemiology Lifestyle Scientific Sessions, New Orleans, LA; Mar. 2018. [Poster presentation]

Travel to Professional Meetings:

- American Heart Association Epidemiology Lifestyle Scientific Sessions, New Orleans, LA; Mar. 20–24, 2018.

Awards:

- National Heart, Lung, and Blood Institute Best Predoctoral Pitch Award 2018.

Shavonne M. Collins

School: Meharry Medical College
Mentor: Jack A. Yanovski, M.D., Ph.D., Section on Growth and Obesity
Institute: National Institute of Child Health and Human Development (NICHD)
Research: Serum Free Fatty Acids as an Indicator of the Non-fasted State in Children

A biochemical test to provide assurance of the fasted state could be valuable to aid interpretation of fasting glucose measurements in children. The objective of this study was to determine if serum free fatty acid (FFA) concentrations, known to be suppressed by feeding, might serve as a marker to differentiate the fed and fasted state in children.

We performed an exploratory study of a convenience sample of non-diabetic children, age 5-18 yrs, who had laboratory-measured glucose, insulin, and FFA reportedly collected in the fasted state, or at baseline and the 2-hour point of an oral glucose tolerance test (OGTT). Three cohorts were developed: children who underwent OGTT; children admitted overnight as inpatients; and children studied as outpatients.

A total of 442 inpatient (assured) fasting and 323 2-hour OGTT (non-fasting) samples were examined by ROC curve analysis and used to identify a cut-point for non-fasting FFA, glucose, and insulin (maximum value of Youden Index). In children studied cross-sectionally at an outpatient (n=442) or inpatient (n=442) visit, we compared mean fasting FFA and percentage of FFA values below the FFA non-fasting cut-point.

ROC curve analysis found the AUC of FFA (0.998±0.001) was significantly better (p's<0.001) than AUC of glucose (0.850±0.016) or insulin (0.906±0.011) for identifying non-fasting. FFA <287 mEq/mL had 99.0% sensitivity and 98.0% specificity for non-fasting. Mean fasting FFA was lower in participants studied as outpatients than those studied as inpatients (592.8±17.7 vs 754.0±17.7 mEq/mL, p<.001). Using the ROC curve-derived cut-point, we found 9.7% outpatient but only 1.6% inpatient FFA values were consistent with non-fasting (p<.001).

Clinicians cannot assume that their pediatric patients are adequately fasted upon arrival for fasting blood work. Our data demonstrate that children appear less likely to be fasting at outpatient than inpatient appointments. FFA value <287 mEq/mL was a sensitive and specific cutoff for non-fasting in children that may prove clinically useful.

Abstract Publications:

- **Collins SM**, Tanofsky-Kraff M, Kelly N, Shank LM, Grammer A, Mi S, Jaramillo M, Courville A, Bernstein S, Broadney MM, Brady SM, Yanovski JA. Associations between parents' view of parent-child relationships and children's energy intake at a buffet meal. Pediatric Academic Societies 2018 Annual Meeting, Toronto, Canada; May 2018. [Poster presentation]
- Ghane N, Broadney MM, **Collins SM**, Davis EK, Brady SM, Yanovski JA. Estimating plasma glucose with a Freestyle Libre Pro continuous glucose monitoring (CGM) device during OGTT in youth. American Diabetes Association Scientific Session, Orlando, FL; June 2018. [Poster presentation]

Travel to Professional Meetings:

- Association of Medicine and Psychiatry 2017 Annual Meeting, Chicago, IL; Sep. 14–17, 2017.

Shazia Dharssi

School: Johns Hopkins University School of Medicine
Mentor: Zhiyong Lu, Ph.D., Senior Investigator, Biomedical Text Mining Group, National Center for Biotechnology Information, National Library of Medicine; Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications.
Institute: National Center for Biotechnology Information at the National Library of Medicine (NLM/NCBI); National Eye Institute (NEI)
Research: EyesNet: A Deep Learning Framework for Classifying Patient-based Age-related Macular Degeneration Severity in Retinal Color Fundus Photographs

Age-related macular degeneration (AMD) is the leading cause of incurable blindness worldwide in people over the age of 65. Although the Age-Related Eye Disease Study (AREDS) group has developed a simplified scale that provides convenient risk categories for the development of late AMD, manual assignment can be time consuming, expensive, and requires domain expertise. While several automated deep learning systems have been developed for classifying color fundus photographs of individual eyes by AMD severity score, none have utilized a patient-based scoring system that employs images from both eyes to obtain one classification score for the individual. A deep learning framework, EyesNet, was developed to automatically classify color fundus images into the 5-step AREDS Simplified Severity Scale. Unlike previous methods, EyesNet mimics the human grading process by first detecting risk factors for each eye (large drusen and pigmentary abnormalities consistent with AMD) and subsequently calculates patient-based AMD severity scores. EyesNet was trained and validated on 59,302 color fundus photographs from the NIH AREDS dataset, one of the largest AMD retinal image datasets to date. EyesNet achieves multi-label classification performance (accuracy=0.671; kappa=0.559) consistently higher than human ophthalmologists (accuracy=0.598; kappa=0.466). On individual risk factor detection, EyesNet also outperforms ophthalmologists in the detection of pigmentary abnormalities and large drusen detection, and has comparable performance to human ophthalmologists on late AMD classification. The source code of EyeNet is publicly available to allow for future study of other retinal diseases in which smaller datasets are currently available for deep learning (https://github.com/ncbi-bionlp/EyesNet).

EyesNet shows high classification accuracy in the AREDS dataset and can be used to assign individual patients to AMD risk categories based on the AREDS Simplified Severity Scale. Its superior performance compared to ophthalmologists' clinical examination of AMD highlights the potential of deep learning systems to enhance clinical decision-making processes and allow for better understanding of retinal disease.

Full Length Publications:

- Peng Y*, **Dharssi S***, Chen C, Wong W, Chew E, Lu Z. EyesNet: A deep learning framework for classifying patient-based age-related macular degeneration severity in retinal color fundus photographs. *Ophthalmology*. [Under review]
- Zheng S*, **Dharssi S***, Wu M, Li J, Lu Z. Text mining for drug discovery. [Under review]

*Equal contribution

Abstract Publications:

- **Dharssi S**, Peng Y, Leaman R, Chew E, Lu Z. Discovering drug and retinal disease association patterns from electronic medical records: a text mining approach. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr. 28–May 3, 2018. [Poster presentation]
- **Dharssi S**, Peng Y, Chen C, Wong W, Chew E, Lu Z. A deep learning approach for automated detection and quantification of geographic atrophy from color fundus photographs. American Academy of Ophthalmology, Chicago, IL; Oct. 27–30, 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr. 28–May 3, 2018.
- American Academy of Ophthalmology 2018 Annual Meeting, Chicago, IL; Oct. 27–30, 2018.

Joshua M. Diamond

School: University of Virginia School of Medicine
Mentor: Kareem A. Zaghloul, M.D., Ph.D., Surgical Neurology Branch
Institute: National Institute of Neurological Diseases and Stroke (NINDS)
Research: The Seizure Onset Zone Drives State-dependent Epileptiform Activity in Susceptible Brain Regions

Interictal epileptiform discharges (IEDs) exhibit spatial and temporal variability due to inconsistent patterns of propagation, and also due to changes in brain state, including state of arousal. As such, qualitative definition of the irritative zone has been challenging. Here, we introduce a quantitative approach which creates IED clusters based on probabilistic relationships between brain regions, permitting exploration of the dynamics of IED propagation within the irritative zone.

We examined intracranial EEG (ice) in nine participants undergoing invasive monitoring for seizure localization. We used an automated IED detector and a community detection algorithm to identify populations of electrodes exhibiting IED activity that co-occur in time. This algorithm identifies instances in which IED activity in one electrode is dependent upon IED activity in another, sorting such pairs of functionally coupled electrodes into separate clusters that exhibit strong coupling among their members. Within our algorithmically identified clusters, IED activity in the seizure onset zone (SOZ) tended to lead IED activity in other functionally coupled brain regions. IED rate was also greater during the asleep state, compared to the awake state, within the SOZ as well as in functionally-coupled regions. The strength of coupling within our clusters was dynamic, with coupled brain regions outside of the SOZ showing increased susceptibility to being entrained into pathological activity by the SOZ during sleep. Together, these findings likely contribute to the observed sleep-wake differences in IED rate in clusters which contain the SOZ.

Evaluation of the dynamic coupling within clusters of IED activity provides further evidence that IED activity, and the associated variability observed between the asleep and awake states, is propagated from a core seizure focus to nearby less pathological brain regions, with surrounding brain regions demonstrating state-related changes in susceptibility to involvement in this activity.

Full Length Publications:

- **Diamond JM**, Chapeton JI, Theodore WH, Inati SK, Zaghloul KA. The seizure onset zone drives state-dependent epileptiform activity in susceptible brain regions. *Epilepsia*. [Under review]

Abstract Publications:

- **Diamond JM**, Sreekumar V, Inati SK, Zaghloul KA. Asleep-awake difference in interictal spike rate is predictive of ictal onset in clusters of electrodes. American Epilepsy Society, Washington, DC; Nov. 2017.

Travel to Professional Meetings:

- American Epilepsy Society 71st Annual Meeting, Washington DC; Nov. 30–Dec. 4, 2017.
- Society for Neuroscience 47th Annual Meeting, Washington DC; Nov. 11–15, 2017.
- American Association of Neurological Surgeons 2018 Annual Meeting, New Orleans, LA; Apr. 28–May 2, 2018.

Awards:

- AΩA Carolyn L. Kuckein Student Research Fellowship, 2018–2019.

Youssef A. Elnabawi

School: Tufts University School of Medicine
Mentor: Nehal N. Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases
Institute: National Heart, Lung, Blood Institute (NHLBI)
Research: Effect of Anti-interleukin 17 Therapy on Coronary Plaque Characteristics

Inflammation is critical to the development and progression of atherosclerosis and drives coronary plaque towards a high-risk phenotype. Mitigation of residual inflammation has been shown to add benefit on cardiovascular (CV) risk reduction, independent of lipid-level lowering. We use psoriasis, an inflammatory disease associated with an increased risk of myocardial infarction, as a model to study the impact of anti-inflammatory therapies on coronary artery indices.

Psoriasis patients (n=45) underwent coronary computed-tomography angiography for quantification of plaque index and high-risk plaque features at baseline and one-year. Anti-inflammatory therapy effect was assessed by observing two treatment groups, one receiving interleukin-17 inhibitors and the other receiving TNF inhibitors, and a referent group receiving no biologic therapy.

Study participants were middle-aged (mean [SD] age, 49.7 [11.7] years), mostly male (n= 29, 64%), at low CV risk by Framingham score (median [IQR], 2 [1-6]) with moderate to severe psoriasis (median [IQR] PASI, 8.9 [4.2-17.5]). Over one-year, the anti-IL17 group had a significant reduction in non-calcified plaque index and high-risk plaque characteristics. After adjustment for CV risk factors, treatment with IL17 inhibitors was associated with a reduction in non-calcified plaque index (β=0.27, p=0.01), total atheroma volume (β=0.61, p=0.001), plaque burden (β=0.49, p<0.001), area of stenosis (β=0.62, p=0.001), and diameter of stenosis (β=0.60, p=0.001).

Anti-IL17 therapy was associated with decreases in coronary plaque burden and high-risk plaque prevalence after one-year of psoriasis treatment compared to anti-TNF treated and referent group. Our study provides evidence to perform larger, randomized controlled trials assessing the potential benefits of anti-inflammatory therapy in reducing subclinical CV disease.

Full Length Publications:

- Goyal A, Dey AK, Chaturvedi A, **Elnabawi YA**, Aberra TM, Chung JH, Belur AD, Groenendyk JW, Lerman JB, Rivers JP, Rodante JA, Harrington CL, Varghese NJ, Sanda GE, Baumer Y, Sorokin AV, Teague HL, Genovese LB, Natarajan B, Joshi AJ, Playford MP, Bluemke DA, Chen MY, Alavi A, Pitman RK, Tawakol A, Powell-Wiley TM, Gelfand JM, Mehta NN. Chronic stress-related neural activity associates with subclinical cardiovascular disease in psoriasis – a prospective cohort study. *JACC Cardiovasc Imaging.* [In press]
- Joshi AA, Lerman JB, Dey AK, Belur AD, Sajja AA, **Elnabawi YA**, Rodante JA, Aberra TM, Chung JH, Goyal A, Rivers JP, Salahuddin T, Natarajan B, Dave J, Teague HL, Playford MP, Bluemke DA, Ahlman MA, Chen MY, Gelfand JM, Mehta NN. Association between aortic vascular inflammation and quantitative burden of coronary artery disease. *JAMA Cardiology.* [In press]
- **Elnabawi YA**, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, Genovese, LD, Rodante J, Harrington CL, Teague HL, Baumer Y, Playford MP, Chen MY, Bluemke DA, Gelfand JM, Mehta NN. Effect of anti-interleukin-17 monoclonal antibody therapy on coronary plaque characteristics in psoriasis. *Circulation.* [Under review]
- Sorokin AV, Kotani K, **Elnabawi YA**, Dey AK, Yamada S, Ueda M, Harrington CL, Baumer YA, Rodante J, Gelfand JM, Joshi AJ, Playford MP, Remaley AT, Mehta NN. The association of oxidation-dodified lipoproteins and coronary plaque in psoriasis: an observational cohort study. *JCI Insight.* [Under review]
- Baumer Y, Harrington CL, **Elnabawi YA**, Ng Q, Sanda GE, Teague HL, Sorokin AV, Varghese NJ, Groenendyk JW, Rodante JA, Yu Z, Powell-Wiley TM, Playford MP, Dey AK, Mehta NN. Exploratory characterization of PCSK9 in psoriasis. *J Invest Dermatol.* [Under review]
- Groenendyk JW, Shukla P, **Elnabawi YA**, Dey A, Genovese LD, Harrington CL, Goyal A, Belur A, Rodante J, Playford MP, Bluemke DA, Gelfand HM, Mehta NN. Aortic wall thickness by MRI in psoriasis: A prospective observational study. *Atherosclerosis*. [Under review]

Abstract Publications:

- **Elnabawi YA**, Dey AK, Genovese L, Goyal A, Belur AB, Groenendyk JW, Rodante J, Playford M, Chen MY, Bluemke D, Mehta NN. Immunomodulatory therapy reduces atherosclerotic plaque burden by coronary computed tomography angiography in psoriasis at one-year. Society for Cardiovascular Angiography and Interventions Scientific Sessions, San Diego, CA; Apr. 25–28, 2018. [Podium presentation]
- **Elnabawi YA**, Groenendyk JW, Dey AK, Goyal A, Belur AD, Chung JH, Shukla P, Ahlman MA, Joshi AA, Playford MP, Chen MY, Mehta NN. Aortic wall thickness by MRI is directly related to non-calcified coronary plaque burden by quantitative coronary CT angiography in psoriasis. American Federation for Medical Research Eastern Regional Meeting, Philadelphia, PA; Mar. 16, 2018. [Podium presentation]
- Belur AD, **Elnabawi YA**, Dey AK, Sajja AA, Goyal A, Harrington CL, Groenendyk JW, Teague HL, Baumer Y, Nanda N, Ahlman MA, Joshi AA, Playford MP, Mehta NN. Interleukin-1b is associated with aortic vascular inflammation assessed by 18-FDG PET/CT in patients with psoriasis. American College of Cardiology, Orlando, FL; Mar. 2018. [Podium presentation]
- Goyal A, Aberra TM, **Elnabawi YA**, Dey AK, Chung JH, Belur AD, Groenendyk JW, Chaturvedi A, Lerman JB, Rivers JP, Harrington CL, Varghese N, Sanda GE, Teague HL, Baumer Y., Rodante JA, Ahlman MA, Bluemke DA, Playford MP, Chen MY, Joshi AA, Mehta NN. Amygdala activity assessed by 18-FDG PET/CT is associated with non-calcified coronary plaque burden quantified by coronary CT angiography in psoriasis. American Federation for Medical Research Eastern Regional Meeting, Philadelphia, PA; Mar. 16, 2018. [Podium presentation]
- Dey AK., Playford MP., Joshi AA., Belur AD., Goyal A., **Elnabawi YA**, Groenendyk JW., Chung JH., Rivers JP., Rodante JA., Genovese LD., Sajja AA., Harrington CL., Sanda GE., Varghese NJ., Shukla P., Teague HL., Baumer Y.,

Continued on the Next Page

Remaley AT., Ahlman MA., Mehta NN. Large density HDL particle number by NMR is associated with vascular inflammation by 18-FDG PET/CT at one-year in psoriasis. American Federation for Medical Research Eastern Regional Meeting, Philadelphia, PA; Mar. 16, 2018. [Podium presentation]

- **Elnabawi YA**, Dey AK, Goyal A, Genovese L, Belur A, Groenendyk J, Rodante J, Chen M, Bluemke D, Remaley A, Playford M, Mehta N. Improvement in Large Density HDL Particle Number by NMR is Associated with Reduction in Coronary Soft Plaque Burden by Coronary Computed Tomography Angiography. Atherosclerosis Thrombosis and Vascular Biology, San Francisco, CA; May 10–12, 2018. [Poster presentation]
- **Elnabawi YA**, Dey A.K., Belur A.D., Goyal A., Groenendyk J.W., Chung J.H., Rodante J.A., Joshi A.A., Playford M.P., Bluemke D.A., Chen M.Y., Mehta N.N. Serum Uric Acid Levels are Associated with Subclin2 FA oral, ical Atherosclerosis by Coronary Computed Tomography Angiography Independent of Traditional Cardiovascular Risk Factors in Patients with Psoriasis. American Heart Association EPI Lifestyle Scientific Sessions, New Orleans, LA; Mar. 20–23, 2018. [Poster presentation]

Travel to Professional Meetings:

- American Federation of Medical Research, Northeast Regional Meeting, Philadelphia, PA; Mar. 16, 2018.
- American Heart Association Epidemiology Lifestyle Sessions, New Orleans, LA; Mar. 20–23, 2018.
- Society for Cardiovascular Angiography and Interventions 2018 Scientific Sessions, San Diego, CA; Apr. 25–28, 2018.
- Atherothrombosis and Vascular Biology, Vascular Discovery: From Genes to Medicine 2018, San Francisco, CA; May 10–12, 2018.

Awards:

- American Federation for Medical Research, Medical Scholar Award.
- Society for Cardiovascular Angiography and Interventions, Best of the Best Abstracts.
- Society for Cardiovascular Angiography and Interventions, Moderated Poster Winner.

Joseph Featherall

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Mentor: Pamela Robey, Ph.D., Senior Investigator, Skeletal Biology Section
Institute: National Institute of Dental and Craniofacial Research (NIDCR)
Research: Repair of a Focal Cartilage Defect in a Rodent Model by Implantation of Human Bone Marrow Stromal Cells Attached to Fibrin Microbeads Cross-Linked to Hyaluronic Acid

Despite tremendous global burden, diseases of cartilage loss are without proven disease-modifying therapy. Transplantation of stem or progenitor cells may mitigate the progression of osteoarthritis due to cartilage loss and help heal focal cartilage defects; however, the reliability and magnitude of these effects are, thus far, modest. Constructs of human bone marrow stromal cells (hBMSCs) attached to fibrin micro-beads crosslinked to hyaluronic acid (FMB-HyA) have shown promise for regenerating hyaline-like cartilage *in vivo*; however, this technology is untested in the setting of joint repair procedures. The goal of this study was to characterize the stem and progenitor cell subpopulations that contribute to the regenerative properties of hBMSCs and investigate their use in a rodent model of OA.

Human marrow aspirate samples underwent immunomagnetic depletion of red cells, CD31+ cells, and CD45+ cells, followed by FACS sorting. Enrichment of cells demonstrating pericyte/hBMSC markers was demonstrated, with a CD146+ cell population that contained 21.3% pericyte/hBMSCs cells, a small fraction of osteogenic cells, and contaminating lymphoid and erythroid cells. A CD271+/CD146+ cell population was found to contain 67.2% pericyte/hBMSCs cells, with the remainder being osteogenic cells. Gene set enrichment analysis using Enrichr computational tools identified transcription factors/pathways that were upregulated in these CD146+ subpopulations, including SMAD3 (pericytes), CBFB (pericytes), ATF 2 (cultured hBMSCs), SP1 (cultured hBMSCs), and ILF3 (osteogenic cells).

The SRG rat, an immunodeficient Rag2/IL2Ry double knock-out that lacks B-, T-, and NK-cells, was investigated as a model for osteochondral defect repair with FMB-HyA+hBMSCs. This model proved highly susceptible to opportunistic infection and demonstrated rapid resorption of all FMB-HyA and cellular material within three weeks. Similarly, testing of the athymic RNU rat demonstrated resorption of the repair material and hBMSCs. In contrast, an osteochondral defect repair model using FMB-HyA+hBMSCs constructs developed in the NSG (NOD SCID gamma) mouse demonstrated technical feasibility, animal tolerance, and short term repair integrity.

Abstract Publications:

- **Featherall J**, Kuznetsov SA, Burks S, Hailu-Lazmi A, Cherman N, Fernandez de Castro L, Gehron-Robey P, Gorodetsky R. In vivo formation of stable hyaline cartilage by transplantation of naive human bone marrow stromal cells. World Congress on Osteoarthritis, Liverpool, UK; Apr. 2018.

Travel to Professional Meetings:

- American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, LA; Mar. 6–10, 2018.
- Orthopaedic Research Society Annual Meeting, New Orleans, LA; Mar. 10–13, 2018.
- Osteoarthritis Research Society International World Congress on Osteoarthritis, Liverpool, UK; Apr. 26–29, 2018.

Kathleen E. Fenerty

School: Indiana University School of Medicine
Mentor: James W. Hodge, Ph.D., Senior Investigator, Laboratory of Tumor Immunology and Biology
Institute: National Cancer Institute (NCI)
Research: Immunotherapy Using the Combination of Natural Killer (NK) Cells and Antibody-Dependent Cellular Cytotoxicity (ADCC)-Mediating Agents with PARP Inhibitors

Poly (ADP-ribose) polymerase inhibitors (PARPi) prevent single-stranded DNA repair and are known to have antitumor activity via synthetic lethality in patients with germline BRCA mutations. Olaparib is a PARPi that is FDA-approved for BRCA-mutant ovarian and breast carcinoma. Emerging clinical data suggest a benefit of combining olaparib with immunotherapy in prostate cancer patients both with and without somatic BRCA mutations. We hypothesized that olaparib, when combined with the antibody-dependent cellular cytotoxicity (ADCC)-mediating monoclonal antibodies (mAbs) cetuximab (anti-EGFR) or avelumab (anti-PD-L1), would increase target cell sensitivity to killing by human healthy donor natural killer (NK) cells independently of BRCA status or checkpoint inhibition. We interrogated the immunomodulatory potential of olaparib *in-vitro*, focusing on two prostate carcinoma cell lines. BRCA mutant and BRCA wildtype (WT) prostate carcinoma cell lines were pretreated with olaparib and then exposed to healthy-donor NK cells with or without cetuximab or avelumab. Flow cytometry, NanoString and apoptotic array were performed on tumor cells treated with olaparib to evaluate phenotypic changes. NK-mediated killing was significantly increased in both cell lines, and was further increased using the ADCC-mediating mAbs. Notably, the expression levels of PD-L1 and EGFR did not change with olaparib treatment, but rather TRAIL-R2 was upregulated. We show for the first time that a) olaparib significantly increased tumor cell sensitivity to NK-mediated killing and ADCC in both BRCA wild-type and BRCA deficient prostate carcinoma cells, independent of PD-L1 or EGFR modulation; b) olaparib treatment significantly enhanced NK killing in a variety of tumor types; and c) mechanistically, treatment with olaparib upregulated death receptor TRAIL-R2. These studies support the combined use of NK and ADCC-mediating agents with PARPi in BRCA mutant and WT prostate carcinoma as well as other tumor types.

Abstract Publications:

- **Fenerty KE**, Padget M, Schlom J, Hodge JW. Immunotherapy using the combination of natural killer (NK) cells and antibody-dependent cellular cytotoxicity (ADCC)-mediating agents with PARP inhibitors. American Society of Clinical Oncology Annual Meeting, Chicago, IL; June 2, 2018. [Poster Presentation]

Travel to Professional Meetings:

- American Society of Clinical Oncology Annual Meeting, Chicago, IL; Jun. 1–5, 2018.

Samuel A. Gold

School: SUNY Downstate College of Medicine
Mentor: Peter A. Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch
Institute: National Cancer Institute (NCI)
Research: Neoadjuvant Enzalutamide and Androgen Deprivation Therapy before Robotic-Assisted Radical Prostatectomy for High-Risk Prostate Cancer: Utility of Multiparametric Magnetic Resonance Imaging for Detection of Treatment Response and Surgical Planning

Newer-generation antiandrogen therapies are being increasingly used in pre-operative multimodality treatment regimens for high-risk prostate cancer (PCa). Little is known about the diagnostic accuracy of preoperative MRI in patients undergoing neoadjuvant treatment. We used multiparametric magnetic resonance imaging (mpMRI) to characterize PCa in the setting of antiandrogen and androgen deprivation therapy prior to robotic-assisted radical prostatectomy (RARP).

Prior to RARP, men received six months of enzalutamide and goserelin. mpMRI consisting of T2 weighted (T2W), b=2000 diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) mapping, and dynamic contrast enhancement (DCE) sequences was acquired before and after neoadjuvant therapy. Custom MRI-based prostate molds were printed to directly compare mpMRI findings to H&E whole-mount pathology as part of a phase II clinical trial (NCT02430480).

Twenty men underwent imaging and RARP after a regimen of antiandrogen and androgen deprivation therapy. Prostate and index tumor volumes on mpMRI decreased by 50.7% and 79.8%, respectively, after antiandrogen therapy. Positive predictive values (PPV) for post-treatment mpMRI diagnosis of extraprostatic extension, seminal vesicle invasion, organ-confined disease, and biopsy-confirmed PCa lesions were 71%, 80%, 80%, and 85%, respectively. Post-treatment mpMRI correctly staged 15/20 (75%) cases confirmed by whole-mount H&E pathology. Of those incorrectly staged, four were falsely positive for higher stage features and one was falsely negative. Post-treatment T2W sequences best depicted presence of PCa lesions as compared to DWI and DCE sequences.

mpMRI proved reliable in detecting lesion changes after antiandrogen therapy, and mpMRI findings correlated well with PCa pathology. Therefore, mpMRI evaluation of prostate tumors following neoadjuvant antiandrogen therapy may be helpful in assessing men for surgical candidacy and planning.

Full Length Publications:

- **Gold SA**, Hale GR, Bloom JB, Smith CP, Rayn KN, Valera V, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Follow-up of negative MRI-targeted prostate biopsy: finding the false negatives. *World J Urol.* 2018 May 21. doi: 10.1007/s00345-018-2337-0. [Epub ahead of print]
- Bloom JB, **Gold SA**, Hale GR, Rayn KN, Sabarwal V, Bakhutashvili I, Turkbey B, Pinto PA, Wood BJ. "Super-active surveillance": MRI ultrasound fusion biopsy and ablation for less invasive management of prostate cancer. *Gland Surg* 2018 Apr;7(2):166-187. [Under review]
- **Gold SA**, Hale GR, Rayn KN, Valera V, Bloom JB, Pinto PA. MRI imaging of seminal vesicle invasion in prostate adenocarcinoma. *Prostate Cancer Imaging: An Engineering and Clinical Perspective.* Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.

Abstract Publications:

- **Gold SA**, Mehralivand S, Bloom JB, Harmon S, Hale GR, Rayn KN, Sabarwal V, Marhamati S, Czarniecki M, Smith C, Valera V, Merino M, Turkbey B, Pinto PA. Using multiparametric magnetic resonance imaging and targeted biopsy to rule out seminal vesicle invasion in prostate cancer. American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- **Gold SA**, Marhamati S, Harmon S, Bloom JB, Karzai F, Hale GR, Rayn KN, Sabarwal V, Mehralivand S, Czarniecki M, Smith CP, VanderWeele DJ, Dahut W, Turkbey B, Pinto PA. Neoadjuvant enzalutamide and androgen deprivation in high-risk prostate cancer: initial imaging and surgical findings from a phase II clinical trial. American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- **Gold SA**, Hale GR, Bloom JB, Rayn KN, Baiocco J, Mehralivand S, Valera V, Smith CP, Czarniecki M, Merino M, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Ten-year upgrading rate after prostatectomy in the MRI and fusion biopsy era. American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018. [Poster presentation]
- **Gold SA**, Bloom JB, Hale GR, Rayn KN, Mehralivand S, Wood BJ, Turkbey B, Pinto PA. Ability of multiparametric magnetic resonance imaging to predict prostate tumor heterogeneity on targeted biopsy. American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA; Feb. 8–10, 2018. [Poster presentation]
- Bloom JB, **Gold SA**, Hale GR, Rayn KN, Baiocco J, Mehralivand S, Valera V, Smith CP, Czarniecki M, Wood BJ, Parnes HL, Choyke PL, Turkbey B, Pinto PA. Active surveillance of prostate cancer in African-Americans during the MRI era. American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- Bloom JB, Baiocco J, **Gold SA**, et al. Active surveillance biopsy criteria during the era of prostate MRI and targeted fusion biopsies. American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018. [Poster presentation]
- Bloom J, Shakir N, Passoni N, **Gold S**, Wong D, Hale G, Rayn KN, Baiocco J, Mehralivand S, Romero VV, Merino M, Wood BJ, Choyke BL, Turkbey B, Roehrborn C, Pinto PA. Multi-institutional comparison experience of upgrading rates of standard vs targeted prostate biopsies. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- Mehralivand S, Kolagunda A, Kambhamettu C, Hammerich K, Cobb K, Romero VV, Bloom J, Sabarwal V, **Gold S**, Hale G, Rayn KN, Czarniecki M. Wood BJ, Choyke PL, Turkbey BL, Pinto PA: A multiparametric magnetic

Continued on the Next Page

resonance imaging-based virtual reality surgical aid for robotic-assisted radical prostatectomy. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]

- Shakir NA, Passoni NM, Wong D, **Gold S**, Hale G, Rayn KN, Baiocco J, Bloom J, Valero V, Merino MJ, Turkbey B, Choyke PL, Wood BJ, Pinto PA, Costa D, Roehrborn CG. Correlation of MRI prostate volume with serum prostate-specific antigen in men with negative standard and MRI-fusion biopsies. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- Shakir NA, Passoni NM, Wong D, **Gold S**, Hale G, Rayn KN, Baiocco J, Bloom J, Valero V, Merino MJ, Turkbey B, Choyke PL, Wood BJ, Pinto PA, Costa D, Roehrborn CG: Delineation of prostate cancer from BPH by excess PSA relative to predicted: a study in men undergoing MRI-targeted biopsy. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]
- Shakir NA, Passoni NM, Wong D, **Gold S**, Hale G, Rayn KN, Baiocco J, Bloom J, Valero V, Merino MJ, Turkbey B, Choyke PL, Wood BJ, Pinto PA, Costa D, Roehrborn CG. Increased detection of higher grade prostate cancer with MRI-fusion prostate biopsy at higher PSA. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Podium presentation]

Travel to Professional Meetings:

- American Urologic Association National Meeting, San Francisco, CA; May 18–21, 2018.
- American Society of Clinical Oncology Genitourinary Cancer Symposium, San Francisco, CA; Feb. 8–10, 2018.
- Society of Urologic Oncology Meeting, Washington, DC; Nov. 29–Dec. 1, 2018.

Morgan C. Graves

School: Georgetown University School of Medicine
Mentor: Carlos Zarate, M.D., Chief, Experimental Therapeutics and Pathophysiology Branch
Institute: National Institute of Mental Health (NIMH)
Research: Examining Hippocampal Volume in Major Depressive Disorder and Healthy Control Subjects Following Ketamine Administration using 7T MRI

Structural magnetic resonance imaging (MRI) at 7T was used to determine if changes in hippocampal volume were associated with ketamine infusion in patients with major depressive disorder (MDD). T1 and T2 weighted images were acquired at baseline, and at 1-2 and 10-12 days post infusion in 32 patients with MDD and 22 healthy control subjects enrolled in a double-blind placebo-controlled crossover trial of ketamine 0.5 mg/kg as a single intravenous infusion. Hippocampal subfield volumes were estimated using Freesurfer brain imaging software. Mixed models were used to evaluate 12 subfields plus the total volume to determine group differences at baseline, group differences in the effect of drug, and the effect of drug on hippocampal volume after controlling for baseline volumes. At baseline, the MDD and healthy control groups did not differ in total hippocampal volume or subfield volume. Following ketamine infusion, a decrease in volume of the left presubiculum was seen in MDD patients but not in healthy controls; however, no other significant drug-by-group interactions were observed. Our preliminary analysis indicated there are no significant hippocampal volume differences in MDD subjects versus healthy controls following ketamine. Further studies will investigate if baseline hippocampal volumes predict response to ketamine.

Abstract Publications:

- **Graves MC**, Evans JW, Zarate CA. Examining hippocampal volume in major depressive disorder and healthy control subjects following ketamine administration using 7T MRI. Society of Biological Psychiatry Conference, New York, NY; May 10–12, 2018. [Poster presentation]

Travel to Professional Meetings:

- Society of Biological Psychiatry Conference, New York, NY; May 10–12, 2018.

Jacob W. Groenendyk

School: Washington University School of Medicine
Mentor: Nehal Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research: The Effects of Chronic Inflammation in Psoriasis on Aortic Wall Thickness

Psoriasis, an inflammatory disease associated with increased subclinical atherosclerosis, provides a useful in vivo model for investigating atherogenesis. Aortic wall thickness (AWT) is known to be associated prospectively with cardiovascular events. The effect of modulating skin inflammation in psoriasis on aortic wall thickness is poorly understood. We hypothesized that improvement in skin inflammation with psoriasis-directed biologic therapies would prevent increases in aortic wall thickness.

Consecutive psoriasis patients (n=177) underwent magnetic resonance imaging at baseline and one year. AWT in the descending aorta was measured using dedicated software (Qplaque 1.0, MEDIS). Psoriasis severity was assessed by Psoriasis Area Severity Index Score (PASI). Patients were middle-aged (mean age 50.4 years) with low Framingham risk score (FRS) (median 3.0). Most patients (76%) were overweight or obese, with mean BMI 28.5 (SD 5.5). There was also a high prevalence of hyperlipidemia (42%) and hypertension (23%). Age, FRS, cholesterol efflux capacity (CEC), diabetes, hyperlipidemia, and TNF-α levels were significantly associated with AWT at baseline. At one year, AWT of patients with improved PASI (median -57%) did not increase, with (median, IQR 3.5, 3-3.8 vs 3.4, 3.2-3.8; $p = 0.46$). However, worsening PASI was associated with an increase in aortic wall thickness (3.2, 3-3.5 vs. 3.5, 3.3-3.8; $p = 0.02$). Additionally, median C-reactive protein of the group with decreased psoriasis severity improved at one year (2.39, 0.80-5.25 baseline vs. 1.1, 0.60-3.25 at one year; $p<0.001$), while that of those with increased severity did not change (1.80, 0.87-3.90 vs. 1.80, 0.90-3.70; $p=0.13$)

Significant determinants of AWT in psoriasis include TNF-α levels, CEC, and traditional cardiovascular risk factors. Reducing skin inflammation with psoriasis-directed biologic therapies is associated with cessation of aortic wall thickness progression, suggesting that modulation of skin and/or systemic inflammation may prevent progression of subclinical atherosclerosis. However, larger randomized studies are needed to confirm these findings.

Full Length Publications:

- **Groenendyk JW**, Mehta NN. Applying the ordinal model of atherosclerosis to imaging science: a brief review. Open Heart. 2018 Jul 30;5(2):e000861. doi: 10.1136/openhrt-2018-000861. eCollection 2018. Review. PubMed PMID: 30094037; PubMed Central PMCID: PMC6074639.
- Goyal A, Dey AK, Chaturvedi A, Elnabawi YA, Aberra TM, Chung JH, Belur AD, **Groenendyk JW**, Lerman JB, Rivers JP, Rodante JA, Harrington CL, Varghese NJ, Sanda GE, Baumer Y, Sorokin AV, Teague HL, Genovese LB, Natarajan B, Joshi AJ, Playford MP, Bluemke DA, Chen MY, Alavi A, Pitman RK, Tawakol A, Powell-Wiley TM, Gelfand JM, Mehta NN. Chronic stress-related neural activity associates with subclinical cardiovascular disease in psoriasis – a prospective cohort study. *JACC Cardiovasc Imaging.* [In press]
- **Groenendyk JW**, Shukla P, Elnabawi YA, Dey A, Genovese LD, Harrington CL, Goyal A, Belur A, Rodante J, Playford MP, Bluemke DA, Gelfand HM, Mehta NN. Aortic wall thickness by MRI in psoriasis: A prospective observational study. *Atherosclerosis.* [Under review]
- Elnabawi YA, Dey AK, Goyal A, **Groenendyk JW**, Chung JH, Belur AD, Genovese, LD, Rodante J, Harrington CL, Teague HL, Baumer Y, Playford MP, Chen MY, Bluemke DA, Gelfand JM, Mehta NN. Effect of anti-interleukin-17 monoclonal antibody therapy on coronary plaque characteristics in psoriasis. *Circulation.* [Under review]
- Baumer Y, Harrington CL, Elnabawi YA, Ng Q, Sanda GE, Teague HL, Sorokin AV, Varghese NJ, **Groenendyk JW**, Rodante JA, Yu Z, Powell-Wiley TM, Playford MP, Dey AK, Mehta NN. Exploratory characterization of PCSK9 in psoriasis. *J Invest Dermatol.* [Under review]

Abstract Publications:

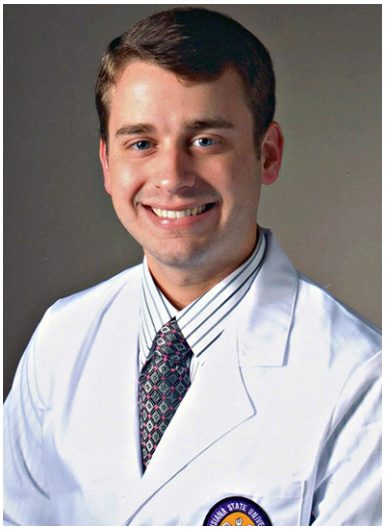
- **Groenendyk J**, Shukla P, Belur A, Dey A, Elnabawi A, Rodante J, Goyal A, Sadek A, Nanda N, Ahlman M, Joshi A, Gelfand J, Playford P, Mehta N. Improvement in skin disease severity is associated with reduced progression of aortic wall thickness in patients with psoriasis. American Federation for Medical Research Eastern Regional Meeting, Philadelphia, PA; Mar. 16, 2018. [Podium presentation]
- **Groenendyk J**, Shukla P, Elnabawi Y, Rivers J, Goyal A, Belur A, Dey A, Sadek A, Nanda N, Rodante J, Ahlman M, Joshi A, Playford M, Yao J, Mehta N. Visceral, but not subcutaneous, adiposity by computed tomography is associated with increased aortic wall thickness in psoriasis patients. American Heart Association Epidemiology Lifestyle Scientific Sessions, New Orleans, LA; Mar. 20–23, 2018. [Poster presentation]

Travel to Professional Meetings:

- American College of Cardiology National Meeting, Orlando, FL; Mar. 10–11, 2018.
- American Heart Association Epidemiology Lifestyle Scientific Sessions, New Orleans, LA; Mar. 22–24, 2018.
- American Foundation for Medical Research Northeast Regional Meeting, Philadelphia, PA; Mar. 16, 2018.

Awards:

- American Federation for Medical Research Scholar Award for Outstanding Abstract.



Russ M. Guidry

School: Louisiana State University Health Sciences Center, New Orleans School of Medicine
Mentor: Brad Wood, M.D., Director, Center for Interventional Oncology
Institute: Clinical Center (CC)
Research: An Image-Based Evaluation of Inferior Vena Cava Filter Implant Healing in a Swine Model: Implications for Performance and Retrievability

With prolonged inferior vena cava filter (IVCF) implantation times in humans, retrieval may become difficult due to neointimal hyperplasia at the implant site. An IVCF implant model which consistently results in an embedded, but retrievable, IVCF within a relatively short period could provide a predictive model for evaluation of filter performance and technology to facilitate retrieval. In this study we define retrieval forces, imaging appearance, and pathologic correlation for IVCF implants in a swine model. Two IVCFs (Gunther Tulip, Cook Medical) were placed sequentially in each swine. Following contrast-enhanced multidetector computed tomography (MDCT) at 15 or 30 days, retrieval of the proximal filter was attempted with measurement of resheathing and withdrawal forces using a force measuring apparatus. Following euthanasia, the inferior vena cava (IVC) was explanted *en bloc* and formalin fixed for microCT and histomorphometrics. The relationship of each filter anchor to the IVC wall on MDCT was graded according to an invasiveness scoring system previously validated and published. This was then compared to the explant microCT and histopathology. We found that filters were retrievable at the upper end of the recommended retrieval force (40 N or 9 lbs) in the 15 day cohort. Thirty-day filters were not retrievable. The mean filter score on MDCT was significantly lower (less invasive) in the 15 day cohort compared to the 30 day cohort (2.5±0.1 vs 2.9±0.1, $p<0.001$), whereas there was no significant difference between scores at 15 and 30 days on microCT (2.4±0.1 vs 2.6±0.1). This study established a 15 day IVCF implant swine model for further study of the consequences of long-term implanted IVC filters. Future work correlating microCT and histomorphometrics of both human and swine IVCF explants will inform the community on IVCF performance and endovascular tissue modelling.

Abstract Publications:

- Karanian J, Seifabadi R, Jones E, **Guidry R**, Krishnasamy V, Esparza-Trujillo J, Bakhutashvili I, Cheng A, Pritchard W, Wood B. Radiographic and pathologic characteristics of IVC filters in a swine model: towards a predictive model for evaluation of filter performance and retrieval technology. Cardiovascular and Interventional Radiological Society of Europe, Lisbon, Portugal; Sept. 22–25, 2018. [Poster presentation]
- Karanian K, Jones E, Bakhutashvili I, **Guidry R**, Esparza-Trujillo J, Seifabadi R, Krishnasamy V, Pritchard W, Wood, B. An image-based evaluation of IVC filter implant healing in a swine model: implications for performance and retrievability. Society for Interventional Radiology, Los Angeles, CA; Mar. 17–22, 2018. [Poster presentation]

Travel to Professional Meetings:

- Society of Interventional Radiology, Los Angeles, CA; Mar. 17–22, 2018.

Awards:

- Society of Interventional Radiology 2018 Student Travel Scholar.

Graham R. Hale

School: Sidney Kimmel Medical College at Thomas Jefferson University
Mentor: Peter Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch
Institute: National Cancer Institute (NCI)
Research: Comparison of Elastic and Rigid Registration during Magnetic Resonance Imaging/Ultrasound Fusion-Guided Prostate Biopsy: A Multi-Operator Phantom Study

The relative value of rigid or elastic registration during Magnetic Resonance Imaging (MRI)/ Ultrasound (US) fusion guided prostate biopsy (FBx) has been poorly studied. The purpose of this was to compare registration error (RE) between rigid and elastic registration during FBx using a prostate phantom model.

Gold fiducial markers (small metal coils or cylinders), visible on MRI and US, were placed in four locations throughout one phantom prostate model. The phantom model underwent MRI and the fiducial markers were labeled as regions of interest (ROIs). Two FBx users with varying degrees of experience (>1000 procedures and <5 procedures) targeted ROIs during FBx and then targeted the corresponding fiducial marker with US alone. The process was repeated using rigid and elastic registration, separately, in random order. REs (distance between ROI and fiducial markers) were compared.

A total of 224 RE measurements were recorded. Overall, elastic registration did not provide significantly improved RE over rigid registration (4.87 ± 3.50 vs 4.11 ± 2.09 mm, p=0.05). However, lesions closer to the phantom's edge experienced increased RE when using elastic registration (5.70 ± 3.43 vs 3.23 ± 1.68 mm, p=0.03). The experienced user reported reduced RE with rigid (3.25 ± 1.49 vs 4.98 ± 2.10 mm, p<0.01) and elastic registration (3.94 ± 2.61 vs 6.07 ± 4.16 mm, p<0.01) compared to the novice user. No differences were seen with different US views (axial vs sagittal).

Our results demonstrate no difference in RE between rigid or elastic registration overall but indicated that rigid registration reduced the RE for targets near the prostate edge. Additionally, operator experience reduces RE, regardless of registration method. The use of elastic registration algorithms cannot act as a replacement for attention to detail to the registration process and use of anatomical landmarks indicating accurate registration at the beginning of the procedure and before targeting each region of interest.

Full Length Publications:

- **Hale GR**, Czarniecki M, Cheng A, Bloom JB, Seifabadi R, Gold SA, Rayn KN, Sabarwal V, Mehrivaland S, Turkbey B, Wood BJ, Pinto PA. Comparison of elastic and rigid registration during magnetic resonance imaging/ultrasound fusion-guided prostate biopsy: A multi-operator phantom study. *J Urol.* 2018 Jun 22. DOI: 10.1016/j.juro.2018.06.028. [Epub ahead of print]
- Bloom JB, Gold SA, **Hale GR**, Rayn KN, Sabarwal V, Bakhutashvili I, Turkbey B, Pinto PA, Wood BJ. Super-active surveillance: MRI ultrasound fusion biopsy and ablation for less invasive management of prostate cancer. *Gland Surgery*. 2018;7(2):166-187.
- Gold SA, **Hale GR**, Bloom JB, Smith CP, Rayn KN, Valera V, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Follow-up of negative MRI-targeted prostate biopsy: finding the false negatives. *World J Urol.* 2018 [Epub ahead of print]
- Rayn KN, Bloom JB, Gold SA, **Hale GR**, Baiocco JA, Merhlivand S, Czarniecki M, Sabarwal VK, Valera V, Wood BJ, Merino MJ, Choyke P, Turkbey B, Pinto PA. Added value of multiparametric magnetic resonance imaging to clinical nomograms in predicting adverse pathology in prostate cancer." *J Urol.* 2018 [Epub ahead of print]
- Gold SA, **Hale GR**, Rayn KN, Valera V, Bloom JB, Pinto PA. MRI imaging of seminal vesicle invasion in prostate adenocarcinoma. *Prostate Cancer Imaging: An Engineering and Clinical Perspective.* Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.

Abstract Publications:

- **Hale GR**, Czarniecki M, Cheng A, Bloom JB, Seifabadi R, Gold SA, Rayn KN, Sabarwal V, Pena-La Grave G, Valera V, Mehrivaland S, Turkbey B, Wood BJ, Pinto PA. Comparison of elastic and rigid registration during magnetic resonance imaging/ultrasound fusion-guided prostate biopsy. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Poster presentation]
- **Hale GR**, Sheng X, Gold SA, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Novel tracked Foley catheter for motion compensation during image guided prostate procedures. American Urologic Association National Meeting, San Francisco, CA; May 2018. [Poster presentation]
- **Hale GR**, Hwang T, Bloom J, Sabarwhal V, Gold S, Rayn KN, Valera V, Turkbey B, Wood B, Pinto P. Are all biopsies created equal? Comparison of extended sextant prostate biopsies performed with and without MRI-TRUS fusion biopsy system. Society of Urologic Oncologists Annual Meeting, Washington DC; Nov. 29–Dec. 1, 2017. [Poster presentation]

Travel to Professional Meetings:

- American Urologic Association Annual Meeting, San Francisco; May 18–21, 2018.
- Society of Urologic Oncology Meeting, Washington, DC; Nov. 29–Dec. 1, 2018.

Awards:

- American Urologic Association Annual Meeting, Best Presentation Award, Technology and Simulation Section, 2018.

Christopher K. Hampton

School: University of Connecticut School of Medicine
Mentor: Kapil Bharti, Ph.D., Stadtman Investigator, Unit on Ocular Stem Cell & Translational Research
Institute: National Eye Institute (NEI)
Research: Engineering Patient-Specific iPSC-derived 3D Retina and RPE on Bioprinted Choroid-like Tissue for Disease Modeling and Drug Discovery

Hypoxia has been reported as a critical driving factor of choroidal neovascularization (CNV) in the wet form of age-related macular degeneration (wet AMD). We induced expression of hypoxia inducible factor 1 alpha (HIF-1α) in iPSC-derived RPE to study the underlying mechanism of CNV initiation/progression using engineered 3D tissues containing RPE and "choroid." We then added iPSC-derived neural retina. This model is being used to understand the pathogenesis of wet AMD and for drug testing.

We developed choroid-like 3D vascularized tissue structures using bioprinting. Optimal "Bioink," which contains endothelial cells (ECs), pericytes, and fibroblasts embedded in hydrogel, was printed on one side of a biodegradable scaffold. iPSC-derived RPE monolayer was formed on the other side. The scaffold served as a temporary Bruch's membrane until RPE and ECs produced extracellular matrix (ECM) proteins. DMOG (100 µM) was added apically to mimic local hypoxia surrounding RPE. Cytokine secretion from RPE, transepithelial/tissue resistance (TER), and angiogenesis of "choroid" were quantified. In parallel, iPSC-derived neural retinas were added over RPE and cultured until photoreceptors matured.

RPE polarity was confirmed by the presence of apical processes and apical EZRIN expression. Fenestration of "choriocapillaris" was confirmed with electron microscopy and expression of a fenestration marker, FELS. DMOG treatment induced secretion of proangiogenic factors, including vascular endothelial growth factor (VEGF), and increased angiogenesis of "choriocapillaris" and vessel growth in the subRPE region, similar to "wet" AMD.

We successfully demonstrate that DMOG induced HIF-1α in RPE causes a type I CNV like vessel growth pattern within RPE/"choroid" tissues. This model shows that increased secretion of VEGF and likely other proangiogenic factors by RPE are critical in directing CNV toward RPE. Interestingly, RPE electrical resistance barrier function is elevated with DMOG treatment, which is presumably a part of the RPE's protective mechanism. Photoreceptors survived for the duration of their culture.

Abstract Publications:

- **Hampton C**, Song MJ, Dejene R, Bose D, Quinn R, Bharti K. Hypoxia of retina pigment epithelium induces type 1 CNV-like morphology within 3D engineered iPSC-RPE/"choroid" tissues. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr., 27–May 3, 2018. [Poster presentation]
- **Hampton C**, Okeagu C, Murphy E, Holmbald M, Whitcomb T, Gross A, Widemann B. Lack of MEK inhibitor induced retinal toxicity in children on AZD6244 treatment for neurofibromatosis type 1 (NF1). American Association for Ophthalmology, Chicago, IL; Oct. 27–30, 2018. [Poster presentation]
- **Hampton C**, Gross A, Okeagu C, Holmblad M, Whitcomb T, Widemann B, Bishop R. Lack of MEK inhibitor induced retinal toxicity in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) treated on a phase II trial with selumetinib (AZD6244, ARRY-142886). Joint Global Neurofibromatosis Conference, Paris, France; Nov. 2–6, 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr. 27–May 3, 2018.

Belen G. Hernandez

School: Colorado State University, College of Veterinary Medicine and Biomedical Sciences
Mentor: R. Mark Simpson, D.V.M., Ph.D., Head, Molecular Pathology Unit, Laboratory of Cancer Biology and Genetics
Institute: National Cancer Institute (NCI)
Research: Whole Exome Sequence Analysis of Naturally Occurring Canine Mucosal Melanoma Reveals Characteristics Analogous to Human Mucosal Melanoma Genomics

Mucosal melanomas (MM), melanomas occurring in mucous membranes, remain a fatal cancer largely unresponsive to treatment. Rare occurrence poses challenges in understanding the disease and the lack of predictive research models further hinders the development of effective treatments. Spontaneously occurring mucosal melanoma in dogs recapitulates the natural progression of human melanoma and therefore represents a valuable preclinical model.

Whole-exome sequences of 24 primary canine MM and matched normal tissues were analyzed to investigate the molecular pathogenesis of MM. Generated sequences were aligned to CanFam 3.1 and compared with published human MM sequences (n=8). Our results indicated that dog and human MM rarely harbor driver mutations in oncogenes such as BRAF-V600E, as in cutaneous melanomas. Few recurrent single nucleotide variants (SNVs) within the same genes were observed in both species. Cytosine to thymine nucleotide transitions, a hallmark of ultraviolet light damage in cutaneous melanoma (80%), occurred in dog and human MM at much lesser frequencies, 25% and 30%, respectively. This relatively minimal rate, comparatively, is consistent with the sun-shielded location of MM.

Contrasting the relative paucity of SNVs, copy number changes were documented throughout the dog genome, as is the case in human MM. The most frequently amplified dog chromosomal regions were on chromosomes 10 and 30; those regions contain genes involved in canonical MAPK and PI3K signaling pathways. Activation of one or both pathways is evident in most canine and human MM tested. Exposure of canine MM cell lines to inhibitors targeting those pathways revealed potential synergistic efficacy, compared to single inhibitor therapy. With no targetable oncogene mutations available in MM, inhibiting multiple signaling pathways essential for tumor growth and survival poses a promising avenue for human MM therapy.

Full Length Publications:

- **Hernandez B**, Adissu HA, Wei BR, Michael HT, Merlino G, Simpson RM. Naturally occurring canine melanoma as a predictive comparative oncology model for human mucosal and other triple wild-type melanomas. *Int J Mol Sci.* 2018 Jan 30;19(2). doi: 10.3390/ijms19020394. [Under review]

Travel to Professional Meetings:

- American College of Veterinary Pathologists Annual Meeting, Vancouver, BC; Nov. 4–8, 2017.

Christopher T. Hogden

School: University of Iowa College of Dentistry and Dental Clinics
Mentor: Eva Mezey, M.D., Ph.D., D.Sci., Senior Investigator; Head, Adult Stem Cell Section
Institute: National Institute of Dental and Craniofacial Research (NIDCR)
Research: Development of Lymphatics in the Mouse Craniofacial Region

Lymphatic vessels maintain tissue fluid homeostasis and transport large molecules, lymphocytes and antigen presenting cells. These vessels are built of a single layer of non-overlapping, terminally differentiated, molecularly distinct cells known as lymphatic endothelial cells (LECs). Previous studies identified four LEC specific makers allowing the study of the exact topography and development of the lymphatic system.

The discovery of the glymphatic system of the brain, lymphatic vessels in the dura mater, and the outflow of cerebrospinal fluid along perineural spaces of cranial nerves led our group to investigate the lymphatic systems in craniofacial areas including the trigeminal nerve. The fifth cranial nerve provides sensory innervation to a large region of the head and neck complex, including the dentition, and motor innervation to various muscles including the muscles of mastication.

To explore the presence of lymphatic vessels in craniofacial regions, C57BL/6J male mice underwent sacrifice-perfusion with fixative at three months. Following removal of the brain, the trigeminal nerve and ganglia were dissected. The tissue was embedded in paraffin and sections were cut for immunocytochemical analysis. Fluorescent immunostaining revealed the presence of podoplanin (PDPN) and lymphatic vessel endothelial hyaluronic receptor 1 (LYVE-1). PDPN was expressed along nerve fibers, in the perineurium, and circumferentially around ganglion cells. T-cells were visualized using the universal T-cell marker CD3 and found traveling among the fibers and between fascicles often localized near PDPN positive structures. The T-cell adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) were also present along the nerve fibers and around a select population of ganglion cells.

The anatomical distribution of these proteins suggests that a unique lymphatic system may exist within peripheral nerve bundles. T-cells might travel in the perineurium and in between neural fascicles allowing for immunosurveillance of this tissue. Experiments to verify the histological data are ongoing.

Tommy Y. Hu

School: Penn State College of Medicine
Mentor: Maximilian Muenke, M.D., Chief, Medical Genetics Branch, Director, NIH Medical Genetics and Genomic Medicine Residency and Fellowship Programs
Institute: National Human Genome Research Institute (NHGRI)
Research: Skeletal and Craniofacial Phenotypes in *PDGFRA* Variants

Platelet derived growth factor receptor alpha (*PDGFRA*) is a receptor tyrosine kinase that binds to four different ligands (platelet derived growth factors A-D) in mammals and plays an important role in embryonic development, cell proliferation, and cell survival. Knockdown of *pdgfra* in mice results in facial clefting, neural tube development abnormalities, and extensive skeletal defects. In humans, the effects of variants in *PDGFRA* remain unknown. We present four patients from three families with missense variants in differing domains of *PDGFRA* and use zebrafish assays to assess the pathogenicity of these variants.

Exome sequencing was used to identify deleterious variants in three families with multiple congenital anomalies. Functional testing of variants was completed in homozygous pdgfra mutant (*pdgfra*^{b1059}) zebrafish, which exhibit impaired trabeculae extension and no ethmoid plate formation in the anterior neurocranium. 150 pg of human mRNA was injected into mutant zebrafish at the 1 to 2-cell stage to rescue the phenotype.

Four individuals from three families with missense variants in *PDGFRA* were evaluated. The phenotypes included craniofacial anomalies, thickened skin, and limb anomalies. Three missense variants were found in these three families, p.K451T, p.E556D and p.S903F. Injection of *pdgfra* mutant zebrafish with wild-type human *PDGFRA* mRNA partially or fully restored the ethmoid plate in 20% (n=6/30) of cases. The p.K451T and p.S903F variants were only able to partially restore the ethmoid plate in 15% (n=2/13) and 21% (n=4/19) of cases, respectively, suggesting that they are loss of function variants of *PDGFRA*. The p.E556D variant, on the other hand, partially or fully restored the ethmoid plate in 27% (n=6/22) of cases, suggesting that it is a gain of function variant.

Based on rare variants found in *PDGFRA* in three families and zebrafish rescue experiments, we show that variants in *PDGFRA* can cause multiple congenital anomalies including craniofacial anomalies.

Full Length Publications:

- Kruszka P, Porras AR, de Souza DH, Moresco A, Huckstadt V, Gill AD, Boyle AP, **Hu T**, Addissie YA, Mok GTK, Tekendo-Ngongang C, Fieggen K, Prijoles EJ, Tanpaiboon P, Honey E, Luk HM, Lo IFM, Thong MK, Muthukumarasamy P, Jones KL, Belhassan K, Ouldim K, El Bouchikhi I, Bouguenouch L, Shukla A, Girisha KM, Sirisena ND, Dissanayake VHW, Paththinige CS, Mishra R, Kisling MS, Ferreira CR, de Herreros MB, Lee NC, Jamuar SS, Lai A, Tan ES, Ying Lim J, Wen-Min CB, Gupta N, Lotz-Esquivel S, Badilla-Porras R, Hussen DF, El Ruby MO, Ashaat EA, Patil SJ, Dowsett L, Eaton A, Innes AM, Shotelersuk V, Badoe Ë, Wonkam A, Obregon MG, Chung BHY, Trubnykova M, La Serna J, Gallardo Jugo BE, Chávez Pastor M, Abarca Barriga HH, Megarbane A, Kozel BA, van Haelst MM, Stevenson RE, Summar M, Adeyemo AA, Morris CA, Moretti-Ferreira D, Linguraru MG, Muenke M. Williams-Beuren syndrome in diverse populations. *Am J Med Genet A.* 2018 May;176(5):1128-1136.
- Hong S, Hu P, Roessler E, **Hu T**, Muenke M. Loss-of-function mutations in FGF8 can be independent risk factors for holoprosencephaly. *Hum Mol Genet.* 2018;27(11):1989-1998.
- **Hu T**, Kruszka P, Martinez AF, Ming JE, Shabason EK, Raam MS, Shaikh TH, Pineda-Alvarez DE, Muenke M. Cytogenetics and holoprosencephaly: A chromosomal microarray study of 222 individuals with holoprosencephaly. *Am J Med Genet C Semin Med Genet.* 2018 [In press]

Abstract Publications:

- **Hu T**, Davis B, Kruszka P, Muenke M. Cornelia de Lange syndrome in diverse populations. National Human Genome Research Institute Symposium, Bethesda, MD; Oct. 26–27, 2017. [Poster presentation]
- **Hu T**, Kruszka P, Sidik A, Bhoj E, Li D, McGowan R, Sutton VR, Gripp E, Martinez A, Tucker SK, Campeau PM, Hong S, Eberhart JK, Muenke M. Skeletal and craniofacial phenotypes in PDGFRA variants. American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, Charlotte, NC; Apr. 10–14, 2018. [Poster presentation]

Travel to Professional Meetings:

- National Human Genome Research Institute Symposium, Bethesda, MD; Oct. 26–27, 2017.
- American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, Charlotte, NC; Apr. 10–14, 2018.

Eileen Hu-Wang

School: Northwestern University Feinberg School of Medicine
Mentor: Marcus Y. Chen, M.D., Director, Cardiovascular Computed Tomography, Advanced Cardiovascular Imaging Laboratory, Cardiovascular Branch
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research: Chest Computed Tomography at Radiation Dose of a Single Chest X-ray: A Proof of Principle in Patients with Lymphangioleiomyomatosis

Given the rising utilization of medical imaging and risks of radiation, there is increased interest in reducing radiation exposure. The potential harms of cumulative radiation exposure with repeated imaging over a lifetime is of particular concern in patients with lymphangioleiomyomatosis (LAM), a rare cystic lung disease diagnosed primarily in young women. LAM severity can be quantified as a Cyst Score (percentage of lung occupied by cysts), an ideal benchmark for validating computed tomography (CT) at chest x-ray doses. The goal of this study was to evaluate in LAM, as a proof of principle, CT scans performed at radiation doses equivalent to that of a single chest x-ray.

We performed a prospective study of 223 subjects with LAM who underwent clinically indicated chest CT scans at standard and ultra-low dose (goal of x-ray equivalent dose). Standard and ultra-low dose images, respectively, used routine iterative and model-based iterative reconstruction. Cyst Scores were quantified using semi-automated software. Main measures were linear correlation and Bland-Altman analysis comparing Cyst Scores measured by ultra-low and standard dose CT.

Nearly all subjects were female (99%). Mean age was 48.2 ± 11.3 years. Overall, ultra-low dose CT scans represented a 93% dose reduction, with median dose equivalent to 4 versus 50 chest x-rays (0.55 mSv [5-95th percentile 0.11-1.6] versus standard 7.5 mSv [2.0-10.0], $p<0.0001$). With the 101 most recent subjects, ultra-low dose represented a 96% reduction to dose of 1 versus 23 chest x-rays (0.13 mSv [0.10-0.21] versus standard 3.4 mSv [1.4-7.3], $p<0.0001$). Mean difference of Cyst Score quantification between ultra-low and standard dose CT was 0.1 ± 2.4 % ($p=0.6$), and the linear correlation coefficient was excellent at 0.96 ($p<0.0001$).

In LAM, chest CT at substantial radiation reduction to doses equivalent to that of a single chest x-ray provides similar Cyst Score quantification as a standard dose CT.

Full Length Publications:

- **Hu-Wang E**, Schuzer JL, Rollison S, Leifer ES, Steveson C, Gopalakrishnan V, Yao J, Machado T, Jones AM, Julien-Williams P, Moss J, Chen MY. Chest computed tomography at radiation dose of a single chest x-ray: a proof of principle in patients with lymphangioleiomyomatosis. [Under review]
- **Hu-Wang E**, Kureshi F, Leifer ES, Acharya T, Sathya B, Yu JH, Groves DW, Bandettini WP, Shanbhag SM, Chen MY. Calcium scoring improves pretest probability estimation of obstructive coronary artery disease in a real world population. [Under review]

Abstract Publications:

- **Hu-Wang E**, Acharya T, Sathya B, Kureshi F, Rollison S, Bronson K, Bandettini P, Shanbhag S, Chen MY. Prevalence of layered testing for coronary artery disease and cost analysis of coronary computed tomography angiography as the initial diagnostic test. American College of Cardiology Scientific Session, Orlando, FL; Mar. 2018. [Poster presentation]
- **Hu-Wang E**, Schuzer JL, Rollison S, Gopalakrishnan V, Machado T, Jones AM, Julien-Williams P, Moss J, Chen MY. Effect of model-based iterative reconstruction in chest computed tomography on lymphangioleiomyomatosis (LAM) cyst score quantification. American Thoracic Society International Conference, San Diego, CA; May 2018. [Poster presentation]
- **Hu-Wang E**, Schuzer JL, Rollison S, Gopalakrishnan V, Machado T, Jones AM, Julien-Williams P, Moss J, Chen MY. Does chest computed tomography body positioning change the cyst score for lymphangioleiomyomatosis (LAM)? American Thoracic Society International Conference, San Diego, CA; May 2018. [Poster presentation]

Travel to Professional Meetings:

- Radiological Society of North America, Chicago, IL; Nov. 26–Dec. 1, 2017.
- American College of Cardiology Scientific Session, Orlando, FL; Mar. 10–12, 2018.
- American Thoracic Society International Conference, San Diego, CA; May 18–23, 2018.

Awards:

- American Thoracic Society International Conference, Winner of the Three Minute Thesis Competition for Student Presentations, San Diego, CA; May 2018.
- American Thoracic Society International Conference, Student Travel Scholarship, San Diego, CA; May 2018.

Sahar Q. Khan

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Mentor: Meredith Shiels, M.H.S., Ph.D., Investigator, Infections and Immunology Branch, Division of Cancer Epidemiology and Genetics
Institute: National Cancer Institute (NCI)
Research: Trends in Infant, Youth, and Young Adult Mortality in the United States by Racial/Ethnic Group and Cause of Death

The United States has higher infant, youth and young adult mortality rates than other high-income countries, with striking disparities amongst some racial/ethnic groups. Understanding the changing trends by age and racial/ethnic group for leading causes of death is imperative for focused intervention. The objective of this study was to estimate trends in U.S. infant, youth, and young adult mortality rates (infancy to age 24) between 1999-2015 by age subgroup and racial/ethnic group, identify leading causes of death, and compare mortality rates with Canada and England/Wales. Our main outcome was the average annual percent change in mortality rates between 1999-2015, and absolute rate change between 1999-2002 and 2012-2015 for each age subgroup and racial/ethnic group, and cause of death. We found that all-cause mortality declined for all age groups in U.S., Canada and England/Wales between 1999-2015; however, rates were highest in the U.S. across all years and age groups. Within the U.S., annual declines occurred in all-cause mortality among all age groups of Blacks, Latinos and Whites, except for 20-24-year-old Whites, whose rates remained stable. Mortality rates declined across most major causes of death from 1999-2002 to 2012-2015, with notable declines observed for SIDS, accidents and homicides. Among infants, we noted increases in accidental suffocation and strangulation in bed (2012-2015 vs. 1999-2002 range: +6.11 to +29.03/100,000). Further, suicide rates among Latino and White 10-24-year-olds (range: +0.21 to +2.63/100,000) and Black 10-19-year-olds (range: +0.10 to +0.45/100,000) increased, as did accidental deaths in White 20-24-year-olds (+0.79/100,000). The rise in accidental deaths is attributed to increases in drug poisonings (+11.7/100,00), also observed among Black and Latino (range: +1.76 to +3.18/100,000) 20-24-year-olds. Mortality rates have generally declined for infant and youth in the U.S. between 1999-2015 due to reductions in SIDS, accidents, and homicide. However, mortality rates remain higher than Canada and England & Wales, and racial/ethnic disparities remain. Further, there is a concerning increase in suicide and drug poisoning death rates among Black, Latino and White adolescents and young adults.

Full Length Publications:

- **Khan SQ**, Berrington de Gonzalez A, Best AF, Chen Y, Haozous EA, Rodriquez E, Spillane S, Thomas D, Withrow D, Freedman ND, Shiels MS. Trends in infant and youth mortality in the United States by racial/ethnic group and cause of death. [Under review]
- Shiels MS, Berrington de Gonzales A, Best AF, Chen Y, Chernyavskiy P, Hartge P, **Khan SQ**, Perez Stable E, Rodriquez E, Spillane S, Thomas D, Withrow D, Freedman ND. Premature mortality from all causes and drug poisonings in the United States according to socioeconomic status and rurality: an analysis of death certificate date by county from 2000-2015. [Under review]

Travel to Professional Meetings:

- American Academy of Emergency Medicine 24th Annual Scientific Assembly; San Diego, CA; Apr. 8–11, 2018.

Alyssa K. Kosturakis

School: Joe and Teresa Lozano Long University of Texas School of Medicine at San Antonio
Mentor: Todd S. Macfarlan, Ph.D., Stadtman Investigator
Institute: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Research: Investigating PRDM9, a Rapidly Evolving Regulator of Genetic Recombination

Unique haploid gametes are formed when parent chromosomes align and engage in reciprocal genetic recombination events known as crossovers. Chromosomal crossovers occur preferentially at 1-2kb regions termed "hotspots". PR/SET domain containing protein 9 (PRDM9) is a KRAB-zinc finger protein that regulates the genome-wide position of hotspots via its DNA binding and methyltransferase activity, which alters chromatin structure and facilitates double strand breaks and crossover. Positive selection pressure on the DNA-binding PRDM9 zinc finger array has resulted in numerous alleles in the human and mouse population, which produce different patterns of hotspots and double strand breaks (DSBs). Little is known about the rules governing PRDM9-DNA binding as well as the downstream mechanisms leading to DSBs and recombination events. We aimed to take advantage of the natural variation of the PRDM9 zinc finger array in mice to explore basic principles of "successful" PRDM9 DNA binding using parallel *in vivo* and *in vitro* approaches. A 3' epitope tag was inserted on the 3' end of *PRDM9* using CRISPR-Cas9 and injected into mouse blastocysts to generate knock-in mice with an epitope tag to map binding of PRDM9 *in-vivo* in testis. PRDM9-binding in epitope-tagged PRDM9 embryonic stem cells (ESCs) was assessed as a potential model for exploring binding *in vitro*. PRDM9-binding of DNA was not detected in ESCs by western blot and chromatin immunoprecipitation assays, presumably secondary to low expression levels in ESCs. ESCs were therefore deemed a poor model to study PRDM9 binding. As an alternate approach, we designed a cloned vector capable of expressing PRDM9 variants in a F9 embryonic carcinoma cell line (previously verified to be biologically relevant) to assess PRDM9 binding *in vitro*. Cloning of the wild type *PRDM9* allele vector was successfully achieved. A strategy for cloning synthesized, codon-optimized, zinc finger arrays from different *PRDM9* allelic variants was also designed.

Abstract Publications:

- Carpinello OJ, **Kosturakis AK**, Hsieh MM, Fitzhugh CD, Tisdale JF, Wolff EF, Plowden TC, Hill MJ, Decherney AH. Post-transplant ovarian function in women with sickle cell disease. American Society for Reproductive Medicine 2018, Denver, CO; Oct. 6–10, 2018.

Jason J. Lau

School: University of Massachusetts Medical School
Mentor: Dina Demner-Fushman, M.D., Ph.D., Staff Scientist; Clement McDonald, M.D., Senior Investigator and Scientific Director, Lister Hill National Center for Biomedical Communications (LHNCBC)
Institute: National Library of Medicine (NLM)
Research: Visual Question Answering in Medicine: A New Dataset in Radiology

Radiology images are an essential part of clinical decision making and population screening, for example, for cancer. Automated systems could help clinicians cope with large amounts of images by answering questions about the image contents. An emerging area of artificial intelligence, Visual Question Answering (VQA) is a computer vision and deep learning problem that aims to answer questions about images. Radiology, with its wealth of images and textual reports, is a prime area where VQA could assist radiologists in reporting findings for a complicated patient or benefit trainees who have questions about the size of a mass or presence of a fracture. Success of such machine learning tools hinges on availability and design of collections composed of medical images augmented with question-answer pairs directed at the content of the image.

We introduce VQA-RAD, a manually constructed VQA dataset in radiology where questions and answers about images are naturally created and validated by clinicians. Trading off quantity of automatic generation, VQA-RAD is a high-quality design with only 60 hours of specialist contributions. Structured like other existing VQA datasets, each question can be answered with a single image alone. The images are a balanced sample from MedPix®, an open-access radiology archive of case reports and teaching cases. These images were presented to clinicians who wrote unguided questions they would ask a colleague or radiologist. To further explore the natural clinical language, clinicians also paraphrased questions in both free-form and templated structures. All question-answer pairs were manually validated and categorized, helping to characterize clinically important areas of focus.

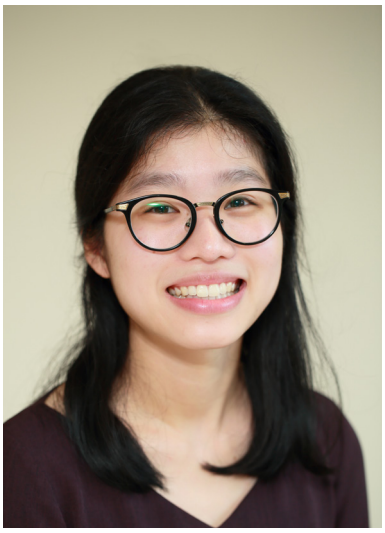
The final VQA-RAD dataset contains 3,515 total visual questions corresponding to 315 radiological images of the head, chest, and abdomen. This is the first manually constructed dataset of visual question-answers pairs of medical images. Our pilot database enables evaluation of artificial intelligence algorithms for clinical image understanding and image related clinical task.

Full Length Publications:

- **Lau JJ**, Gayen S, Ben Abacha A, Demner-Fushmen D. A dataset of clinically generated visual questions and answers about radiology images. *Scientific Data.* [Under review]

Travel to Professional Meetings:

- American Medical Informatics Association Annual Symposium, Washington, DC; Nov. 4–8, 2018.



Michelle M. Lee

School: Sidney Kimmel Medical College at Thomas Jefferson University
Mentor: Carsten G. Bönnemann, M.D., Senior Investigator; Chief, Neuromuscular and Neurogenetic Disorders of Childhood Section
Institute: National Institute of Neurological Disorders and Stroke (NINDS)
Research: PIEZO2 Deficiency Syndrome: Clinical Manifestations and *in vitro* Cellular Modelling

PIEZO2 is a mechanically activated ion channel responsible for light touch sensation and proprioception, the perception of body position and movement. Individuals with rare inactivating mutations in PIEZO2 have profound loss of gentle touch discrimination and display strikingly uncoordinated motor movements. PIEZO2 patients thereby exhibit delays in achieving developmental motor skills, heavily relying on visual compensation. While the clinical phenotype of PIEZO2 loss of function is unique and consistently discernible, our understanding of how PIEZO2 deficiency impacts human peripheral sensory neuron development and physiology is incomplete. We have established a method to produce sensory neurons *in vitro* by forced overexpression of two developmental transcription factors, NGN2 and BRN3A, known to be involved in sensory neuron development. Here, we applied this technique to rapidly generate sensory neurons directly from PIEZO2 patient induced pluripotent stem cells. These induced neurons displayed morphological and biochemical hallmarks of human peripheral sensory neurons through expression of specific neurotrophin receptors, neurofilaments, and transcription factors, including TRKA, TRKB, TRKC, PRPH, NF200, ISL1 and BRN3A. Importantly, we did not observe any differences in the efficiency of differentiation or expression of sensory neuron markers between control and patient neurons. Because the differentiation proved robust across multiple cell lines, we considered this model system well-suited to assess sensory neuron disease phenotypes *in vitro*. When presented with a mechanical stimulus, high amplitude PIEZO2-mediated currents were reliably evoked in 50% of neurons from an unaffected control. However, no responses were detected in patient-derived neurons. Consistent with previous findings, our model system confirms that PIEZO2 is an essential component of human mechanosensation, and may provide a unique opportunity to elucidate the physiological consequences of PIEZO2 loss of function in human sensory neurons.

Abstract Publications:

- Saade D, **Lee M**, Bharucha-Goebel D, Donkervoort S, Neuhaus S, Solomon B, Nickolls AR, Micheil Innes A, Mah JK, Grosmann C, Nascimento A, Munnell F, Haliloglu G, Foley AR, Chesler AT, Bönnemann CG. The distinct clinical phenotype of PIEZO2 loss of function. 2018 Muscular Dystrophy Association Clinical Conference, Arlington, VA; Mar. 13, 2018.
- **Lee M**, Nickolls AR, Szczot M, Ward M, Chesler AT, Bönnemann CG. An in vitro human sensory neuron model of PIEZO2 deficiency. 2018 International Society for Stem Cell Research, Melbourne, Australia; June 21, 2018.
- Nickolls AR, **Lee M**, Szczot M, Espinoza D, Patel R, Ward M, Chesler AT, Bönnemann CG. Rapid conversion of human sensory neurons from pluripotent stem cells. 2018 International Society for Stem Cell Research, Melbourne, Australia; June 22, 2018
- Nickolls AR, Zukosky K, **Lee M**, Bönnemann CG. A 3D model of human embryonic development indicates dispensable nature of dystroglycan in basement membrane assembly. 2018 International Society for Stem Cell Research, Melbourne, Australia; June 22, 2018.
- Saade D, **Lee M**, Bharucha-Goebel D, Donkervoort S, Neuhaus S, Solomon B, Nickolls AR, Micheil Innes A, Mah JK, Grosmann C, Nascimento A, Munnell F, Haliloglu G, Foley AR, Chesler AT, Bönnemann CG. The distinct clinical phenotype of PIEZO2 loss of function. 2018 Peripheral Nerve Society, Baltimore, MD; July 22–25, 2018.

Travel to Professional Meetings:

- Muscular Dystrophy Association Clinical Conference, Arlington, VA; Mar. 11–14, 2018.
- International Society for Stem Cell Research, Melbourne, Australia, June 20–23, 2018.
- Peripheral Nerve Society, Baltimore, MD; July 22–25, 2018.

Andrew G. Lum

School: Tufts University School of Dental Medicine
Mentor: Niki Moutsopoulos, D.D.S., Ph.D., Clinical Investigator, Oral Immunity and Inflammation Unit
Institute: National Institute of Dental and Craniofacial Research (NIDCR)
Research: Fibrin Accumulation in the Oral Mucosa Leads to Severe Periodontal Bone Loss

While fibrin is known to participate in protective physiologic processes such as hemostasis and tissue remodeling, humans with defects in fibrin degradation due to type 1 plasminogen deficiency exhibit excess fibrin accumulation and serious pathologic consequences such as mucosal immunopathology. In the oral cavity, patients with plasminogen defects present with chronic gingival inflammation, destruction of tooth supporting bone, and premature tooth loss. Our project goal was to elucidate mechanisms involved in fibrin-mediated periodontal pathology by investigating periodontal bone loss in mice and characterizing the cellular infiltration in oral mucosal tissues.

For our studies we employed murine models of defective fibrinolysis, as well as models with combined fibrinolysis defects and fibrinogen mutations aimed at rescuing the pathology caused by inadequate fibrin removal. We evaluated the immunopathology of relevant oral lesions of mice by staining for hematoxylin/eosin and Fraser-Lendrum for histologic evaluation, or with monoclonal antibodies against F4/80, CD11b, Mac-1, Ly6G, and fibrin.

We found that all murine models of defective fibrinolysis develop spontaneous and significant periodontal immunopathology (inflammation and bone loss) by 24 weeks of life. Importantly, knocking out or selectively mutating fibrin to a nonfunctional form reversed the phenotype of immunopathology and prevented periodontal bone loss, revealing the critical role of fibrin and specifically fibrin Mac-1 signaling in periodontal immunopathology.

Immunohistochemistry revealed fibrin accumulation in oral lesions of mice with defective fibrinolysis and associated inflammatory infiltrate. Tissue inflammation was dominated primarily by neutrophil and secondarily monocyte infiltration. Furthermore, infiltrating neutrophils were found in close proximity to fibrin deposits, revealing an intimate association with areas of bone destruction. Our ongoing studies are interrogating fibrin-neutrophil interactions and their role in oral inflammatory bone loss.

Abstract Publications:

- **Lum AG**, Silva LM, Dutzan N, Sibree M, Faxel S, Greenwell-Wild T, Castellino FJ, Flick MJ, Bugge TH, Moutsopoulos N. Localized fibrin accumulation in the oral gingiva leads to severe periodontal bone loss. Gordon Research Conference and Seminar on Plasminogen Activation and Extracellular Proteolysis, Ventura, CA; Feb. 10–16, 2018. [Poster presentation]

Travel to Professional Meetings:

- Gordon Research Conference and Seminar on Plasminogen Activation and Extracellular Proteolysis, Ventura, CA; Feb. 10–16, 2018.

Uchenna C. Okoro

School: University of Michigan Medical School
Mentor: Anthony Suffredini, M.D., Deputy Chief, Critical Care Medicine Department
Institute: Clinical Center (CC)
Research: A Rapid Genoproteomic Approach to Identify Species-specific Peptide Markers for *Serratia marcescens* and *Achromobacter xylosoxidans*

Serratia marcescens and *Achromobacter xylosoxidans* are important nosocomial pathogens that are associated with high morbidity and mortality. Rapid identification of infection with these organisms to allow initiation of targeted antimicrobial therapy is important to improve outcomes. However, identification may require 24-72 hours of growth in culture of clinical specimens, followed by phenotypic or mass spectrometric confirmation of the presence of the organisms. We previously developed a culture-free genoproteomic approach to identify bacterial pathogens using liquid chromatography and tandem mass spectrometry (LC-MS/MS) to reliably detect bacteria to the species level. We used this approach to discover peptide markers to characterize *S. marcescens* and *A. xylosoxidans* isolates to the species level.

Core peptidomes were developed through *in-silico* tryptic digestion of 238 and 33 genome assemblies for *S. marcescens* and *A. xylosoxidans*, respectively. For assay development, bacterial isolates underwent rapid tryptic digestion and high-confidence peptides markers were detected using Orbitrap LC-MS/MS. Peptides specific to each organism were identified by lowest common ancestor analysis and then analyzed with protein BLAST to confirm their species specificity. An MRM assay was used to develop rules for positive identification of these species within a blinded validation.

2,498 and 2,709 core peptide candidates were identified for *S. marcescens* and *A. xylosoxidans*. These were then screened based on their relative abundance and transition quality which yielded two optimal peptides for each organism. Among 102 unknown samples, the markers were able to detect *Serratia* with a sensitivity of 100% and specificity of 98.8% and *Achromobacter* with a sensitivity of 91.6% and specificity of 100%.

Unique peptide markers of *S. marcescens* and *A. xylosoxidans* can be identified and detected in bacteria from clinical isolates using a genoproteomic approach. These markers may be used for the basis of a culture-independent LC-MS/MS assay to rapidly identify these important pathogens in primary clinical specimens.

Kristen S. Pan

School: University of Cincinnati College 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: Chiari I Malformation and Basilar Invagination in Fibrous Dysplasia: Prevalence, Mechanisms, and Clinical Implications

Fibrous dysplasia (FD) is a mosaic disorder of benign fibro-osseous lesions, which may be associated with extraskeletal features as part of McCune-Albright syndrome (MAS). Cranial base abnormalities, including Chiari I malformation (CM1), in which the cerebellum extends below the foramen magnum, and secondary basilar invagination (BI), in which the odontoid process prolapses into the posterior cranial fossa, are potentially serious complications of metabolic bone disorders. The purpose of this study was to determine the prevalence, natural history, and risk factors for CM1 and BI in patients with FD/MAS, and to determine mechanisms of cranial base deformities. Clinical and radiographic data from subjects in an FD/MAS natural history study were evaluated and compared to normal controls. In 158 patients with craniofacial FD, 10 (6.3%) cases of CM1 and 12 (7.6%) cases of BI were diagnosed. No cranial base abnormalities were identified in 10 control subjects. Craniomorphometric and volumetric analyses identified cranial constriction and cranial settling as the primary mechanisms of cranial base abnormalities, indicated by decreased foramen magnum length and posterior cranial fossa volume ($p<0.05$) and increased Boogaard angle and odontoid position ($P<0.05$), respectively. Longitudinal analyses found progression of odontoid position with age ($p<0.001$), but no progression of tonsillar position. No endocrinopathies were associated with CM1. MAS endocrinopathies associated with BI included hyperthyroidism (OR = 12.0, 95% confidence interval (CI) = 2.9-55.6; $p<0.01$), precocious puberty (OR = 5.6, 95% CI = 1.2-26.0; $p<0.05$), and hypophosphatemia (OR = 7.7, 95% CI = 1.9-27.0; $p<0.01$). Scoliosis was associated with both CM1 (OR = 4.8, 95% CI = 1.1-22.8; $p<0.05$) and BI (OR = infinity, 95% CI = 4.7- infinity; $p<0.01$). This study is the first to characterize cranial base abnormalities in FD/MAS and evaluate the pathophysiological connection between them. These findings support routine screening for cranial base abnormalities in patients with craniofacial FD, as well as aggressive management of contributory risk factors.

Full Length Publications:

- **Pan KS**, FitzGibbon EJ, Lee JS, Collins MT, Boyce AM. Optical coherence tomography in the management of skull base fibrous dysplasia with optic nerve involvement. *World Neurosurg.* 2018 Jun;114:427-428. [Letter]
- **Pan KS**, Heiss JD, Brown SM, Collins MT, Boyce AM. Chiari I malformation and basilar invagination in fibrous dysplasia: prevalence, mechanisms, and clinical implications. *J Bone Miner Res.* 2018 Jun 20. doi: 10.1002/jbmr.3531 [Epub ahead of print]

Abstract Publications:

- **Pan KS**, Brown SM, Whitaker A, Heiss JD, Collins MT, Boyce AM. Mechanisms, prevalence, and clinical implications of Chiari Malformation type I in craniofacial fibrous dysplasia. The Endocrine Society's 100th Annual Meeting and Expo (ENDO 2018), Chicago, IL; Mar. 16–20, 2018.
- **Pan KS**, FitzGibbon EJ, Lee JS, Collins MT, Boyce AM. Utility of optical coherence tomography in the diagnosis of optic neuropathy in fibrous dysplasia of bone. American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada; Sept. 28–Oct. 1, 2018.
- Florenzano P, **Pan KS**, Brown SM, Guthrie LC, de Castro LF, Collins MT, Boyce AM. Age-related changes and the effect of bisphosphonates on bone turnover and disease progression in fibrous dysplasia of bone. American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada; Sept. 28–Oct. 1, 2018.
- de Castro LF, Burke AB, Wang HD, Tsai J, Florenzano P, **Pan KS**, Bhattacharyya N, Boyce AM, Gafni RI, Molinolo AA, Robey PG, Collins MT. Activation of the RANKL/OPG pathway is central to the pathophysiology of fibrous dysplasia and is associated with disease burden and pain. American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada; Sept. 28–Oct. 1, 2018.

Travel to Professional Meetings:

- 3rd Annual International FD/MAS Consortium Meeting, Leiden, Netherlands; Nov. 15–17, 2017.
- The Endocrine Society's 100th Annual Meeting & Expo (ENDO 2018), Chicago, IL; Mar. 16–20, 2018.
- Fibroblast Growth Factor-23 (FGF23) associated diseases for Latin American endocrinologists, Santiago, Chile; July 1–3, 2018.
- American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada; Sept. 28–Oct. 1, 2018.

Priya K. Patel

School: Jacobs School of Medicine and Biomedical Sciences at University of Buffalo
Mentor: Clint Allen, M.D., Principal Investigator, Translational Tumor Immunology Program, Head and Neck Surgery Branch; Carter Van Waes, M.D., Ph.D., Clinical Director, NIDCD; Chief, Tumor Biology Section, Head and Neck Surgery Branch
Institute: National Institute of Deafness and Communication Disorders (NIDCD)
Research: Rejection of Established Oral Cancers with Wee1 Kinase Inhibition, Ionizing Radiation and Immune Checkpoint Blockade

Ionizing radiation (IR) is an important modality of treatment in head and neck squamous cell carcinoma (HNSCC). IR induces DNA damage that results in G2/M cell cycle checkpoint activation to allow time for DNA repair. Wee1 kinase is a tyrosine kinase master regulator of the G2/M checkpoint through phosphorylation of CDK-1. We hypothesized that Wee1 Kinase inhibition would reverse G2/M cell cycle pause after IR, sensitizing cancer cells to radiation-induced DNA damage and cell death. Treatment of carcinogen-induced HPV-negative mouse oral cancer 1 (MOC1) cells *in vitro* with IR demonstrated dose-dependent G2/M cell cycle pause, with a single dose of 8Gy inducing more G2/M block and greater phosphorylation of yH2AX, a surrogate marker of DNA damage, compared to 2Gy. Physiologically relevant doses of the WEE1 kinase inhibitor AZD1775 (AZD) induced significantly greater levels of DNA damage and loss of tumor cell viability when combined with 8Gy but not 2Gy IR. This effect of AZD + 8GyIR was abrogated in the presence of exogenous nucleosides, implicating replicative catastrophe as a putative mechanism. Treatment of established MOC1 tumors *in vivo* with combination AZD + 8GyIR enhanced tumor growth control over either treatment alone, and resulted in rejection of 10% of established tumors. Furthermore, addition of PD-1 mAb to the *in vivo* regimen of AZD + IR resulted in rejection of 60% of established tumors and significant growth delay in the remaining tumors. In conclusion, while WEE1 kinase inhibition with AZD1775 and 8Gy IR can control MOC1 tumor growth through tumor cell-specific effects, the addition of PD-1 immune checkpoint blockade (ICB) significantly enhances tumor control and leads to rejection of a subset of tumors *in vivo*. Definitive mechanisms of how T-cell killing is enhanced with AZD + IR are currently being explored. Cumulatively, these results provide a pre-clinical rationale for exploring the combined use of IR, WEE1 kinase inhibition, and ICB in HNSCC.

Full Length Publications:

- Xiao R, Allen C T, Tran L, **Patel P**, Park S, Chen Z, Van Waes, C, Schmitt NC. (2018). Antagonist of cIAP1/2 and XIAP enhances anti-tumor immunity when combined with radiation and PD-1 blockade in a syngeneic model of head and neck cancer. *OncoImmunology.* doi: 10.1080/2162402X.2018.1471440. [In Press]

Abstract Publications:

- **Patel P**, Friedman J, Clavijo P, Van Waes C, Mitchell J, Allen CT. Rejection of established oral cancers with Wee1 kinase inhibition, ionizing radiation, and immune checkpoint blockade. International Federation of Head and Neck Oncologic Societies (IFHNOS), Buenos Aires, Argentina; Sept. 1–4, 2018. [Poster presentation]

Grant J. Randall

School: University of Missouri Kansas City School of Medicine
Mentor: Kenneth Kraemer, M.D., Laboratory of Cancer Biology and Genetics
Institute: National Cancer Institute (NCI)
Research: Hematologic Abnormalities in Trichothiodystrophy

Trichothiodystrophy (TTD) is a rare, autosomal recessive disease with mutations in transcription/nucleotide excision repair genes. TTD is associated with multi-system clinical abnormalities and early mortality. We wanted to determine if hematologic abnormalities in TTD patients (neutropenia and hypogammaglobulinemia) were associated with poor outcome. We studied a cohort of 40 TTD patients examined at the NIH from 2001 to 2017. Twenty-five had mutations in XPD (ERCC2), three in TTDA, five in TTDN1, one in GTF2E2, and six unknown. We gathered clinical information from NIH visits using the electronic medical record systems. We assembled 43 laboratory variables. We performed Kaplan Meier survival analysis and hierarchical clustering. Eight of the 25 TTD patients with mutations in XPD died (median survival 15 yr) compared to only one death in the 15 TTD patients with mutations in other genes (median survival 36 yr) (p=0.02). Of the 40 patients in the cohort, 23 had an absolute neutrophil count (ANC) below 1.5 K/uL, 16 had an ANC below 1.0, and 7 had an ANC below 0.5 (normal 1.5 to 7.9 K/uL). Within the group of TTD patients with mutations in XPD, the subgroup with an ANC below 0.5 had a hazard ratio (HR) (logrank) for death of 2.5 and a median survival of 8 yr compared to the other XPD TTD patients with a median survival of 15 yr (p=0.05). Within the total cohort, IgG was low in 12 out of 40 (normal 642-1730 mg/dL). There were five XPD and one unknown mutation patient with IgG below 500 mg/dL however, the IgG supplement status was not known for the entire group. Based on observed early mortality in our cohort, we propose surveillance of TTD patients for neutropenia and hypogammaglobulinemia. Patients with low levels might be considered for prophylaxis with granulocyte growth factors or supplemental immunoglobulins.

Full Lenth Publications:

- **Randall GJ**, Kraemer KH, Pugh J, Tamura D, DiGiovanna JJ, Khan SG, Oetjen KA. Mortality associated abnormalities in trichothiodystrophy: correlation of reduced levels of immunoglobulin and neutrophils with poor patient survival. *Brit J Hematol.* [In press]

Abstract Publications:

- **Randall GJ**, Oetjen KA, J. Pugh J, Khan SG, Tamura D, DiGiovanna JJ, Kraemer KH. Hematologic abnormalities in trichothiodystrophy. Society of Investigative Dermatology, Orlando, FL; May 17, 2018. [Podium presentation]

Travel to Professional Meetings:

- International Investigative Dermatology Meeting, Orlando, FL; May 16–19, 2018.
- American Academy of Dermatology Annual Meeting, San Diego, CA; Feb. 16–20, 2018.

Corinne E. Rauck

School: University of Cincinnati College of Medicine
Mentor: Glenn Merlino, PhD, Senior Investigator, Laboratory of Cancer Biology and Genetics; Head, Cancer Modeling Section, Center for Cancer Research; Scientific Director for Basic Research
Institute: National Cancer Institute (NCI)
Research: Assessing CEACAM1 Blockade as a Therapeutic Strategy using a CRISPR-Cas9-based Mouse Melanoma Model

Immune checkpoint (IC) blockade has become the first-line treatment in malignant melanoma. However, successful remission is limited due to efficacy in only subsets of patients. Different IC molecules and pathways may contribute to the resistance to current IC blockers. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is an IC molecule expressed on activated T cells and tumors. We found that CEACAM1 is highly expressed at both RNA and protein levels in melanomas that develop following neonatal UV exposure in our mutant BRAF mouse model. We hypothesized that CEACAM1 promotes immune evasion and inhibition alone or in combination with PD-1/PD-L1/CTLA-4, and that CEACAM1 blockade could be a novel therapy to treat melanoma. In our preliminary study, CEACAM1 knockout in constitutive CRISPR-Cas9 melanoma cells resulted in growth delay and high lymphocytic infiltration. To avoid the confounding effect of the antigenicity of Cas9, we created inducible Cas9 melanoma cells and injected the CEACAM1 knockout cells with Cas9 turned off into immunocompetent and immunodeficient mice to evaluate the effects of CEACAM1 on melanoma growth and its response to adaptive immunity. Overall, we have validated CEACAM1 expression in a BRAF mutant melanoma model and created CEACAM1 knockout cells for mechanistic studies. Amid current immunotherapies, blockade of CEACAM1 may offer an alternative treatment strategy for advanced melanoma.

Full Lenth Publications:

- Michael H, Graff-Cherry C, Chin S, **Rauck CE**, Habtemichael A, Bunda P, Smith T, Bharti K, Arnheiter H, Merlino G, Day C. Partial rescue of ocular pigment cells and structure by inducible expression of Mitf-M in Mitf-deficient mice. [Under review]

Abstract Publications:

- **Rauck CE**, Perez-Guijarro E, Day CP, Merlino G. Assessing CEACAM1 blockade as a therapeutic strategy using a CRISPR-Cas9-based mouse melanoma model. International Investigative Dermatology Meeting, Orlando, FL; May 16–19, 2018. [Poster presentation]
- **Rauck CE**, Perez-Guijarro E, Ohler ZW, Meskini RE, Yang H, Vodnala S, Graff-Cherry C, Chin S, Fon A, Michael H, Lee M, Dyke TV, Sharan S, Merlino G, Day CP. Developing a preclinical immunotherapy platform using syngeneic mouse models of human melanoma. American Association for Cancer Research Annual Meeting, Chicago, IL; Apr. 14–18, 2018. [Poster presentation]
- Marie K, Michalowski A, Michael H, Guo T, Tsai Y, Weissman A, Yang H, Lee M, Zaidi R, Perez-Guijarro E, Sassano A, Day CP, **Rauck CE**, Kishton R, Arnheiter H, Davis S, Meltzer P, Mishra P, Merlino G. Melanoma cells co-opt hardwired embryonic pathways to facilitate metastasis. Seed and Soil: *In Vivo* Models of Metastasis Meeting, Berlin, Germany; Nov. 27–29, 2017. [Poster presentation]

Travel to Professional Meetings:

- International Investigative Dermatology Meeting, Orlando, FL; May 16–19, 2018.
- American Association for Cancer Research Annual Meeting, Chicago, IL; Apr. 14–18, 2018.
- American Academy of Dermatology Annual Meeting, San Diego, CA; Feb. 16–20, 2018.

Kareem N. Rayn

School: SUNY Downstate College of Medicine
Mentor: Piyush K. Agarwal, M.D., Bladder Cancer Section Head, Urologic Oncology Branch
Institute: National Cancer Institute (NCI)
Research: Characterization of Urinary Bladder Paragangliomas in Patients with Germline Mutations

Data on the genetic characteristics of patients with urinary bladder paragangliomas (UBPGLs) is limited. The goal of this study was to examine the clinical characteristics of a series of patients with UBPGLs, with a focus on their genetic profiles.

We analyzed the medical records of patients who presented to the National Institutes of Health with UBPGLs from 2000 to 2017 to tabulate their presenting symptoms, clinical characteristics and outcomes. Patients were stratified by presence vs absence of metastases and presence vs absence of multiple paragangliomas (PGLs).

Eighteen of 28 patients (64%) with UBPGLs had associated genetic mutations: 15 (54%) in the succinate dehydrogenase subunit B gene (*SDHB*), and 3 (11%) in the von Hippel-Lindau gene (*VHL*). Mean age at onset of symptoms was significantly younger in patients with germline mutations compared to patients without mutations (22.3 ± 2.52 years vs 37.3 ± 5.95 years, p=0.01). Seven patients (39%) with germline mutations developed metastases, at either initial presentation or follow-up, compared to 7 patients (70%) without mutations, p=0.15. Ten patients (59%) with germline mutations had multiple PGLs compared to one patient (11%) without mutations, p=0.02. Patients with germline mutations had a greater mean diameter size of the largest lesion compared to patients without mutations (3.7 ± 2.6 cm vs 3.1 ± 2.2 cm, p=0.51).

Our data suggest that patients with UBPGLs should be screened for underlying germline mutations, since such mutations are frequently present. Patients with UBPGLs and underlying germline mutations are significantly younger than patients without such mutations. Although patients with UBPGLs and underlying mutations are significantly more likely to develop multiple PGLs, we did not observe a statistically significant difference in occurrence of metastases between the two groups. Our data suggest that all patients with UBPGLs should be followed closely for metastatic development.

Full Lenth Publications:

- **Rayn KN**, Hale GR, Grave GP, Agarwal PK. New therapies in nonmuscle invasive bladder cancer treatment. *Indian J Urol.* 2018 Jan-Mar; 34(1): 11-19.
- Sabarwal VK, Ritchie C, **Rayn KN**, Turkbey B, Pinto P. The disappearing PI-RADS 5 prostate lesion: a case report. *Can J Urol.* 2018 Apr; 25(2): 9281-9283.
- **Rayn KN**, Ritchie C, Folio LR, Stamatakis L, Verghesel MM, Agarwal PK. Bilateral ureteroenteric strictures: a case of the "Reverse 7." *Urol.* 2018 May. doi: 10.1016/j.urology.2018.04.022. [Epub ahead of print]
- **Rayn KN**, Bloom JB, Gold SA, Hale GR, Baiocco JA, Mehralivand S, et al. Added value of multiparametric magnetic resonance imaging to clinical nomograms in predicting adverse pathology in prostate cancer. *J Urol.* 2018 May 28. doi: 10.1016/j.juro.2018.05.094. [Epub ahead of print]
- **Gold SA**, **Hale GR**, **Rayn KN**, Valera V, Bloom JB, Pinto PA. MRI imaging of seminal vesicle invasion in prostate adenocarcinoma. *Prostate Cancer Imaging: An Engineering and Clinical Perspective.* Eds. El-Baz A, Pareek G, Suri JS. CRC Taylor and Francis Group, 2018.

Abstract Publications:

- Baiocco J, Pappajohn AK, **Rayn KN**, Boyle SL, Linehan M, Metwalli AR. Repeat multiplex partial nephrectomy in a solitary kidney: the NCI experience with initial and repeat partial nephrectomy for three or more tumors in patients with a solitary kidney. Society of Urologic Oncology National Annual Meeting, Washington DC; Nov. 29–Dec. 1, 2017. [Poster presentation]
- **Rayn KN**, Bloom J, Gold S, Hale GR, Elnabawi YA, Mehralivand S, Wood BJ, Turkbey B, Pinto PA. Prediction of adverse pathology after radical prostatectomy on multiparametric MRI in the Prostate Imaging-Reporting and Data System version 2 (PIRADS v2) era. American Society of Clinical Oncology Genitourinary Cancers Symposium National Annual Meeting, San Francisco, CA; Feb. 8–10, 2018. *J Clin Oncol.* 2018; 36(6 suppl):121. [Poster presentation]
- **Rayn KN**, Gold S, Hale GR, Baiocco J, Bloom J, Valera V, Wood BJ, Turkbey B, Pinto PA. Is BMI a risk factor for active surveillance progression in patients with prostate cancer diagnosed by MRI-TRUS fusion biopsy? American Society of Clinical Oncology Genitourinary Cancers Symposium National Annual Meeting, San Francisco, CA; Feb. 8–10, 2018. *J Clin Oncol.* 2018; 36(6 suppl):124. [Poster presentation]
- **Rayn KN**, Weintraub MD, Pena-LaGrave G, Gold S, Hale GR, Bloom J, Brancato SJ, Agarwal PK. Long-term follow-up of clinical presentation and outcomes of patients with urinary bladder paragangliomas. American Society of Clinical Oncology Genitourinary Cancers Symposium National Annual Meeting, San Francisco, CA; Feb. 8–10, 2018. *J Clin Oncol.* 2018; 36(6 suppl):507. [Poster presentation]
- **Rayn KN**, Weintraub MD, Pena-La Grave GR, Hale GR, Gold S, Bloom J, Brancato SJ, Agarwal PK. Characterization of urinary bladder paragangliomas in patients with germline mutations. American Society of Clinical Oncology Genitourinary Cancers Symposium National Annual Meeting, San Francisco, CA; Feb. 8–10, 2018. *J Clin Oncol.* 2018; 36(6 suppl):508. [Poster presentation]
- Bloom J, Hale GR, **Rayn KN**, Gold S, Baiocco J, Mehralivand S, Romero VV, Smith C, Czarniecki M, Merino M, Wood BJ, Parnes HL, Choyke PL, Turkbey B, Pinto PA. Follow up for patients on active surveillance following a confirmatory prostate MRI-fusion biopsy. American Urologic Association Annual Meeting, San Francisco, CA; May 18–21, 2018. [Poster presentation]

Travel to Professional Meetings:

- Society of Urologic Oncology National Annual Meeting, Washington, DC; Nov. 29–Dec. 1, 2017.
- American Society of Clinical Oncology Genitourinary Cancers Symposium National Annual Meeting, San Francisco, CA; Feb. 8–10, 2018.

Aakash V. Sathappan

School: UC San Diego School of Medicine
Mentor: Sarah H. Lisanby, M.D., Director, Division of Translational Research; Director, Noninvasive Neuromodulation Unit, Experimental Therapeutics and Pathophysiology Branch, Division of Intramural Research Program
Institute: National Institute of Mental Health (NIMH)
Research: Ictal EEG Expression and Relation to Antidepressant Response in Electroconvulsive Therapy and Magnetic Seizure Therapy

Magnetic seizure therapy (MST) is under investigation as an alternative to electroconvulsive therapy (ECT), offering the promise of more focal seizure induction and fewer adverse neurocognitive effects than ECT. The objective of this study was to characterize neurophysiological differences between MST and ECT seizure expression and determine whether patterns of ictal (seizure) EEG expression at the start of treatment were predictive of antidepressant response (>50% reduction in HDRS-24) within each group. A two-center, randomized controlled trial was conducted to contrast the antidepressant efficacy of right unilateral ECT and circular coil MST in treatment-resistant depressive patients. The 24-item Hamilton Depression Rating Scale (HDRS-24) was administered at baseline and after each treatment session. Four channel ictal EEG (Fp1, Fp2, P3, P4) was recorded at each treatment session for ECT (n= 17) and MST (n= 19) patients. Discrete wavelet transformation was performed using 4th order Daubechies wavelet, which decomposed the ictal EEG into 5 frequency bands (delta, theta, alpha, beta, gamma). Nonparametric unpaired permutation testing was performed to compare ictal EEG power. Our results demonstrated that MST and ECT induced differential patterns in ictal EEG expression. Specifically, ECT displayed significantly greater mean ictal power than MST in the theta, alpha, and beta bands over Fp1, Fp2, P4 ($p<0.05$, 50,000 repetitions). During the first treatment session, ECT responders (n=7) had a significantly higher ictal beta and gamma power ($p<0.05$, 50,000 repetitions) compared to ECT non-responders (n=10) over Fp1 and P3; MST responders (n=8) had significantly higher postictal theta power ($p<0.05$, 50,000 repetitions) compared to MST non-responders (n=11) over Fp1 and Fp2. These results corroborate previous findings that ECT induces greater ictal power than MST, particularly in the theta, alpha, and beta frequency bands. Increased ictal beta and gamma power in the ECT group was associated with antidepressant response while increased postictal theta power in the MST group was associated with antidepressant response. While the clinical utility of these findings awaits replication with larger sample size, ictal EEG may provide a potential biomarker of clinical response to seizure therapy.

Abstract Publications:

- **Sathappan A**, De-Deng Z, Lisanby S. Ictal EEG expression and relation to antidepressant response in electroconvulsive therapy and magnetic seizure therapy. Carolina Neurostimulation Conference, Chapel Hill, NC; May 21–23, 2018. [Poster presentation]

Travel to Professional Meetings:

- Carolina Neurostimulation Conference, Chapel Hill, NC; May 21–23, 2018.

Clayton P. Smith

School: Georgetown University School of Medicine
Mentor: Peter L. Choyke, M.D., Director, Molecular Imaging Program
Institute: National Cancer Institute (NCI)
Research: Computer Aided Diagnosis of Prostate Cancer using Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the prostate is an emerging technology that is being increasingly used for the detection, localization, and classification of prostate cancer. However, prostate MRI has limitations including moderate inter-reader agreement and modest sensitivity and specificity. Computer-aided diagnosis (CAD) systems utilize machine learning algorithms to assist radiologists in the interpretation of prostate MRIs. This multi-reader, multi-center study was performed to test an in-house CAD system.

The CAD was designed using intensity and Haralick-based features from prostate MRI. The features were sorted through a Random Forest Classifier to produce regions of interest that populated the MRI. Nine radiologists evaluated 252 total MRIs consisting of a 2:1 case to control ratio in two rounds. The first round was read in a normal clinical scenario without any CAD assistance (MRI Round). After a three-week washout period, radiologists read the same MRIs in a randomized, de-identified format with CAD assistance (CAD + MRI Round). Sensitivity and specificity were calculated for each round of scoring to determine whether CAD provided true assistance to the radiologists.

All lesion sensitivity was 50.8% and 50.7% for MRI Round and CAD + MRI Round, respectively. Index lesion sensitivity was 71.8% and 69.1% for MRI Round and CAD + MRI Round, respectively. Clinically significant cancer (≥ Gleason 3+4=7) sensitivity was 52.8% and 51.6% for MRI Round and CAD + MRI Round, respectively. Patient level specificity was 58.1% and 56.9% for MRI Round and CAD + MRI Round, respectively. All lesion CAD sensitivity (all lesions captured by the CAD, disregarding reader acceptance or rejection) was 79%. Expert experience level readers showed improved sensitivity with the CAD while novice experience readers showed worsened sensitivity with CAD.

Reader sensitivity and specificity for CAD + MRI Round and MRI Round are similar. After further investigation into reader-CAD interaction, prospective CAD research should be carried out to test its effectiveness in real clinical scenarios.

Full Length Publications:

- **Smith CP**, Czarniecki M, Mehralivand S, Stoyanova R, Choyke PL, Harmon S, Turkbey B. Radiomics and radiogenomics of prostate cancer. Abdom Radiol 2018 Jun 20, doi: 10.1007/s00261-018-1660-7. [Epub ahead of print]
- **Smith CP**, Türkbey B. PI-RADS v2: Current standing and future outlook. *Turk J Urol.* 2018;44(3):189-194. [Under review]
- **Smith CP**, Harmon, SA, Barrett T, Bittencourt LK, Law YM, Shebel H, An JY, Czarniecki M, Mehralivand S, Wood BJ, Pinto PA, Shih JH, Choyke PL, Turkbey B. Intra and inter-reader reproducibility of PI-RADSv2: A multi-reader study. *Abdom Radiol.* [Under review]
- An JY, Harmon SA, Mehralivand S, Czarniecki M, **Smith CP**, Peretti JA, Wood BJ, Pinto PA, Choyke PL, Shih J, Turkbey B. Evaluating the size criterion for PI-RADSv2 category 5 upgrade: is 15 mm the best threshold? *Abdom Radiol.* 2018 May 11, doi: 10.1007/s00261-018-1631-z. [Epub ahead of print]
- Lay N, Tsehay Y, Sumathipala Y, Cheng R, Gaur S, **Smith CP**, Barbu A, Lu L, Turkbey B, Choyke PL, Pinto P, Summers RM. A decomposable model for the detection of prostate cancer in multi-parametric MRI. *Med Image Comput Comput Assist Interv.* [In press]

Abstract Publications:

- **Smith CP**, Harmon SA, Mehralivand S, Czarniecki M, An JY, Choyke PL, Wood BJ, Pinto PA, Turkbey B. mpMRI features of PI-RADS 5 lesions with benign histopathology results. Society for Abdominal Radiology Annual Meeting, Scottsdale, AZ; Mar. 4, 2018. [Podium presentation]
- **Smith CP**, Lay N, Harmon SA, Gaur S, Benarova S, Czarniecki M, Mehralivand S, Argun B, Barrett T, Girometti R, Purysko A, Oto A, Choyke PL, Summers RM, Turkbey B. Computer-aided diagnosis (CAD) detected regions overlaid on bi-parametric prostate MRI (bMRI): A pilot study investigating reader-CAD interaction. Society for Abdominal Radiology Annual Meeting, Scottsdale, AZ; Mar. 4–9, 2018. [Poster presentation]
- **Smith CP**, Harmon SA, Barrett T, Bittencourt L, Law YM, Shebel H, Czarniecki M, Wood BJ, Pinto PA, Choyke PL, Turkbey B. A multi-reader investigation of intra and inter-reader repeatability of PI-RADS version 2. Society for Abdominal RadiologyAnnual Meeting, Scottsdale, AZ; Mar. 4–9, 2018. [Poster presentation]
- **Smith CP**, Chaurasia A, Harmon S, Rowe L, Greer MD, Valle L, Choyke P, Citrin DE, Turkbey B. Associations between MRI findings and urinary tract symptoms after IMRT for prostate cancer. 60th Annual Meeting of American Society for Radiation Oncology, San Antonio, TX; Oct. 21–24, 2018. [Poster presentation]
- **Smith CP**, Lay N, Harmon S, Gaur S, Czarniecki M, Mehralivand S, Wood BJ, Pinto P, Choyke PL, Summers R, Turkbey B. Computer-aided diagnosis (CAD) detected regions overlaid on bi-parametric prostate MRI (bMRI): a pilot computer vs. human eye study to investigate the ability to detect prostate cancer. 104th Annual Meeting of the Radiological Society of North America, Chicago, IL; Nov. 25–30, 2018. [Poster presentation]
- **Smith CP**, Harmon S, Coskun M, Bloom J, Czarniecki M, Mehralivand S, Wood BJ, Pinto P, Choyke PL, Turkbey B. Prostate mpMRI index lesion size change and its implications on pathological disease progression among an active surveillance cohort. 104th Annual Meeting of the Radiological Society of North America, Chicago, IL; Nov. 25–30, 2018. [Poster presentation]
- **Smith CP**, Gold SA, Hale G, An JY, Czarniecki M, Harmon S, Mehralivand S, Wood BJ, Pinto P, Choyke PL, Turkbey B. Histopathological correspondence of PI-RADSv2 inter-pulse-sequence score discordances. 104th Annual Meeting of the Radiological Society of North America, Chicago, IL; Nov. 25–30, 2018. [Poster presentation]
- **Smith CP**, Rowe L, Laucis A, Chaurasia A, Czarniecki M, Harmon S, Mehralivand S, Choyke PL, Citrin DE, Turkbey B. Radiologists in the radiation treatment planning room: how increased collaboration between prostate imagers and radiation oncologists fosters best practices in the treatment of prostate cancer. 104th Annual Meeting of the Radiological Society of North America, Chicago, IL; Nov. 25–30, 2018. [Poster presentation]

Continued on the Next Page

- Horn AR, **Smith CP**, Harmon S, Ning H, Pomper G, Schlott EE, Cooley-Zgela T, Choyke P, Mena Gonzalez E, Turkbey B, Citrin DE, Lindenberg L, Rowe L. Evaluating patterns of prostate cancer recurrence on 18F-DCFBC PET/CT imaging in relationship to RTOG consensus post-prostatectomy and pelvic lymph node treatment volumes. 60th Annual Meeting of the American Society for Radiation Oncology, San Antonio, TX; Oct. 21–24, 2018. [Poster presentation]
- Czarniecki M, Harmon SA, Mehralivand S, **Smith CP**, Merino M, Choyke PL, Wood BJ, Pinto PA, Turkbey B. PIRADS category 1 and 2 lesions: impact of discordance between dominant and non-dominant pulse sequence scores on histopathology results. Society for Abdominal Radiology Annual Meeting, Scottsdale, AZ; Mar. 4–9, 2018. [Poster presentation]
- Mehralivand S, Czarniecki M, Harmon SA, **Smith CP**, Bloom J, Gold S, Hale G, Rayn K, Merino M, Wood BJ, Choyke PL, Pinto PA, Turkbey B. Learning curve of prostate imaging-reporting and data system version 2: two-year single-center experience. Society for Abdominal Radiology Annual Meeting, Scottsdale, AZ; Mar. 4–9, 2018. [Poster presentation]

Travel to Professional Meetings:

- American Society for Radiation Oncology, 59th Annual Meeting, San Diego, CA; Sept. 24–27, 2017.
- Society for Abdominal Radiology Annual Meeting, Scottsdale, AZ; Mar. 4–9, 2018.

Dattanand M. Sudarshana

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Mentor: Daniel S. Reich, M.D., Ph.D., Senior Investigator, Translational Neuroradiology Section
Institute: National Institute of Neurological Disorders and Stroke (NINDS)
Research: Manganese-Enhanced MRI (MEMRI) of the Brain in Healthy Volunteers and People with Multiple Sclerosis (MS)

Manganese (Mn) has been used as an MRI contrast agent to study neuronal function in animal models. Mangafodipir (Teslascan®) is a chelated Mn-based contrast agent which is FDA-approved for imaging in humans. Manganese can be taken up into cells and transported along neurons, enabling enhancement of tissues and neural connections. The objective of this study was to use MEMRI with mangafodipir to understand the dynamics and pattern of Mn-related brain enhancement in healthy controls and participants with multiple sclerosis (MS). Healthy and MS participants provided informed consent. Mangafodipir was administered at 1 mL/min for total dose of 5 µmol/kg body weight. Participants completed a baseline history/exam, MRI, and blood work. MRI (3T) was performed at various timepoints, ranging from immediate to one month post-mangafodipir administration.

Nine healthy controls and four relapsing-remitting MS (3 with stable lesions; 1 with active lesion) volunteers underwent mangafodipir infusion. Enhancement of the anterior pituitary and choroid plexus was seen in all participants as early as 30 minutes post administration and persisted for up to one and seven days, respectively. Enhancement of the exocrine glands (parotid, submandibular, sublingual, and lacrimal) was noted as early as one hour post administration and persisted for one month. Active, but not chronic, lesions were noted to have slight enhancement after mangafodipir infusion, likely arising from Mn entry into the lesion. Mangafodipir was well tolerated and did not result in clinically relevant changes in laboratory values.

This study demonstrates that manganese released from mangafodipir is readily taken up in areas of the brain with absent/compromised blood-brain-barrier and in some extracranial structures. Our results suggest that MEMRI with mangafodipir has the potential to provide new and important information about MS lesion biology, and, as such, we are continuing recruitment of both stable and active MS participants.

Abstract Publications:

- **Sudarshana D**, Sati P, Nair G, Absinta M, Reich DS. Manganese-enhanced MRI (MEMRI) of the brain in healthy volunteers. American Society of Neuroradiology 56th Annual Meeting, Vancouver, BC, Canada; June 2–7, 2018. [Podium presentation]

Travel to Professional Meetings:

- American Academy of Neurology 70th Annual Meeting, Los Angeles, CA; Apr. 21–27, 2018.
- American Society of Neuroradiology 56th Annual Meeting, Vancouver, BC, Canada; June 2–7, 2018.

Enock B. Teefe

School: Chicago Medical School at Rosalind Franklin University
Mentor: Karen Faith Berman, M.D., Chief, Clinical and Translational Neuroscience Branch
Institute: National Institute of Mental Health (NIMH)
Research: Chromosomal Locus 7q11.23 Copy Number Variation Impacts White Matter Microstructure as Measured by Magnetic Resonance Imaging using Multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2 Sequences

Williams syndrome (WS) is a rare neurodevelopmental disorder caused by hemizygous deletion resulting in one copy of the 7q11.23 chromosomal locus. Individuals with WS are typically hypersocial, with deficits in visuospatial construction, and relative sparing of language abilities. Another rare neurodevelopmental disorder, 7q11.23 duplication syndrome (Dup7), results in three copies of this same locus. In contrast to the neurobehavioral profile of WS, individuals with Dup7, which has been associated with autism, typically show expressive speech delay and social anxiety but preserved visuospatial abilities. To better understand the neurobiological basis for these 7q11.23-associated clinical features, we used advanced neuroimaging techniques to obtain quantitative measures of brain myelination in individuals with one, two and three copies of this critical genetic region (WS, typical development and Dup7, respectively).

Fifteen children with WS (age 13.3 ± 3.9 years, 11 girls), 11 children with Dup7 (age 13.1 ± 3.4, five girls), and 32 unrelated typically-developing children ([TD], age 13.3 ± 3.7, 15 girls) underwent 3 Tesla MRI scanning using Multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT) sequences. Voxel-wise maps of myelin water fraction (MWF) were calculated for each participant. Multivariate modeling was used to determine regions where MWF was associated with 7q11.23 copy-number ($p<0.05$, FWE-corrected for multiple comparisons).

Nine clusters showed association between MWF and 7q11.23 copy-number (Dup7>TD>WS). These included white-matter underlying bilateral occipito-temporal junction, inferior parietal lobules, orbitofrontal cortex, left superior temporal gyrus and frontal operculum. No associations in the opposite direction were observed.

These results indicate that 7q11.23 copy-number variations alter myelination of brain regions implicated in visuospatial and social processing. These gene-dosage effects build upon our previous findings showing structural changes in the intraparietal sulcus and insula. Taken together, this suggests that dysregulated myelination during brain development may result from 7q11.23 copy-number variations and may play a role in the cognitive and behavioral features of these patients.

Abstract Publications:

- **Teefe EB**, Gregory MD, Kippenhan JS, Nash TA, Currin D, O'Brien MM, Grogans S, Boroshok A, Elliott S, Kuhney F, Eisenberg DP, Mervis CB, Berman KF. 7q11.23 Copy number variation impacts white matter microstructure as measured by mcDESPOT. Society of Biological Psychiatry, New York, NY; May 10–12, 2018. [Poster presentation]
- Gregory MD, Kohn P, Kippenhan JS, **Teefe EB**, Morse J, Mattay VS, Weinberger DR, Callicott JH, Berman KF. Aggregating genetic and brain networks associated with risk for schizophrenia via spectral clustering of working memory activation and PGC2 loci. Society of Biological Psychiatry, New York, NY; May 1, 2018. *Biological Psychiatry,* 83(9), S431. [Poster presentation]

Travel to Professional Meetings:

- Society of Biological Psychiatry, New York, NY; May 10–12, 2018.
- American College of Neuropsychopharmacology, Palm Springs, CA; Dec. 3–7, 2017.
- Society for Neuroscience, Washington, DC; Nov. 11–15, 2017.

Alison M. Treichel

School: Jacobs School of Medicine and Biomedical Sciences at University at Buffalo
Mentor: Joel Moss, M.D., Ph.D., Senior Investigator, Pulmonary Branch; Thomas Darling, M.D., Ph.D., Chair, Department of Dermatology, Uniformed Services University
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research: The Onset and Burden of Skin Tumors in Tuberous Sclerosis Complex Correlates with the Onset and Severity of Lymphangioleiomyomatosis

Tuberous sclerosis complex (TSC) is a genetic syndrome resulting in growth of hamartomatous tumors. Disease severity is highly variable and cannot be reliably predicted by genotype. Our goal was to determine if TSC-associated skin lesions correlate with pulmonary lymphangioleiomyomatosis (LAM). A retrospective analysis was performed on 92 adult women with TSC-LAM. Data recorded were onset age for skin manifestations and LAM symptoms, age at diagnosis, and initial pulmonary function test data (%DLCO and %FEV1). Burden of cysts within the lungs was quantified using a computer-aided diagnostic system to measure percentage of the lungs occupied by cysts (Cyst Score). The burden of cutaneous tumors was quantified using a cutaneous severity scoring system to stratify patients into mild, moderate or severe skin disease. Patients were grouped by onset age for ungual fibroma (UF) (<15, 15-<30, >30 years; N=24, 39, 17). The mean age of LAM diagnosis was earlier in those with earlier UF onset (32.1, 35.0, 43.1 years, p=0.008). Pearson correlation of UF onset age was significant for age of LAM symptom onset (R=0.285, N=58, p=0.030), DLCO (R=0.265, N=66, p=0.032) and nearly significant for FEV1 (R=0.241, N=66, p=0.051). Patients with UF onset <15y were five times more likely to present with a Cyst Score of >20 (OR=5.0, p=0.034). A cutaneous severity scoring system was developed and calculated for 86 of 92 TSC-LAM patients (64 mild, 12 moderate, 10 severe). Patients with severe cutaneous disease were 6.4-fold more likely to present with a FEV1 <70% predicted compared to those with mild or moderate cutaneous disease (OR=6.4, p=0.007). They were also 13.9-fold more likely to present with a DLCO <70% predicted (OR=13.9, p=0.002). Correlations between cutaneous tumors and pulmonary disease suggest similarities in underlying genetic or environmental predisposing factors that confer an overall increased risk for tumor formation.

Full Length Publications:

- Oyerinde O, Buccine D, **Treichel A**, Hong C, Lee CR, Moss J, Darling T. Fibrous cephalic plaques in tuberous sclerosis complex. *J Am Acad Dermatol.* 2018 Apr;78(4):717-724.

Abstract Publications:

- **Treichel A**, Gopalakrishnan V, Steagall WK, Moss J, Darling T. Cutaneous tumors in tuberous sclerosis complex correlate with pulmonary disease severity. International Investigative Dermatology Meeting, Orlando, FL; May 17, 2018. [Poster presentation]
- **Treichel A**, Lee CR, Moss J, Darling T. Histological analysis of fibrous cephalic plaques in tuberous sclerosis complex. The American Society of Dermatopatholoy Annual Meeting, Chicago, IL; Nov. 8-11, 2018. [Accepted for poster presentation]

Travel to Professional Meetings:

- American Academy of Dermatology, San Diego, CA; Feb. 16–20, 2018.
- International Investigative Dermatology Meeting, Orlando, FL; May 16–19, 2018.

Awards:

- Doris Duke Clinical Research Mentorship Award, Aug. 2018–July 2019.

Fernando A. Vazquez

School: Geisel School of Medicine at Dartmouth
Mentor: Andrew J. Mannes, M.D., Chief, Department of Perioperative Medicine
Institute: Clinical Center (CC)
Research: Molecular and Transcriptomic Analyses of Spinal Pain Circuits

Interoceptive and exteroceptive signals, and the corresponding coordinated control of internal organs and mechanical responses to pain, are received and orchestrated by multiple neurons within the peripheral and autonomic nervous systems. The present research examines the molecular interplay of nodose, sympathetic (superior cervical), and dorsal root ganglia and their corresponding spinal connectivity in the rat using next-gen RNA-Seq and immunocytochemistry in order to obtain quantitative and anatomical assessments of signaling pathways and transmitters mediating ganglion-specific functions.

Markedly distinct patterns of expression were observed among the three ganglia, especially for genes related to ion channel function, G-protein coupled receptors (GPCRs) including orphan GPCRs, transporters, neurotransmitters, neuropeptides and associated biosynthetic enzymes. Contrast is also made to sciatic nerve to identify the embedded Schwann cell signature. To evaluate the relationship between expression of a transcript within a whole ganglion and the localization of the corresponding protein, immunocytochemistry was performed on select genes that had high sFPKM values in one of the ganglia and low expression in another. The nodose ganglion contained high levels of the mu opioid receptor and the 5HT3A and 3B receptor subunits, suggesting roles in postoperative- and chemotherapy-induced nausea and vomiting.

The transcriptomic results can also be used to guide drug development efforts and predict potential side effects. For example, the very high levels of TrkA expression in SCG may underlie the unintended effects of nerve growth factor deprivation on the sympathetic nervous system by anti-NGF antibody-based analgesics. The nicotinic acetylcholine receptor subunit α7 has been targeted for analgesic drug development, though our analysis shows α6 is more specifically enriched in sensory ganglia. This initial quantitative comparison provides a data-rich evaluation of peripheral ganglion transcriptomics that has uses in multiple neurobiological and pharmacological contexts.

Abstract Publications:

- Iadarola, MJ, Sapio MR, **Vazquez FA**, LaPaglia DM, Puhl H, Lu V, Ikeda S, Mannes AJ. Molecular composition of nodose, superior cervical, dorsal root ganglia and intermediolateral cell column in rats: an RNA-Seq perspective on sensory cutaneous, visceral, and autonomic function. IASP World Congress on Pain, Boston, MA; Sept. 12–16, 2018.
- **Vazquez FA**, Sapio MR, Iadarola MJ, Mannes AJ. Molecular and transcriptomic analyses of spinal pain circuits. NIH Pain Consortium Symposium, Washington, DC; May 31–June 1, 2018. [Poster presentation]

Travel to Professional Meetings:

- Society for Vascular Surgery Annual Meeting, Boston, MA; June 20-23, 2018.
- Latino Medical Student Association 13th Annual National Conference, Miami, FL; Apr. 13–15, 2018. [Board of Directors]
- National Hispanic Medical Association National Conference, Washington, DC; Mar. 22–25, 2018.
- Latino Medical Student Association 45th Annual Northeast Regional Conference, Philadelphia, PA; Feb. 17, 2018. [Director]
- Neuroscience 2017, Washington, DC; Nov. 11-15, 2017.
- Latino Medical Student Association National Policy Summit, Washington, DC; Oct. 20–22, 2017. [Board of Directors]

Awards:

- Society for Vascular Surgery Annual Meeting, Diversity Medical Student Travel Scholarship, 2018.

Jeannette J. Yu

School: Duke University School of Medicine
Mentor: Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications
Institute: National Eye Institute (NEI)
Research: Natural History and Genetics of Drusenoid Pigment Epithelial Detachments Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2

Age-related macular degeneration (AMD) is the most common cause of vision loss in elderly individuals in industrialized countries. The hallmark of AMD is macular drusen. Drusenoid pigment epithelial detachment (DPED) is a related lesion formed by the confluence of many drusen. DPED has been shown to be an independent risk factor for progression to late AMD in the Age-Related Eye Disease Study (AREDS). The purpose of this study was to investigate the natural history and genetic associations of DPED associated with AMD in the Age-Related Eye Disease Study 2 (AREDS2).

We performed Kaplan-Meier analyses and proportional hazard regressions for progression to late AMD and losing ≥ three lines of visual acuity (VA) for eyes with DPED without late AMD at DPED detection. We also investigated five single nucleotide polymorphisms (SNPs) (CFH [rs10611670], C3 [rs2230199], CFI [rs10033900], C2/CFB [rs114254831], ARMS2 [rs10490924]) and genetic risk score (GRS) group for association with DPED development in AREDS2 participants with DPED and a similar cohort of AREDS.

We found that the presence of DPED was associated with increased risk of progression to late AMD (hazard ratio [HR]=2.38, 95% confidence interval [CI]=1.99-2.84, $p<0.001$); 67% of eyes progressed to late AMD five years after DPED detection. DPED also significantly increased risk of ≥ three lines of VA loss (HR=3.08, CI=2.41-3.93, $p<0.001$); 46% of all eyes, with or without progression to late AMD, experienced vision loss at five years. Finally, while ARMS2 and C3 risk alleles, as well as increasing GRS group, were associated with DPED development, only increasing GRS group (4 vs. 1) (HR=5.21, CI=2.55-10.66, $p<0.001$) remained statistically significant following Bonferroni correction.

Our study replicates the results of previous natural history studies of eyes with DPED, including high rates of progression to late AMD and vision loss. The genetic associations may reflect genes associated with AMD progression.

Full Length Publications:

- **Yu JJ**, Agron E, Clemons TE, Domalpally A, van Asten F, Keenan TD, Cukras C, Chew EY; Age-Related Eye Disease Study 2 (AREDS2 Report No. 17). The natural history and genetics of drusenoid pigment epithelial detachments associated with age-related macular degeneration. Ophthalmology 2018 Aug 21. pii: S0161-6420(18)31752-4. doi: 10.1016/j.ophtha.2018.08.017. [Epub ahead of print]

Abstract Publications:

- **Yu J**, Agron E, Cukras C, Clemons T, Chew E. Clinical course and outcomes of drusenoid pigment epithelial detachment in age-related macular degeneration in AREDS2. Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr. 29–May 3, 2018. [Poster presentation]

Travel to Professional Meetings:

- Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, HI; Apr. 29–May 3, 2018.

Awards:

- Association for Research in Vision and Ophthalmology Annual Meeting, Members-in-Training Outstanding Poster Award in Clinical/Epidemiologic Research, 2018.
- Knights Templar Eye Foundation Travel Grant, Association for Research in Vision and Ophthalmology Annual Meeting, 2018.

Index of Scholars by NIH Institutes and Centers

Clinical Center (CC)

Russ M. Guidry
Louisiana State University Health Sciences Center, New Orleans School of Medicine
Brad Wood, M.D., Director, Center for Interventional Oncology

Uchenna C. Okoro
University of Michigan Medical School
Anthony Suffredini, M.D., Deputy Chief, Critical Care Medicine Department

Fernando A. Vazquez
Geisel School of Medicine at Dartmouth
Andrew J. Mannes, M.D., Chief, Department of Perioperative Medicine

National Cancer Institute (NCI)

Fatima Barragan
Michigan State University College of Human Medicine
Carol J. Thiele, Ph.D., Deputy Chief, Pediatric Oncology Branch

Rebecca O. Breese
University of North Carolina Chapel Hill School of Medicine
Zhengping Zhuang, M.D., Ph.D., Senior Investigator, Neuro-Oncology Branch

Kathleen E. Fenerty
Indiana University School of Medicine
James W. Hodge, Ph.D., Senior Investigator, Laboratory of Tumor Immunology and Biology

Samuel A. Gold
SUNY Downstate College of Medicine
Peter A. Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch

Graham R. Hale
Sidney Kimmel Medical College at Thomas Jefferson University
Peter Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch

Belen G. Hernandez
Colorado State University, College of Veterinary Medicine and Biomedical Sciences
R. Mark Simpson, D.V.M., Ph.D., Head, Molecular Pathology Unit, Laboratory of Cancer Biology and Genetics

Sahar Q. Khan
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Meredith Shiels, M.H.S., Ph.D., Investigator, Infections and Immunology Branch, Division of Cancer Epidemiology and Genetics

Grant J. Randall
University of Missouri Kansas City School of Medicine
Kenneth Kraemer, M.D., Laboratory of Cancer Biology and Genetics

Corinne E. Rauck
University of Cincinnati College of Medicine
Glenn Merlino, Ph.D., Senior Investigator, Laboratory of Cancer Biology and Genetics; Head, Cancer Modeling Section, Center for Cancer Research; Scientific Director for Basic Research

Kareem N. Rayn
SUNY Downstate College of Medicine
Piyush K. Agarwal, M.D., Bladder Cancer Section Head, Urologic Oncology Branch

Clayton P. Smith
Georgetown University School of Medicine
Peter L. Choyke, M.D., Director, Molecular Imaging Program

National Eye Institute (NEI)

Sonny Caplash
University of Connecticut School of Medicine
H. Nida Sen, M.D., Director, Uveitis and Ocular Immunology Fellowship Program

Katherine G. Chen
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
Catherine Cukras, M.D., Ph.D., Staff Clinician, Division of Epidemiology and Clinical Applications

Shazia Dharssi
Johns Hopkins University School of Medicine
Zhiyong Lu, Ph.D., Senior Investigator, Biomedical Text Mining Group, National Center for Biotechnology Information, National Library of Medicine
Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications

Christopher K. Hampton
University of Connecticut School of Medicine
Kapil Bharti, Ph.D., Stadtman Investigator, Unit on Ocular Stem Cell & Translational Research

Jeannette J. Yu
Duke University School of Medicine
Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications

National Human Genome Research Institute (NHGRI)

Tommy Y. Hu
Penn State College of Medicine
Maximilian Muenke, M.D., Chief, Medical Genetics Branch; Director, NIH Medical Genetics and Genomic Medicine Residency and Fellowship Programs

National Heart, Lung, and Blood Institute (NHLBI)

Sophie E. Claudel
Wake Forest School of Medicine
Tiffany M. Powell-Wiley, M.D., M.P.H., Chief of the Social Determinants of Obesity & Cardiovascular Risk Laboratory, Cardiovascular & Pulmonary Branch

Youssef A. Elnabawi
Tufts University School of Medicine
Nehal N. Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases

Jacob W. Groenendyk
Washington University School of Medicine
Nehal Mehta, M.D., M.S.C.E., Chief, Section of Inflammation and Cardiometabolic Diseases

Eileen Hu-Wang
Northwestern University Feinberg School of Medicine
Marcus Y. Chen, M.D., Director, Cardiovascular Computed Tomography, Advanced Cardiovascular Imaging Laboratory, Cardiovascular Branch

Alison M. Treichel
Jacobs School of Medicine and Biomedical Sciences at University at Buffalo
Joel Moss, M.D., Ph.D., Senior Investigator, Pulmonary Branch
Thomas Darling, M.D., Ph.D., Chair, Department of Dermatology, Uniformed Services University

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Mairead R. Baker
Loyola University Stritch School of Medicine
Isaac Brownell, M.D., Ph.D., Investigator, Dermatology Branch

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

Shavonne M. Collins
Meharry Medical College
Jack A. Yanovski, M.D., Ph.D., Section on Growth and Obesity

Alyssa K. Kosturakis
Joe and Teresa Lozano Long University of Texas School of Medicine at San Antonio
Todd S. Macfarlan, Ph.D., Stadtman Investigator

National Institute on Deafness and Other Communication Disorders (NIDCD)

Priya K. Patel
Jacobs School of Medicine and Biomedical Sciences at University of Buffalo
Clint Allen, M.D., Principal Investigator, Translational Tumor Immunology Program, Head and Neck Surgery Branch
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)

Joseph Featherall
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Pamela Robey, Ph.D., Senior Investigator, Skeletal Biology Section

Christopher T. Hogden
University of Iowa College of Dentistry and Dental Clinics
Eva Mezey, M.D., Ph.D., D.Sci., Senior Investigator; Head, Adult Stem Cell Section

Andrew G. Lum
Tufts University School of Dental Medicine
Niki Moutsopoulos, D.D.S., Ph.D., Clinical Investigator, Oral Immunity and Inflammation Unit

Kristen S. Pan
University of Cincinnati College of Medicine
Michael T. Collins, M.D., Chief, Skeletal Disorders and Mineral Homeostasis Section

National Institute of Mental Health (NIMH)

Morgan C. Graves
Georgetown University School of Medicine
Carlos Zarate, M.D., Chief, Experimental Therapeutics and Pathophysiology Branch

Aakash V. Sathappan
UC San Diego School of Medicine
Sarah H. Lisanby, M.D., Director, Division of Translational Research; Director, Noninvasive Neuromodulation Unit, Experimental Therapeutics and Pathophysiology Branch, Division of Intramural Research Program

Enock B. Teefe
Chicago Medical School at Rosalind Franklin University
Karen Faith Berman, M.D., Chief, Clinical and Translational Neuroscience Branch

National Institute on Minority Health and Health Disparities (NIMHD)

Jennifer E. Bayly
Rutgers Robert Wood Johnson Medical School
Kelvin Choi, Ph.D., M.P.H., Stadtman Investigator, Social and Behavioral Group

National Institute of Neurological Disorders and Stroke (NINDS)

Jacqueline N. Boyle
University of Illinois College of Medicine at Peoria
Prashant Chittiboina, M.D., M.P.H., Assistant Clinical Investigator, Surgical Neurology Branch

Joshua M. Diamond
University of Virginia School of Medicine
Kareem A. Zaghloul, M.D., Ph.D., Surgical Neurology Branch

Michelle M. Lee
Sidney Kimmel Medical College at Thomas Jefferson University
Carsten G. Bönnemann, M.D., Senior Investigator; Chief, Neuromuscular and Neurogenetic Disorders of Childhood Section

Dattanand M. Sudarshana
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Daniel S. Reich, M.D., Ph.D., Senior Investigator, Translational Neuroradiology Section

National Library of Medicine (NLM)

Shazia Dharssi
Johns Hopkins University School of Medicine
Zhiyong Lu, Ph.D., Senior Investigator, Biomedical Text Mining Group, National Center for Biotechnology Information, National Library of Medicine
Emily Y. Chew, M.D., Deputy Clinical Director, National Eye Institute; Director, Division of Epidemiology and Clinical Applications

Jason J. Lau
University of Massachusetts Medical School
Dina Demner-Fushman, M.D., Ph.D., Staff Scientist
Clement McDonald, M.D., Senior Investigator and Scientific Director, Lister Hill National Center for Biomedical Communications

The Foundation for the National Institutes of Health (FNIH) procures funding and manages alliances with public and private institutions in support of the mission of the National Institutes of Health (NIH), the premier medical research agency. The Foundation, also known as the FNIH, works with its partners to accelerate biomedical research and strategies to fight against diseases in the United States and across the world. The FNIH organizes and administers research programs; supports education and training of new researchers; organizes educational events and symposia; and administers a series of funds supporting a wide range of health challenges.

The FNIH was established by Congress in 1990 as a not-for-profit 501(c)(3) charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the NIH and worldwide. As an independent organization, it raises private funds and creates public private partnerships to support the mission of the NIH—making important discoveries that improve health and save lives.

Since 2012, the FNIH has raised more than $5.2 million for the MRSP from the following donors:

Alexandria Real Estate Equities, Inc.
American Association for Dental Research*
William and Buffy Cafritz Foundation*
Colgate-Palmolive Company*
Doris Duke Charitable Foundation*
Genentech, Inc.*
The Leona M. and Harry B. Helmsley Charitable Trust
Howard Hughes Medical Institute
Newport Foundation, Inc.
Pfizer Inc
Alumni of student research programs and other individual supporters*

***2017-2018 MRSP Donors**