NIH MEDICAL RESEARCH SCHOLARS PROGRAM (MRSP)

2020-2021 Research Compendium

NIH National Institutes of Health

Turning Discovery into Health

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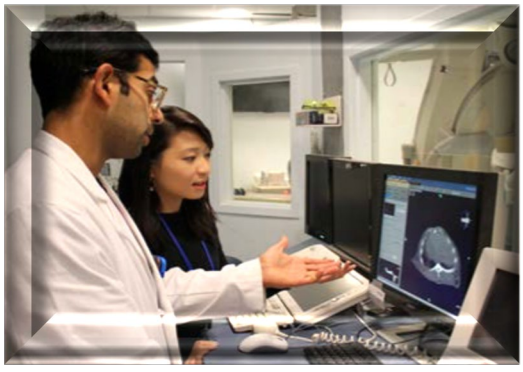


"The future promises remarkable advances in biomedical research. To attain that goal, we need broad, transformative training for clinician scientists. It is time to invest boldly in new ways of learning so that the next generation of innovative thinkers can open new frontiers in knowledge and transform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

Francis S. Collins, M.D., Ph.D.
National Institutes of Health Director

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.

The National Institutes of Health (NIH) Clinical Center's Office of Clinical Research Training and Medical Education is pleased to present the 2020-2021 Medical Research Scholars Program Research Compendium.

The 2020-2021 Class of MRSP Scholars reflects a rich diversity of backgrounds and interests. Composed of 51 students from 42 different schools in 19 states, the District of Columbia, and Puerto Rico, the class composition is 61% female and 29% underrepresented minorities. Second year students comprise 14% of the cohort, with the remainder 3rd year students; 48 of the scholars are in medical school, with one each in dental and veterinary school.

A unique challenge faced by the Class was the SARS-CoV-2 pandemic. In response to the national public health emergency, NIH leadership imposed preventative measures by minimizing physical staffing in research laboratories and suspending all in-person seminars and conferences. However, as this compendium illustrates, the overall quantity and quality of the research achievements by the MRSP scholars remained exceptional and on par with previous MRSP classes. Additionally, by shifting the research symposium, curriculum seminars, and journal clubs to virtual platforms, the MRSP curriculum successfully continued without interruption.

About the NIH Medical Research Scholars Program

The NIH's mission is to strengthen our nation's research capacity, broaden our research base and inspire a passion for science in current and future generations of clinician-scientists. Recognizing that successful biomedical research depends on the talent and dedication of the scientific workforce, the NIH supports MRSP and other innovative training programs that foster scientific creativity and exploration. MRSP is a 12-month residential research immersion program in which scholars engage in mentored basic, clinical, or translational research projects that match their professional interests and career goals.

The MRSP is distinguished from other training programs by the scholars' unique access to the full continuum of NIH biomedical research—the bench, the bedside, and beyond—from crystallography to molecular biology, from computational biology to clinical trials and epidemiology. The MRSP scholars join laboratories and clinical research facilities that are among the most extensive and highly regarded in the world, with access to the NIH's 27 intramural Institutes and Centers, NIH lectures and tutorials, and teaching rounds at the NIH Clinical Center, America's Research Hospital. Scholars spend the majority of time in their research laboratories, under the mentorship of a fulltime NIH investigator whom they select, and also participate in a complementary curriculum of professional development and leadership opportunities.

The MRSP academic curriculum offers:

- A "Process of Discovery" seminar series on basic, translational and clinical research topics that highlight the continuum of discovery, including issues in bioethics, science policy and emerging technologies. This provides scholars with opportunities to meet and interact with NIH leaders (institute directors, scientific and clinical directors) and established investigators from leading national academic medical centers and universities.
- Participation in mentored Journal Clubs
- MRSP Clinical Teaching Rounds focusing on the patient population participating in clinical protocols at the NIH Clinical Center
- "Great Teachers" colloquia, small group sessions with nationally renowned clinician-scientists who are invited to the NIH as part of the Clinical Center Grand Round series.
- Workshops in CV writing, interviewing, and professional development

History of the Medical Research Scholars Program

The Class of 2020-2021 is the 9th MRSP Class since inception. 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. Since 2012, MRSP has supported 419 scholars in pursuing basic, translational, and clinical research.

Support

Support for the MRSP occurs through a public-private partnership, supported by the NIH and private donations procured by the Foundation for the National Institutes of Health (FNIH).

The Shared Resources Subcommittee (SRS) of the NIH Board of Scientific Directors funds the MRSP as a signature program in the NIH's mission of training future clinician-scientists. The MRSP also works in partnership with the National Institute of General Medical Sciences (NIGMS) to fund students from NIGMS Institutional Development Award (IDeA) states and commonwealths, to promote scientific careers in those states.

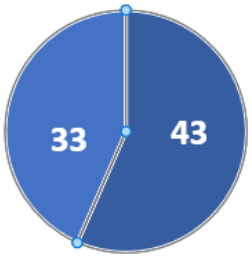
The FNIH was established by Congress in 1990 as a not-for-profit 501(c)(3) charitable organization. As an independent organization, it raises private funds and creates public private partnerships to support the mission of the NIH—making important discoveries that improve health and save lives. Generous support for the NIH Medical Research Scholars Program was received through the FNIH from the Doris Duke Charitable Foundation, the American Association for Dental Research, the Colgate-Palmolive Company, and other private donors.

Research Achievements and Scholarly Output

MRSP Class of 2020-2021

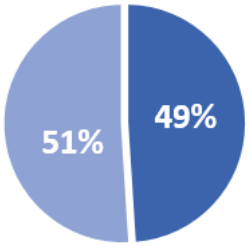
During the 2020-2021 MRSP year, the scholars celebrated many research accomplishments, as shown by the number of manuscripts they produced (Graph 1); the number of scholars who were first authors on these manuscripts (Graph 2); the number of scholars who presented at professional meetings (Graph 3); and the number of scholars who attended virtual professional meetings (Graph 4). Specifically, 35 scholars (69%) produced a total of 76 manuscripts for peer-reviewed publication; 43 scholars (84%) attended 83 professional meetings where they presented a total of 71 abstracts; and 9 scholars (18%) received awards for outstanding research achievement. Four scholars were accepted into NIH PhD Partnership Programs: three will pursue doctoral degrees in the NIH Oxford-Cambridge Scholars Program and one will pursue doctoral research at Rutgers New Jersey Medical School. Three additional scholars were invited to spend a second year at NIH as an intramural research training awardee (IRTA).

Graph 1. Completion of 76 MRSP Manuscripts



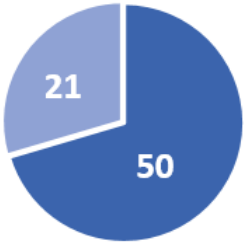
- Published or in press in peer-reviewed journals
- Under review

Graph 2. Authorship of MRSP Publications



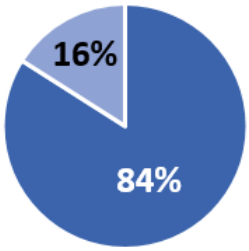
- Scholars were first author (37/76)
- Scholars were second author or more

Graph 3. Presentations at Scholarly Meetings
n=71 total abstracts



- Poster presentations (first author, 64%)
- Podium presentations (first author, 76%)

Graph 4. Attendance at Professional Meetings



- Scholars who attended (43/51)
- Scholars who did not attend

MRSP publications, awards and honors, as of August 2021

In Print or In Press

1. **Acree R**, Miller CM, Abel BS, Neary NM, Campbell K, Nieman LK. Patient and provider perspectives on post-surgical recovery of Cushing's syndrome. *J Endocrine Society*. 2021 June 14, https://doi.org/10.1210/jendso/bvab109
2. Shoucri S, Purpura L, DeLaurentis C, **Adan MA**, Theodore D, Irace A, Robbins-Juarez S, Khedagi A, Letchford D, Harb A, Zerihun L, Lee K, Gambina K, Lauring M, Chen N, Sperring C, Mehta S, Myers E, Shih H, Argenziano M, Bruce S, Slater C. Characterizing the long-term clinical outcomes of 1190 hospitalized patients with Coronavirus Disease 2019 in New York City: a retrospective case series. *BMJ Open*. 2021 June;11(6):e049488.
3. Alter K, Cipriano K, Astrow J, **Banerjee R**. Cervical dystonia. *PM&R KnowledgeNOW*. [In press]
4. **Bryant JP**, Heiss JD, Banasavadi-Siddegowda YK. Arginine methylation in brain tumors: tumor biology and therapeutic strategies. *Cells*. 2021, 10(1), 124. doi: 10.3390/cells10010124.
5. **Bryant JP**, Perez-Roman RJ, Burks SS, Wang MY. Antiresorptive and anabolic medications used in the perioperative period of patients with osteoporosis undergoing spine surgery: its impact on the biology of fusion and systematic review of the literature. *Neurosurg Focus*. 2021 Jun 1; 50(6): E13. doi: 10.3171/2021.3.FOCUS201049.
6. **Bryant JP**, **Nwokoye DI**, Cox MF, Mbabuike NS. The progression of diversity: Black women in neurosurgery. *Neurosurg Focus*. 2021 Mar 1;50(3): E9. doi: 10.3171/2020.12.FOCUS20945.
7. **Bryant JP**, Levy A, Heiss JD, Banasavadi-Siddegowda YK. Review of PP2A tumor biology and anti-tumor effects of PP2A inhibitor LB100 in the nervous system. *Cancers*. 2021, 13(12), 3087; doi: 10.3390/cancers13123087.
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10. Mastorakos P, Pomeraniec IJ, **Bryant JP**, Chittiboina P, Heiss J. Flexible thecoscopy for extensive spinal arachnoiditis. *J Neurosurg Spine*. [In press]
11. **Bryant JP**, Niazi T. Embryonal Brain Tumors. In "Pediatric Neurosurgery for Clinicians." Springer-Nature Publishing Group. Chapter 19. [In press]
12. Kaczanowska S, Beury DW, Gopalan V, Tycko AK, Qin H, Clements ME, Drake J, Nwanze C, Murgai M, Rae Z, Ju W, Alexander KA, Kline J, **Contreras CF**, Wessel KM, Patel S, Hannenhalli S, Kelly MC, Kaplan RN. Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis. *Cell*. 2021 Apr 15;184(8):2033-2052.e21. doi: 10.1016/j.cell.2021.02.048.

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15. **Gupta N**,* Huang TT,* Horibata S, Lee JM. Cell cycle checkpoints and beyond: exploiting new strategies of ATR/CHK1/WEE1 pathway inhibition for PARP inhibitor–resistant cancer treatment. *Cancers* 2021 [mdpi.com/journal/cancers/special_issues/cell_cycle_proteins_cancer_therapy#planned]

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41. Gonzalez A*, **Teklu M***, Sorokin A, Prussick R, Gonzalez-Cantero J, Martin-Rodriguez J, **Patel NH**, Manyak G, Teague H, Rodante J, Keel A, Perez-Hortet C, Sanchez-Moya AI, Jiminez N, Ballester A, Solis J, Fernandez-Friera L, Barderas MG, Gonzalez-Calvin JL, Jaen P, Playford M, Dey A, Gelfand J, Mehta NN. Subclinical liver disease is associated with subclinical atherosclerosis in psoriasis: results from two observational studies. *J Invest Dermatol.* [In press]

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*Equal contribution

Under Review

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2. **Dave AD**, Thavikulwat AT, De Silva T, Wiley HE, Keenan TDL, Wong WT, Cukras CA. Longitudinal characterization and treatment response of retinal arterial macroaneurysms in adult-onset Coats disease. [Under review]
3. **Hoke A**, Malfitano M, Zanation A, Ebert C, Senior B, Kimple A, Thorp B. Postoperative pain management and perceived patient outcomes following endoscopic pituitary surgery. *The Laryngoscope.* [Under review]
4. **Hoke A**, Padget M, Fabian K, Nandal A, Gallia G, Bilusic M, Soon-Shiong P, Hodge J, London N. Combinatorial natural killer cell based immunotherapy approaches selectively target chordoma cancer stem cells. *JCI Insight.* [Under review]
5. **Hosseini M**, Kassavetis P, Hallett M. Blink rate in blepharospasm. *Mov Disord Clin Pract.* [Under review]
6. Lichtenstein D, Schischlik F, Shao L, Steinberg SM, Yates B, Wang HW, Wang Y, Inglefield J, Dulau-Florea A, Ceppi F, **Jess J**, Hermida LC, Stringaris K, Dunham K, Homan P, Jailwala P, Mirazee J, Robinson W, Chisholm K, Yuan C, Stetler-Stevenson M, Ombrello A, Jin J, Fry T, Taylor N, Highfill SL, Jin P, Fardner R, Shalabi H, Ruppin E, Stroncek D, Shah N. HLH-like manifestations associated with CD22 CAR T-cells provide novel insights into cytokine release syndrome-related toxicities. *Blood* [Under review]
7. **Khondakar NR**, Ahdoot M, Daneshvar M, Gomella PT, Yerram N, **Williams C**, O'Connor LP, Parnes H, Merino M, Wood B, Choyke P, Turkbey B, Pinto PA. Use of multiparametric MRI targeted biopsy to reclassify patients eligible for active surveillance on systematic biopsy. [Under review]
8. **Khondakar NR**, Daneshvar M, **Williams C**, O'Connor LP, Gomella P, Turkbey B, Pinto PA. Advances in multiparametric-MRI and PET-CT for prostate cancer: a narrative review. *BJU Int.* [Under review]
9. **Kumnick, A,** Hanfling, S, Dowlut-McElroy, T, Maher, J, Gomez-Lobo, V. An intersectional analysis of contraceptive types chosen among sexually-active minority women: a nationally representative study. [Under review]
10. Maher J, **Kumnick A**, Sinaii N, Meacham L, Gomez-Lobo V. Implications of anti-Müllerian hormone levels in female childhood and adolescent cancer survivors: a meta-analysis. [Under review]
11. **Letchuman V***, Al-Louzi O*, Manukyan S, Beck ES, Roy S, Ohayon J, Pham DL, Cortese I, Sati P, Reich DS. Central vein sign profile of newly developing lesions in multiple sclerosis: a 3-year longitudinal study. *Neurology.* [Under Review]

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18. **Owens-Walton J**, **Williams C,** Rompre-Brodeur A, Pinto P, Ball MW. Minority enrollment in phase II and III clinical trials in urologic oncology. [Under review]

19. **Owens-Walton J**, Pinto PA. Translational Urology: Handbook for Designing and Conducting Clinical and Translational Research. Elsevier Clinical and Translational Urology Research. Public Health, Chapter 101. [Under review]

20. **Patel NH**, Osborne M, Teague H, Parel P, Svirydava M, Sorokin AV, **Teklu M**, Manyak G, Zhou W, Pantoja C, Scott C, Playford M, Kapoor P, Rodante J, Keel A, Chen M, Tawakol A, Mehta NN. Heightened leukopoietic activity associates with systemic inflammation and subclinical atherosclerosis; results from two observational studies. *Circ Cardiovasc Imaging.* [Under review]

21. Manyak G, **Patel NH**, Dey A, Svirydava M, Parel P, Teague H, Sorokin A, **Teklu M**, Zhou W, Rodante J, Keel A, Playford M, Mehta NN. Chronic inflammation in psoriasis promotes visceral adipose tissue association with lipid-rich necrotic core through atherogenic myeloid score. *Arterioscler Thromb Vasc Biol.* [Under review]

22. Pritchard WF, Karanian JW, Jung C, Bakhutashvill I, **Reed SL**, Froelke BR, Barnes T, Wood BJ, Walsh BK, Mannes AJ. Miniature 3D printed pressure-driven ventilator maintains respiratory homeostasis in swine with induced acute pulmonary injury. [Under review]

23. Nápoles AM, Stewart AL, Strassle PD, Quintero S, Bonilla J, Alhomsi A, **Santana-Ufret V**, Maldonado AI, Perez-Stable EJ. Racial/ethnic disparities in intent to obtain a COVID-19 vaccine: a nationally representative survey. *Prev Med*. [Under review]
24. **Selzer EB**, Blain D, Hufnagel RB, Lupo PJ, Mitchell LE, Brooks BP. Evidence for environmental causes of uveal coloboma. *Surv Ophthalmol.* [Under review]
25. Shaw P, Blizzard S, **Shastri GG**, Kundzicz P, Curtis B, Ungar L, Koehly L. A daily diary study into the effects on mental health of COVID-19 pandemic-related behaviors. *Psychol Med.* [Under review]
26. **Teklu M**, Zhou W, Kapoor P, **Patel NH**, Playford M, Sorokin A, Dey A, Teague H, Manyak G, Rodante J, Keel A, Chen M, Bluemke D, Mehta NN. Abdominal subcutaneous adipose tissue negatively associates with subclinical coronary artery disease in men with psoriasis. *Am J Prev Cardiol*. [Under review]
27. Zhou W, **Teklu M**, Bui Vy, Manyak G, Kapoor P, Dey A, Sorokin A, **Patel NH**, Teague H, Playford M, Erb-Alvarez J, Rodante J, Keel A, Shanbhag S, Hsu LY, Bluemke D, Chen M, Carlsson M, Mehta NN. The relationship between systemic inflammation and increased left ventricular mass is partly mediated by noncalcified coronary artery disease burden in psoriasis. *Am J Prev Cardiol*. [Under review]
28. **Theng EH**, German A, Pan KS, Isaac S, Boyce AM, Collins MT. Recurrent periorbital inflammation associated with craniofacial fibrous dysplasia. [Under review]
29. Ovejero, D, Hartley IR, Fernandez de Castro Diaz, **Theng EH**, Li XB, Gafni RI, Collins MT. PTH and FGF23 Exert interdependent and synergistic effects on renal phosphate handling: evidence from patients with hypoparathyroidism and hyperphosphatemic familial tumoral calcinosis treated with synthetic human PTH 1-34. [Under review]
30. Ahdoot MA*, **Williams C***, Daneshvar MA, Hague C, Wilbur AR, Shih J, **Khondakar NR**, Gomella PT, Yerram NK, Mehralivand S, Gurram S, Siddiqui M, Pinsky P, Parnes H, Merino M, Wood BJ, Turkbey B, Pinto PA. Why does MRI-targeted biopsy miss clinically significant prostate cancers? [Under review]
31. **Williams C**, **Khondakar NR**, Pinto PA, Turkbey B. The importance of quality in prostate multiparametric MRI. *Semin Roentgenol* [Under review]
32. **Williams C,** Gomella PT, Daneshvar MA, **Khondakar NR**, O'Connor LP, Egan J, Yerram NK, Gurram S, Choyke PL, Wood BJ, Merino MJ, Parnes HL, Turkbey B, Pinto PA. Risk of adverse pathology after deferred prostatectomy for grade group 1 and 2 prostate cancer. [Under review]
33. **Williams C,** Gomella PT, Pinto PA. Case series in translational urology. In "Translational Urology: Handbook for Designing and Conducting Clinical and Translational Research." Ed. Siddiqui M. Amsterdam: Elsevier. Chapter 35. [Under review]

*Equal contribution

Awards and Honors

- International AIDS Society 2021 Scholarship, IAS Conference on HIV Science, July 2021.
- Society of Behavioral Medicine Annual Meeting, Student Award for Outstanding Abstract Submission, 2021.
- AANS/CNS Section on Pediatric Neurological Surgery 2020 Annual Meeting, Best Oral Abstract Award.
- Society for Interventional Oncology 2021, Resident and Fellows Scholarship.
- Kaiser Permanente Northern California Medical Student Scholarship for Demonstrated Commitment to Underserved Communities, 2021
- Foundation of the Consortium of Multiple Sclerosis Centers, Medical Student Research Scholarship, 2021.
- America's Committee for Treatment and Research in Multiple Sclerosis, Educational Grant, 2020.
- PanAmerican Society for Pigment Research, Trainee's Spotlight 2021.
- Columbia University Vagelos College of Physicians & Surgeons Student Research Day, Best Abstract Award (2nd place), 2021.
- Warren Alpert Medical School of Brown University 3rd Annual Student Neurology/Neurosurgery Conference 2021, Top Abstract Award, Oral Presentation.
- John B. Graham Student Research Day, University of North Carolina School of Medicine; Best Translational Research Oral Presentation Award. April, 2021.
- Donald M. Mode Urology Research Symposium. Best Student Presentation, Second Place 2021. Medical College of Georgia Department of Urology. (Two scholars received this award.)
- Best Pre-Doctoral Talk, Annual NIDCD Research Retreat, May, 2021.
- NINDS Clinical Research Excellence Award, 2021

Rachel V. Acree

School: David Geffen School of Medicine
Mentor: Lynnette Nieman, M.D., Senior Investigator, Diabetes, Endocrinology, and Obesity Branch
Institute: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Research Project Title: Resting Energy Expenditure is Decreased in Cushing's Syndrome and Recovers in Parallel with the Hypothalamic-Pituitary-Thyroid Axis after Surgical Cure

Cushing's syndrome (CS) is associated with significant changes in body composition, including increased total fat and central adiposity, which contribute to elevated cardiometabolic risk. Despite wide recognition of weight gain as a clinical phenomenon in CS, its mechanism is not fully understood. The primary objective of this study was to evaluate resting energy expenditure (REE) during active CS and after surgical cure. A secondary objective was to evaluate the relationship between the hypothalamic-pituitary--thyroid (HPT) axis, known to be affected in CS, and REE.

Forty-seven patients with active CS planning to undergo surgery were recruited from a clinical research center for this prospective observational study. REE measured by indirect hood calorimetry, body composition, and hormone levels were assessed before and after curative surgery.

During active CS, the mean ratio of REE/expected REE (eREE, calculated by the Mifflin-St. Jeor equation) was 84.7% (95% CI 80.3-89.0%). REE/eREE increased to 101% (95% CI 97.4-106%) 6 months after surgical cure ($p<0.0001$) and remained stable at 12 months (99.1%, 95% CI 95.2-103%, $p<0.0001$ compared to baseline). BMI, total adipose tissue (TAT), trunk, extremity, and visceral adipose tissue (VAT), and VAT/TAT ratio decreased at 6 and 12 months compared to baseline ($p<0.05$) while lean body mass (LBM) did not change significantly. TSH, T4, fT4, T3, fT3, and T3/fT4 ratio increased at 6 and 12 months ($p<0.01$) compared to baseline. Within-subject repeated measures correlation demonstrated linear relationships between REE and T4 ($r=0.71$, $p<0.0001$), fT3 ($r=0.64$, $p<0.001$), T3 ($r=0.63$, $p<0.0001$), and fT4 ($r=0.35$, $p=0.01$), but notTSH ($r=0.27$, $p=0.06$).

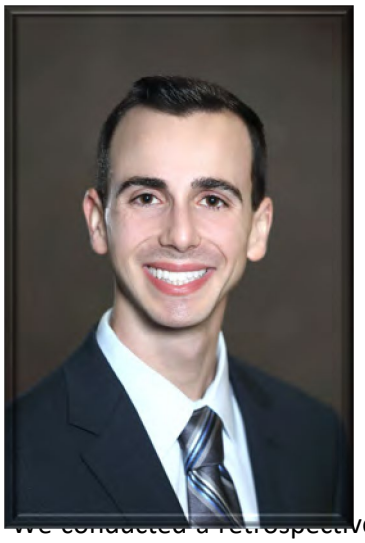
In summary, these data demonstrate a reduction in REE during active CS that recovers in parallel with the HPT axis 6-12 months after surgical cure, in the setting of fat loss. Determining whether these are causal relationships will require further interventional study.

Full Length Publications:

- **Acree R**, Miller CM, Abel BS, Neary NM, Campbell K, Nieman LK. Patient and provider perspectives on post-surgical recovery of Cushing's syndrome. *J Endocrine Society*. 2021 June 14; doi.org/10.1210/jendso/bvab109.
- **Acree R**, McGlotten RN, Abel BS, Nieman LK. Resting energy expenditure is decreased in Cushing's syndrome and recovers in parallel with the hypothalamic-pituitary-thyroid axis after surgical cure. [In preparation]

Professional Meetings:

- Endocrine Society Annual Meeting (ENDO 2021); March 20–23, 2021.



Matthew A. Adan

School: Columbia University Vagelos College of Physicians & Surgeons
Mentor: Frank Maldarelli, M.D., Ph.D., Head, Clinical Retrovirology Section, Host-Virus Interaction Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Relationship between HIV Reservoir Size, Proviral Gene Deletion, and Immune Activation during Antiretroviral Therapy

Antiretroviral therapy (ART) cannot cure HIV infection due to a reservoir of virions integrated into host immune cell DNA, called proviruses. Immune activation persists during ART and is linked to all-cause mortality. Understanding the relationship between immune activation and the HIV reservoir will inform HIV treatment and cure strategies.

We conducted a retrospective, cross-sectional analysis of cellular immune parameters and HIV DNA copies in HIV-infected adults on suppressive ART for ≥3 years. Flow cytometry was used for immunophenotyping a panel of CD4 and CD8 subsets. Cell-associated HIV long terminal repeats (LTR), which estimate reservoir size, and *gag* DNA were measured using multiplexed droplet digital PCR. We also conducted a multiple T-cell marker recovery (MTMR) analysis, a composite estimate of immune recovery. Patients were dichotomized into those meeting MTMR criteria (CD4 T-cell count>500 + CD4%>29% + CD4/CD8 ratio>1) and those who did not. Groups were compared via T-test or Wilcoxon rank-sum test as appropriate, and correlates investigated with Pearson correlations; all p-values were Bonferroni-adjusted.

Study participants (N=75) had a median age and CD4 count of 50 years and 624 cells/µL, respectively. Median log LTR and *gag* DNA copies were 3.39 and 2.79 copies/10^6 CD4 cells, respectively. LTR and *gag* DNA copies correlated positively with percent memory CD8+ (CD8+CD45RO+) cells (LTR: r=0.43, p=0.003; *gag*: r=0.49, p=0.0002). Despite prolonged ART, we found a negative correlation between *gag* DNA and nadir CD4 (r=-0.37, p=0.024). In the MTMR analysis, individuals who met all MTMR criteria (N= 35) had significantly less LTR and *gag* DNA (p=0.044, p=0.038 respectively) than those who did not.

Immune activation during ART may shape the proviral landscape or vice versa, given greater percentages of CD8 memory cells in those with larger reservoirs and *gag*-burden. Individuals with smaller reservoirs containing less *gag* DNA may more effectively reconstitute immune function on ART.

Full Length Publications:

- Shoucri S, Purpura L, DeLaurentis C, **Adan MA**, Theodore D, Irace A, Robbins-Juarez S, Khedagi A, Letchford D, Harb A, Zerihun L, Lee K, Gambina K, Lauring M, Chen N, Sperring C, Mehta S, Myers E, Shih H, Argenziano M, Bruce S, Slater C. Characterizing the long-term clinical outcomes of 1190 hospitalized patients with Coronavirus Disease 2019 in New York City: a retrospective case series. *BMJ Open*. 2021 June;11(6):e049488.
- Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, He J, Thompson A, Murn M, Fountain J, Rosen A, Robbins-Juarez S, **Adan MA**, Satish T, Madhavan M, Gupta A, Agerstrand C, Yip NH, Burkart KM, Beitler J, Baldwin MR, Brodie D, Calfee CS, O'Donnell MR. Latent class analysis derived classes in COVID-19 ARDS and their comparison to ARDS subphenotypes: A prospective single-centre cohort study. *Lancet*. [Under review, May 2021]

Abstract Publications:

- **Adan MA**, Lau C, Dewar R, Higgins J, Rehm C, Ganesan A, McMahon D, Anderson EM, Luke B, Gorelick RJ, Maldarelli F. Relationship between T-cell recovery and proviral *gag* deletion during long-term antiretroviral therapy. Eastern-Atlantic Student Research Forum. Feb. 19-21, 2021. [Virtual poster presentation]
- **Adan MA**, Lau C, Dewar R, Higgins J, Rehm C, Ganesan A, McMahon D, Anderson EM, Luke B, Gorelick RJ, Maldarelli F. Analysis of T-cell recovery and levels of HIV proviruses during long-term antiretroviral therapy. Dynamics and Evolution of Human Viruses Conference. May 5-7, 2021. [Virtual oral presentation]
- **Adan MA**, Lau C, Dewar R, Higgins J, Rehm C, Ganesan A, McMahon D, Anderson EM, Luke B, Gorelick RJ, Maldarelli F. Role of host immune activation in enrichment in proportion of deleted proviruses during ART. Retroviruses 2021 Cold Spring Harbor Laboratory Meeting. May 25-28, 2021. [Virtual poster presentation]
- **Adan MA**, Lau C, Dewar R, Higgins J, Rehm C, Ganesan A, McMahon D, Anderson EM, Luke B, Gorelick RJ, Maldarelli F. Role of cellular immune activation in enrichment of deleted proviruses during ART. International AIDS Society Conference on HIV Science. July 18-21, 2021. [Virtual poster presentation]
- Shoucri S, **Adan MA**, Purpura L, DeLaurentis C, Theodore D, Yin MT, Sobieszczyk M, Castor D, Zucker J, Columbia Longitudinal COVID Group. Long-term sequela of SARS-CoV-2 infection in a retrospective New York City cohort. Conference on Retroviruses and Opportunistic Infections. March 6-10, 2021. [Virtual oral presentation]

Virtual Professional Meetings:

- Infectious Disease Society of America IDWeek 2020; Sep. 29-Oct. 3, 2020.
- Eastern-Atlantic Student Research Forum; Feb. 19-21, 2021.
- Conference on Retroviruses and Opportunistic Infections; March 6-10, 2021.
- HIV Dynamics and Evolution of Human Viruses; May 5-7, 2021
- Retroviruses 2021 Cold Spring Harbor Laboratory Meeting; May 25-28, 2021.
- International AIDS Society Conference on HIV Science, July 18-21, 2021.

Awards:

- Columbia University Vagelos College of Physicians & Surgeons Student Research Day, Best Abstract Award (2nd place), 2021.
- International AIDS Society 2021 Scholarship, IAS Conference on HIV Science, Virtual conference, July 18 – 21, 2021.

Simran Arjani

School: Rutgers New Jersey Medical School
Mentor: Rachael Stolzenberg-Solomon, Ph.D., Senior Investigator, Metabolic Epidemiology Branch
Institute: National Cancer Institute, Division of Cancer Epidemiology and Genetics (NCI/DCEG)
Research Project Title: Body Mass Index Trajectories Across the Adult Life Course and Pancreatic Cancer Risk

Body mass index (BMI) during adulthood has been associated with pancreatic cancer, however patterns of body size across the adult life-course and risk of pancreatic cancer have not been studied extensively. The objective of this study was to evaluate the association of adiposity across adulthood, modelled by BMI trajectories, with incident pancreatic ductal adenocarcinoma (PDAC).

We performed a prospective cohort analysis of 269,480 participants (162,735 men, 106,745 women) in the NIH-AARP Diet and Health Study cohort, aged 50-71 years, who successfully completed questionnaires at baseline (1995-1996) and six months later that queried self-reported height and weight history at ages 18, 35, 50, and baseline. Participants were followed through December 31, 2011. Pre-diagnostic BMI trajectories were determined from latent-class trajectory modeling and based on BMI (kg/m^2) from the four ages and World Health Organization BMI classification. Hazards Ratios (HR) and 95% confidence intervals (CI) for incident primary PDAC were calculated using Cox proportional hazard models with age as the time metric adjusted for sex, smoking, and heavy alcohol consumption. Interactions by sex, smoking status, and diabetes status were analyzed using cross-product terms.

During follow-up of up to 13.1 years, 3,092 incident PDAC cases were identified. Four BMI trajectories were created. Compared to normal weight maintainers, normal-to-overweight, normal-to-obese I, and overweight-to-obese III trajectories had HR of 1.19 (95% CI, 1.10-1.29), 1.43 (CI, 1.24-1.60), and 1.27 (CI, 0.89-1.80), respectively. BMI at ages 18, 35, 50, and baseline were significantly associated with increased PDAC risk (HRs per 5-unit kg/m^2 increase, HR =1.09 to 1.13). Additional adjustment for diabetes did not substantially attenuate these associations. Interactions by sex, with higher male risk, were significant for BMI at 35y (p-interaction=.041), 50y (p-interaction=.0128), and at baseline (p-interaction=.0289). There were no significant interactions by smoking or diabetes ($p > 0.05$). Our results suggest BMI trajectories that result in becoming overweight or obese during adulthood are associated with an elevated risk of PDAC.

Full Length Publications:

- **Arjani S**, Saint-Maurice PF, Julian-Serrano S, Pfeiffer RM, Stolzenberg-Solomon RZ. Body mass index trajectories across the adult life course and pancreatic cancer risk. [In preparation]

Abstract Publications:

- **Arjani S**, Saint-Maurice PF, Julian-Serrano S, Stolzenberg-Solomon R. Body mass index trajectories across the adult life course and pancreatic cancer risk. American Association of Cancer Research Annual Meeting; April 10-15, 2021. [Virtual poster presentation]
- **Arjani S**, Julian-Serrano S, Saint-Maurice PF, Stolzenberg-Solomon R. Lifetime BMI, central adiposity and pancreatic cancer risk in a large US cohort. American Society of Preventive Oncology Annual Meeting; March 29-April 1, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Association of Cancer Research Special Conference: Pancreatic Cancer; Sep. 29-30, 2020.
- Society for Epidemiologic Research Annual Meeting; Dec. 16-18, 2020.
- American Association of Cancer Research Annual Meeting; April 10-15, 2021
- American Society of Preventive Oncology Annual Meeting; March 29-April 1, 2021.

Rajit Banerjee

School: University of Toledo College of Medicine and Life Sciences
Mentors: Diane Damiano, Ph.D., Chief, Functional and Applied Biomechanics Section; Thomas Bulea, Ph.D., Staff Scientist, Functional & Applied Biomechanics Section
Institute: Clinical Center Rehabilitation Medicine Department (CC-RMD))
Research Project Title: Effect of Bodyweight Unloading on Muscle Synergy Activation Patterns during Treadmill Walking in Individuals with and without Cerebral Palsy

Partial body weight supported treadmill training with variable unloading is an intervention used to help improve walking in children with cerebral palsy (CP). However, assessing varying levels of body weight support (BWS) and determining an optimum level to use in improving gait impairments remains poorly defined.

The aim of our study was to examine two levels of unweighting (20% and 40%), compared to baseline, during treadmill gait in a unilateral CP group and a typical development (TD) group using muscle synergy analyses. We postulated that the condition in CP with the greatest similarity in synergy number and structure to the unweighted condition in those with TD would represent the optimal practice condition for improving muscle coordination. Electromyography was recorded on bilateral lower extremity muscles for both cohorts in 3 walking conditions: no BWS, 20% BWS, and 40% BWS. The data wereanalyzed using signal processing, non-negative matrix factorization to extract synergies, and k-means clustering to group similar synergies. No statistical differences were observed in optimal synergy numbers for both groups that were able to do all 3 conditions or 2 conditions. Clustering analysis of the TD cohort demonstrated that of all possible synergy changes at different BWS levels, about 21.9% actually showed changes (50 cluster changes), with one subject demonstrating no changes among different BWS levels. For the CP cohort, 11.5% showed synergy changes (24 cluster changes), with 4 subjects demonstrating no synergy changes among different BWS levels, and also unable to perform the 40% BWS condition. Thus, increasing the BWS seems to have an effect on alteration of synergies, particularly on the TD cohort. This suggests that the CP cohort may not be able to modulate muscle activity to meet increasing BWS demands, especially since more participantswith CP were not able to perform the 40% BWS condition.

Full Length Publications:

- Alter K, Cipriano K, Astrow J, **Banerjee R**. Cervical dystonia. *PM&R KnowledgeNOW*. [In press]
- **Banerjee R**, Bulea T, Damiano D. Effect of bodyweight unloading on muscle synergy activation patterns during treadmill walking in individuals with and without cerebral palsy. *Arch Phys Med Rehab*. [In-preparation]

Virtual Professional Meetings:

- Association of Academic Physiatry Annual Meeting; Feb. 9–13, 2021.

H. Matthew Berns

School: Ohio University Heritage College of Osteopathic Medicine
Mentor: William Pavan, Ph.D., Chief, Genetics Disease Branch
Institute: National Human Genome Research Institute (NHGRI)

Research Project Title: Single-Cell Gene Expression Profiling of *In Vivo* Melanocytes Towards Discovery of Novel Genes and Pathways in Pigmentation and Disease

Melanoma is the most lethal form of cutaneous cancer. Activation of the melanocortin-1-receptor (MC1R) in melanocytes leads to production of a photoprotective black-brown pigment, eumelanin, while inhibition maintains production of a yellow-red pigment, pheomelanin, increasing the risk of UV damage. Human *MC1R* variants disproportionately produce pheomelanin and carriers of such variants present with fair skin, poor tanning response, and increased susceptibility to melanoma development. Regulation of pigment production downstream of MC1R is well established. However, little is known regarding global gene expression changes upon activation or inhibition of MC1R.

The goal of our study was to characterize gene expression profiles of primary melanocytes isolated from a constitutive MC1R inhibition mouse model producing high levels of pheomelanin (*Lethal Yellow* A^y/a) compared to MC1R-activated melanocytes producing eumelanin only (*Non-agouti a*/*a*). Using a single-cell RNA sequencing approach, we identified 568 genes differentially expressed between the eumelanin and pheomelanin-producing melanocytes (FDR <0.05 and fold-change ±2.0). These genes provide important candidates for MC1R-mediated transcriptional regulation that may highlight pathways impacting melanogenesis and cellular protection against UV damage. Gene ontology assays revealed alterations in several cell and molecular pathways with no established role in pigment production. One gene of particular interest was the T-box transcription factor family member *Tbx3*.

T-box family members have many established roles in embryonic development. TBX3 has an established role in human melanoma invasiveness, while mutations of *TBX3* in horses are known to affect coat color. We hypothesize that TBX3 regulates melanin production through inhibition of key enzymes necessary for eumelanin production, thus resulting in increased pheomelanin synthesis and a lighter coat color in mice. Future work will be aimed at addressing the function of this transcription factor in melanocytes. A broader understanding of protein function may lead to more precise pharmacological interventions of human melanomas high in TBX3.

Virtual Professional Meetings:

- American Society of Human Genetics; Oct. 27-30, 2020.

Awards:

- PanAmerican Society for Pigment Research Trainee's Spotlight, 2021

Jean-Paul Bryant

School: University of Miami Miller School of Medicine
Mentor: John Heiss, M.D., Head, Clinical Unit, Surgical Neurology Branch
Institute: National Institute of Neurological Disorders and Stroke (NINDS)
Research Project Title: ENAH Regulates Stemness and Self-renewal Properties of Patient-derived Primary Glioblastoma Neurospheres

Glioblastoma (GBM) is the most common primary malignant brain tumor. Standard of care includes maximal surgical resection, radiation, and chemotherapy with temozolomide. Despite this treatment approach, the median survival time of patients with GBM is only 15 months, emphasizing the need for additional therapeutic strategies. Enabled homolog (ENAH, also known as Mena) is a member of the Ena/VASP protein family. ENAH, as well as its paralogs, VASP and EVL, are well-established regulators of actin dynamics and are required for normal nervous system development.

While elevated ENAH protein expression has been implicated in tumorigenesis of a variety of cancers, its role in brain tumors remains undefined. In our study, we sought to understand the role of ENAH in GBM tumor biology.

Expression of ENAH in GBM tumor specimens was assessed by immunohistochemistry (IHC). Patient-derived primary GBM neurosphere (GBMNS) models were transfected with scrambled siRNA (negative control) or target-specific ENAH siRNA and were subjected to viability, apoptosis, and neurosphere formation assays, and cell cycle and western blot analysis.

IHC analysis suggested that ENAH expression is higher in GBM tumor samples compared to low grade gliomas and normal brain tissues. *In vitro* experiments demonstrated that ENAH knockdown reduced the viability of GBMNS by greater than 50% and significantly decreased self-renewal ability. Further, depletion of ENAH induced apoptosis in GBMNS but did not affect cell cycle progression. Following ENAH knockdown, phospho-ERK was upregulated in GBMNS, suggesting that constitutive activation of ERK drives these cells towards apoptosis. Our results indicate that ENAH is required for both survival and self-renewal of GBMNS and further suggest that ENAH can serve as a potential target for GBM therapy.

Full Length Publications:

- **Bryant JP**, Heiss JD, Banasavadi-Siddegowda YK. Arginine methylation in brain tumors: tumor biology and therapeutic strategies. *Cells*. 2021, 10(1), 124. doi: 10.3390/cells10010124.
- **Bryant JP**, Perez-Roman RJ, Burks SS, Wang MY. Antiresorptive and anabolic medications used in the perioperative period of patients with osteoporosis undergoing spine surgery: its impact on the biology of fusion and systematic review of the literature. *Neurosurg Focus*. 2021 Jun 1; 50(6): E13. doi: 10.3171/2021.3.FOCUS201049.
- **Bryant JP**, Nwokoye DI, Cox MF, Mbabuike NS. The progression of diversity: black women in neurosurgery. *Neurosurg Focus*. 2021 Mar 1;50(3): E9. doi: 10.3171/2020.12.FOCUS20945.
- **Bryant JP,** Levy A, Heiss JD, Banasavadi-Siddegowda YK. Review of PP2A tumor biology and anti-tumor effects of PP2A inhibitor LB100 in the nervous system. Cancers. [2021, 13(12), 3087; doi: 10.3390/ cancers13123087.
- **Bryant JP,** Chandrashekhar V, Cappadonna A, Lookian P, Chandras hekhar V, Vortmeyer A, Heiss JD, Zhuang Z, Rosenblum J. Multimodal atlas of the murine inner ear: from embryo to adult. Front Neurol. 12:699674. doi: 10.3389/fneur.2021.699674.
- Mastorakos P, Pomeraniec IJ, **Bryant JP**, Chittiboina P, Heiss J. Flexible thecoscopy for extensive spinal arachnoiditis. *J Neurosurg Spine*. [In press]
- Hyslop AS, Wang S, **Bryant JP**, Bhatia S, Sandoval-Garcia C, Kalyani K, Ragheb J. Stereo-electroencephalography (SEEG) in pediatric epilepsy: utility in children with and without prior epilepsy surgery failure. *Epilepsy Res*. [In press]
- Lookian P, Chandrashekhar V, Cappadonna A, **Bryant JP**, Chandrashekhar V, Tunacao J, Smirniotopoulos J, Heiss JD, Zhuang Z, Rosenblum J. Tentorial venous anatomy of mice and men. *JCI Insight*. [Under review]
- Cappadona A, Lookian P, Knutsen R, Donahue D, Chandrashekhar V, **Bryant JP**, Zhao D, Chandrashekhar V, Kozel B, Heiss JD, Zhuang Z. Non-invasive *in situ* visualization of the murine cranial vasculature. *Cell Rep Methods*. [Under review]
- **Bryant JP**, Niazi T. Embryonal Brain Tumors. Pediatric Neurosurgery for Clinicians. Springer-Nature Publishing Group. Chapter 19. [In press]

Abstract Publications

- **Bryant JP**, Rosenblum J, Lookian P, Munasinghe J, Donahue D, Cappadonna A, Zhuang Z, Heiss JD. *Ex Vivo* 14T MR imaging of whole mouse brain. American Association of Neurological Surgeons Annual Meeting; Aug. 21-25, 2021. [Virtual poster presentation]
- **Bryant JP**, Chowdhury AC, Heiss JD, Banasavadi-Siddegowda YK. ENAH regulates stemness and self-renewal properties of patient-derived primary glioblastoma neurospheres. American Association of Neurological Surgeons Annual Meeting; Aug. 21-25, 2021. [Virtual poster presentation]

Abstract Publications (continued)

- **Bryant JP**, Chowdhury AC, Heiss JD, Banasavadi-Siddegowda YK. ENAH regulates stemness and self-renewal properties of patient-derived primary glioblastoma neurospheres. Brown University School of Medicine 3rd Annual Student Neurology/Neurosurgery Conference. Jan. 9, 2021. [Virtual oral presentation]
- **Bryant JP**, Wang S, Hyslop A, Bhatia S,Sandoval-Garcia C, Karkare K, Ragheb J. Stereo-electroencephalography (SEEG) in pediatric epilepsy surgery: a 5-year single center experience. AANS/CNS Section on Pediatric Neurological Surgery 49th Annual Meeting. Dec. 2020. [Virtual oral presentation]

Virtual Professional Meetings

- Brown University School of Medicine 3rd Annual Student Neurology/Neurosurgery Conference. Jan. 2021.
- AANS/CNS Section on Pediatric Neurological Surgery 49th Annual Meeting. Dec. 2020.

Awards:

- AANS/CNS Section on Pediatric Neurological Surgery 2020 Annual Meeting, Best Oral Abstract Award.
- Warren Alpert Medical School of Brown University 3rd Annual Student Neurology/Neurosurgery Conference, 2021, Top Abstract Award, Oral Presentation.

Cristina F. Contreras Burrola

School: Indiana University School of Medicine
Mentor: Rosandra Kaplan, M.D., Head, Tumor Microenvironment and Metastasis Section, Pediatric Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: *In vitro* Characterization of Myeloid Cell Immunosuppressive Phenotype and Function in Metastatic Cancers

Myeloid cells are a heterogeneous group of innate immune cells that play both pro- and anti-tumoral roles in metastatic solid tumors. Their function in the tumor microenvironment is pleiotropic, from phagocytosis, induction of tumor cell death and stimulation of immunosurveillance to suppression of T cells, promotion of angiogenesis and remodeling of extracellular matrix. Outside the tumor, myeloid cells in circulation also maintain a dichotomous role between immune activation and suppression.

However, little is known about changes in myeloid cell functionality in cancer-bearing patients compared to healthy controls. To better understand their involvement in disease progression, we sought to characterize the phenotypic and functional diversity of circulating myeloid cells in patients with metastatic solid malignancies.

Peripheral blood mononuclear cells were isolated from three healthy donors and three pediatric patients with metastatic sarcomas. Through flow cytometric analysis and functional assays, we determined the subpopulation distributions as well as the phagocytic activity and markers of suppression in the myeloid compartment in patients compared to controls. Non-classical monocytes, which have been implicated in cancer immunosurveillance, were significantly lower in patients with advanced sarcoma (14.53 vs 4.20% of total myeloid cells; $p = 0.025$). Patients and healthy donors showed similar levels of reactive oxygen species production upon staining with 2',7'-dichlorofluorescin diacetate. However, patients trended higher in the proportion of myeloid cells with intracellular staining of arginase, a known marker for T-cell suppression. Lastly, patients showed a trend towards a lower proportion of myeloid cells phagocytosing fluorescently-labeled Hu09H3 osteosarcoma cells.

These preliminary results shed light on altered myeloid function in metastatic cancer and warrant further investigation, including analysis of untreated newly diagnosed patients and larger cohorts of patients and controls. In future work, we aim to employ these assays in a genome-wide CRISPR/Cas9 screen to identify key genes that drive myeloid cell function. Our findings emphasize the need to consider circulating myeloid cells in immune-targeting approaches in metastatic solid malignancies.

Full Length Publications:

- Kaczanowska S, Beury DW, Gopalan V, Tycko AK, Qin H, Clements ME, Drake J, Nwanze C, Murgai M, Rae Z, Ju W, Alexander KA, Kline J, **Contreras CF**, Wessel KM, Patel S, Hannenhalli S, Kelly MC, Kaplan RN. Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis. *Cell*. 2021 Apr 15;184(8):2033-2052.e21. doi: 10.1016/j.cell.2021.02.048
- Kaczanowska S, **Contreras CF**, Kaplan RN. Functional diversity of circulating myeloid cells in healthy donors and patients with metastatic solid tumors. [In preparation]

Abstract Publications:

- **Contreras CF**, Kaczanowska S, Kaplan RN. 2021. Function of circulating myeloid cells in healthy donors and patients with metastatic solid tumors. IMMUNOLOGY 2021, Annual Meeting of The American Association of Immunologists, May 10-15, 2021. [Virtual presentation]

Virtual Professional Meetings

- IMMUNOLOGY 2021™, Annual Meeting of The American Association of Immunologists, May 10-15, 2021.
- Society for Immunotherapy of Cancer (SITC) 35th Annual Meeting, Nov. 10-15, 2020.

Amisha Dave

School: University of Connecticut School of Medicine
Mentor: Catherine Cukras, M.D., Ph.D., Lasker Clinical Research Scholar, Unit on Clinical Investigation of Retinal Disease
Institute: National Eye Institute (NEI)

Research Project Title: Comparison of Cone Density Measurements in Patients with Retinitis Pigmentosa and Healthy Controls using Adaptive Optics

Adaptive optics (AO) is a retinal imaging technique with potential to characterize the photoreceptor mosaic and improve current diagnostics. However, variability in acquisition protocols, instrumentation, and image quality requires further study to measure and interpret pathology in AO images.

AO images in our study were acquired using the rtx1 flood-illuminated AO camera (Imagine Eyes, Orsay, France) from the eyes of 20 retinitis pigmentosa (RP) patients and 6 healthy controls (HC) in a clinical setting. Subjects had five 4°x4° images acquired, centered at the following locations relative to the fovea: (0°,0°), (2T°,0°), (2N°,0°), (0°,+2°), (0°,-2°). Automation facilitated counting of approximately 190 densely-sampled regions of interest using AOdetect per 4°x4° image. Comparisons of cone density (CD) were made between healthy eyes and RP eyes with varying severities as determined by 24-2 Humphrey visual field mean deviations. Intrasession repeatability of CD measures was investigated using three images in four overlapping 2°x2° quadrants.

HC had statistically higher CDs (mean 18,844 ±1714 [SD] cones/mm^2) across the sampled region when compared to all RP patients (mean 10,869 ±916 cones/mm^2, p =<.0001). There was a significant decrease in CD in all severities of RP compared to HC. Within the RP patients, the CD of severe RP patients (mean 5,385 ±1187 cones/mm^2) was significantly decreased compared to mild and moderate RP patients. Within a single image, there was a statistically significant difference in CD at 1° radius versus a 3° radius from the fovea in the HCs, mild RP, and severe RP patients. HCs and RP patients showed excellent intrasession repeatability and there was no statistically significant difference in repeated CD measurements in overlapping 2°x2° quadrants.

CD measurements in AO images acquired in a clinical setting reveal gradual changes that correlate with disease severity in RP. Quantitative measurements from AO imaging could help effectively measure and interpret changes due to RP.

Full Length Publications:

- **Dave AD,** Thavikulwat AT, De Silva T, Wiley HE, Keenan TDL, Wong WT, Cukras CA. Longitudinal characterization and treatment response of retinal arterial macroaneurysms in adult-onset Coats disease. [Under review]

Abstract Publications:

- **Dave AD**, Malley C, Mays R, Arango M, Huryn L, Zein WM, Brooks BP, De Silva T, Cukras CA. Comparison of cone density measurements in patients with retinitis pigmentosa and healthy controls using adaptive optics. Association for Research in Vision and Ophthalmology Annual Meeting; May 1-7, 2021. [Virtual poster presentation]
- **Dave AD,** Hess K, Chen KG, Wiley H, Keenan TDL, Agron E, Chew EY, Cukras CA. Correlations between renal function and age-related macular degeneration (AMD) phenotypes. American Society of Nephrology Kidney Week; Nov. 2-7, 2021. [Submitted]

Virtual Professional Meetings:

- American Association of Ophthalmology Annual Meeting; Nov. 13-15, 2020.
- Association for Research in Vision and Ophthalmology Annual Meeting; May 1-7, 2021.

James M. Dickey

School: Medical College of Georgia at Augusta University
Mentor: Daniel Chertow, M.D., M.P.H., Head, Emerging Pathogens Section, Critical Care Medicine Department
Institute: NIH Clinical Center

Research Project Title: Quantification of SARS-Cov-2 RNA in Hospital Room Air of Acutely Ill COVID-19 Patients

It is hypothesized that certain medical procedures, termed "aerosol-generating procedures" (AGP), may increase emission of respiratory particles from a patient, thereby increasing transmission risk of respiratory pathogens such as severe acute respiratory syndrome coronavirus (SARS-CoV)-2. Evidence supporting this hypothesis is inconclusive, and no studies have assessed whether environmental contamination with SARS-CoV-2 increases following an AGP in a clinical setting.

We identified a protocol previously used to quantify SARS-CoV-2 from aerosolized particles in a laboratory setting. We optimized this protocol for application in a real-world clinical environment and measured RNA in air of rooms of acutely ill COVID-19 patients admitted to the National Institutes of Health Clinical Center Intensive Care Unit (ICU).

After optimizing RNA extraction from air filters, we increased recovery of SARS-CoV-2 nucleocapsid gene targets (N1 and N2), compared with published protocols, from 1.76% to 31.5% ($p<.0001$) and 9.11% to 33.2% ($p<.001$), respectively. We observed low levels of SARS-CoV-2 RNA in air samples collected within and beyond six feet from two of three patients tested. SARS-CoV-2 RNA in air did not increase following bronchoscopy, a putative AGP, in a patient with high levels of SARS-CoV-2 RNA in upper and lower respiratory tract samples. However, a significant increase in SARS-CoV-2 RNA levels in air was observed in patients following talking and physical exertion (n=2).

Overall, we observed low levels of RNA in ICU rooms of acutely ill COVID-19 patients, likely attributable to effective engineering controls including a high rate of air exchanges. Contrary to existing dogma, we did not detect increased RNA in air following bronchoscopy but did detect increases following other activities. This study provides proof of principle that RNA in air can be effectively measured during relevant clinical situations. Similarly designed larger studies will shed light on transmission risk of respiratory pathogens within the healthcare environment.

Full Length Publications:

- Stein SR, Ramelli SC, **Dickey JM**, Ramos-Benitez MJ, Hewitt SM, Kleiner DE, Ylaya K, Chung JY, Grazioli A, Herr D, Rabin J, Saharia KK, Vannella KM, Singh M, Claude Yinda K, de Wit E, Munster VJ, Burbelo PD, Cohen JI, Ko SH, Bayat Mokhtari E, Aljanahi A, Bortiz EA, NIH COVID-19 Autopsy Consortium, Chertow DS. Broad SARS-CoV-2 tropism and persistence across the human body and brain. [In preparation]

Allison I. Distler

School: The George Washington University School of Medicine and Health Sciences
Mentor: Mark Roschewski, M.D., Clinical Director, Lymphoid Malignancies Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Clonal Evolution in Follicular Lymphoma: Using Circulating Tumor DNA to Monitor for Minimal Residual Disease

Circulating tumor DNA (ctDNA) correlates with tumor burden and predicts outcomes in lymphoma. Few studies have explored the predictive value of ctDNA in follicular lymphoma (FL). We aimed to identify the most effective collection tube for analyzing ctDNA in FL and determine if levels are predictive of disease progression in patients within a prospective clinical trial.

We collected baseline peripheral blood in K_2EDTA and cell-free blood collection DNA (Streck) tubes from 32 untreated FL patients. Peripheral blood mononuclear cells (PBMCs) and plasma were isolated, and amplification and sequencing of the CDR3 segment was performed (Adaptive Biotechnologies). Tumor clonotypes were identified and used to quantify ctDNA. The primary endpoint was 2-year time to progression (TTP). 30 (94%) patients had trackable clonotypes in PBMC, K_2EDTA, and Streck samples. Samples were distributed into low, low-intermediate, intermediate, and high sequence expression quartile groups. In EDTA samples, 2-year TTP was 87.5%, 87.5%, 21.4%, and 28.6% for low, low-intermediate, intermediate, and high groups, respectively, with significant difference between low and intermediate (Hazard Ratio [HR] 0.29, 95%CI 0.07-1.27; p=0.0259), low and high (HR 0.28, 95%CI 0.07-1.1; p=0.0294), low-intermediate and intermediate (HR 0.19, 95%CI 0.04-0.94; p=0.019), and low-intermediate and high (HR 0.16, 95%CI 0.04-0.71; p=0096) groups. In Streck samples, 2-year TTP was 100%, 100%, 60% and 14.3% for low, low-intermediate, intermediate, and high groups, respectively, with significant difference between low and high (HR 0.14, 95%CI 0.03-0.59; p=.0003), low-intermediate and high (HR 0.22, 95%CI 0.06-0.82; p=.0046), and intermediate and high (HR 0.23, 95%CI 0.06-0.85, p=.0049) groups. There was no significant difference in TTP between any groups from PBMC samples.

Our preliminary findings suggest that clonotypes from ctDNA can be detected in plasma from most FL patients, and correlate with tumor burden and TTP. Further studies are ongoing to validate these findings, including sequential analyses of ctDNA throughout disease course.

Abstract Publications:

- **Distler A**, Lakhotia R, Phelan J, Pittaluga S, Roschewski MR. Clonal evolution in follicular lymphoma: using circulating tumor DNA to monitor disease. American Society of Hematology Annual Meeting; Dec. 11-14, 2021. [Submitted]

Virtual Professional Meetings:

- American Society of Hematology 63rd Annual Meeting, Dec. 11-14, 2021.

Maureen C. Farrell

School: Drexel University College of Medicine
Mentors: Robert Hufnagel, M.D., Ph.D., Chief, Ophthalmic Genomics Laboratory; Laryssa Huryn, M.D., Medical Officer, Ophthalmic Clinical Genetics Section
Institute: National Eye Institute (NEI)
Research Project Title: Genetic Testing Yield among Patients with Primary Heritable Optic Atrophy

The clinical and genetic heterogeneity of suspected primary heritable optic atrophy (phOA) poses genetic diagnostic challenges. Patients with suspected phOA were retrospectively analyzed to determine genetic testing yield and clinical correlates.

Medical records of patients with genetic testing for suspected phOA were reviewed. Sex, age at vision symptom onset (VSO) and OA diagnosis (OAD), clinical diagnosis subgroup, presence of syndromic features, and family history were analyzed. Clinical diagnosis subgroups included 1) Dominant Optic Atrophy (DOA) (OPA1 or OPA3), 2) Leber Hereditary Optic Neuropathy (LHON), 3) unspecified isolated OA, and 4) syndromic/other cause of OA. Probands underwent Sanger Sequencing, Next Generation Sequencing, and/or whole exome sequencing. Molecular confirmation indicated presence of pathogenic variants.

Fifty unique probands with suspected phOA were identified (32 male, 18 female). Mean (± SD) ages were 23±20 years for VSO and 27±21 years for OAD. Testing confirmed molecular causes in 28% of cases (14/50). Molecular testing result stratified by clinical diagnosis subgroup confirmed disease-causing genotypes in 6/23 with suspected DOA, 4/8 with suspected LHON, 2/8 with unspecified isolated OA, and 2/13 with suspected syndromic OA. Age at VSO and OAD between molecularly confirmed vs. unconfirmed cases were not statistically different. Isolated OA was reported in 42 probands (84%) and suspected syndromic OA in 8 probands (16%); genetic testing yield was not different between these groups (29% vs. 25% respectively; Fisher's test). Family history of phOA was reported in 32% of probands (n=15/47), including 60% of probands with molecular confirmation (9/15) and 16% without (5/32) (p=0.0047; Fisher's test). Genetic testing yield was 60% for probands with family history (9/15) and 16% for singletons (5/32) (p=0.0047; Fisher's test).

Consistent with prior studies, family history was positively associated with testing yield. Genetic testing yield was not significantly affected by sex, clinical diagnosis subgroup, or presence of syndromic features.

Abstract Publications:

- **Farrell MC**, D'Amanda C, Ullah E, Guan B, Blain D, Turriff A, Wong WT, Cukras CA, Stasheff S, FitzGibbon EJ, Zein WM, Brooks BP, Huryn LA, Hufnagel RB. Genetic testing yield among patients with primary heritable optic atrophy. Association for Research in Vision and Ophthalmology (ARVO); May 1-7, 2021. [Virtual poster presentation]
- Vitale S, Agron E, Bhandari S, Peprah D, **Farrell MC**, Clemons TE, Keenan, TD, Domalpally A, Chew EY. Does cataract surgery increase the risk of future development of late AMD? A nested case-control study from the AREDS2 and AREDS2 Follow-On studies. Association for Research in Vision and Ophthalmology (ARVO); May 1-7, 2021. [Virtual poster presentation]
- Bhandari S, Agron E, Vitale S, Peprah D, **Farrell MC**, Clemons TE, Keenan TD, Domalpally A, Chew EY. Cataract surgery and the risk of progression to late age-related macular degeneration: the Age-Related Eye Disease Study 2. Association for Research in Vision and Ophthalmology (ARVO); May 1-7, 2021. [Virtual oral presentation]

Travel to Professional Meetings:

- American Association for Pediatric Ophthalmology and Strabismus 46th Annual Meeting; April 9-11, 2021.
- Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; May 1-7, 2021.

Haidn E. Foster

School: University of Cincinnati College of Medicine
Mentors: Christopher Buck, Ph.D., Head, Tumor Virus Molecular Biology Section, Laboratory of Cellular Oncology; Gabriel Starrett, Ph.D., Independent Research Scholar, Laboratory of Cellular Oncology
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Meta-transcriptome Analysis of Bladder Cancers in HIV+ Patients

Immune suppression from organ transplantation anti-rejection regimens or from HIV/AIDS is a common risk factor for numerous types of cancer, many of which are associated with infectious agents. Curiously, the incidence of bladder cancer is significantly increased in solid organ transplant recipients (SOTR), but not in HIV+ individuals.

The former result is explained by growing evidence that oncogenic polyomavirus infection can contribute to bladder carcinogenesis; however, the latter currently has no clear explanation. To elucidate whether there are distinct differences in the virome or tumor transcriptomes of these two patient groups, we performed total RNA sequencing from FFPE specimens of bladder cancers from HIV+ patients (n=19) and SOTR (n=48). Unlike the SOTR bladder cancers, in which approximately one third of tumors confidently harbored viral transcripts, predominantly from polyomaviruses, five of 19 tumors from HIV+ patients had weak RNA evidence of viral infection—three with HIV-1 only, one with HIV-1 and possible human T-lymphotropic virus, and one with an anellovirus. We further analyzed these tumors by clustering them based on known differentially expressed genes that define molecular subtypes of bladder cancer. These clusters were then manually annotated into known subtypes. 53 of 67 samples could be assigned to known bladder cancer subtypes, with samples from HIV+ and transplant patients distributed across most groups. Seven of 19 (36.8%) samples from HIV+ patients were likely stroma-rich muscle-invasive bladder cancers—a subtype with intermediate overall prognosis but poor outcomes following neoadjuvant chemotherapy—presenting important implications for treatment. Overall, this study suggests that there are distinct differences in the viromes between HIV+ and SOTR bladder cancers, explaining the differences in incidence between these groups. Future whole genome sequencing of these tumors will facilitate the detection of transcriptionally silent DNA viruses and allow further classification of these tumors based on mutations and copy number variations.

Ashley H. Gallagher

School: Rutgers New Jersey Medical School
Mentor: Mitchell Ho, Ph.D., Deputy Chief, Laboratory of Molecular Biology
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Development of Nanobody-based CAR-T cell therapy to Target Tumor-specific MHC-associated Peptides

Chimeric antigen receptor (CAR) T cells feature a recombinant receptor that combines the variable binding domain of an antibody with the CD3-activating domain of a T cell receptor. This effectively traffics T cells towards specific tumor-associated antigens. Most CAR T cells are designed to target surface antigens. However, many promising tumor targets are intracellular, and are surface-accessible only when presented as a peptide in association with major histocompatibility complex (MHC) proteins.

We decided to test the ability of CAR T cells to target MHC-associated peptides by targeting PRAME (preferentially expressed antigen in melanoma), an intracellular antigen expressed in multiple tumor types with limited expression in normal tissue.

Single domain antibodies in camels (called “nanobodies”) exhibit a unique binding profile due to their small size. They can bind to buried pockets in protein ligands and receptors. We used nanobodies to create a novel CAR construct targeting a PRAME peptide known to be specifically expressed on a common HLA allele. A panel of unique nanobodies that bound to PRAME peptide were isolated by phage display of our camelid nanobody libraries. To test the specificity of our nanobodies for PRAME peptide vs MHC, we created an ELISA that compared nanobody binding against HLA complexed with PRAME peptide to HLA complexed with an irrelevant peptide. All new nanobodies bound the PRAME/HLA complex and did not show binding to a control peptide HLA complex. On live cell testing, 3/6 nanobodies consistently bound multiple solid tumor lines of varied HLA and tumor types. Strongest binding was seen in ovarian adenocarcinoma cells. CAR T cells featuring our nanobodies that showed binding on live cells exhibited moderate killing while nonbinders did not. Further analysis and optimization are needed to propel these nanobody-based CAR T cells targeting PRAME peptide-MHC complexes into cancer therapy trials. We conclude that there is potential for our nanobody CAR construct to target PRAME-positive tumors.

Virtual Professional Meetings:

- American Surgical Association 141st Annual Meeting; April 15-16, 2021

Veronica C. Gray

School: Eastern Virginia Medical School
Mentor: Tiffany Powell-Wiley, M.D., Stadtman Investigator and Chief, and Yvonne Baumer, Ph.D., Staff Scientist; Social Determinants of Obesity and Cardiovascular Risk Laboratory, Cardiovascular Branch
Institute: National Heart, Lung, and Blood Institute (NHLBI)

Research Project Title: Social Isolation Associates with NKp46 Expression on Natural Killer Cells through a Relationship Partially Mediated by RANTES in African-American Women

Chronic exposure to psychosocial and environmental stressors (PSES) has been shown to increase risk for diabetes, obesity, and cardiovascular disease and alter immune cell distribution and function. Among natural killer (NK) cells, PSES has been demonstrated to induce a loss of NK cell numbers or NK cell function and/or a shift in NK cell subpopulations. Less is known about NK cell receptor profiles and potential connections to PSES. NKp46 is an activating receptor on NK cells crucial for NK cell function. In this study, we aimed to determine if chronic PSES is associated with altered NKp46 expression.

We recruited 27 African-American women (age 60 ± 9.94; BMI 34.06 ± 8.65), characterized NKp46 expression from blood samples utilizing flow cytometry, and determined serum cytokine/chemokine levels using Luminex. Participants also answered comprehensive questionnaires to determine various psychosocial measures, individual-level socioeconomic status (SES), and home address for neighborhood deprivation (NDI).

First, we found that social isolation, a psychosocial measure, significantly associated with NKp46 expression (β=-0.51, p=0.02), while NDI and SES did not. Second, we identified biomarkers that associated with social isolation. Social isolation significantly associated with the chemokine RANTES (β=0.64, p=0.01) after adjustment for cardiovascular risk and BMI. Third, we determined that RANTES also significantly associated with NKp46 expression after adjustment (β=-0.54, p=0.01). Lastly, we performed a mediation analysis using structural equation modeling to determine if RANTES could be a potential biological mediator between social isolation and NKp46 expression. It revealed RANTES mediates 51.07% of the association.

In summary, our study highlights the impact of PSES on immune cells and inflammation. Further work to unravel the biology of adversity is crucial to address health disparities. Larger studies should be conducted to identify underlying signaling molecules and pathways altering NK cells during chronic PSES that accelerate disease development and progression, and may ultimately serve as targets for intervention.

Full Length Publications:

- Tamura K, Curlin K, Neally SJ, Vijayakumar NP, Mitchell VM, Collins BS, Gutierrez-Huerta C, Troendle JF, Baumer Y, Osei Baah F, Turner BS, **Gray V**, Tirado BA, Ortiz-Chaparro E, Berrigan D, Mehta NN, Vaccarino V, Zenk SN, Powell-Wiley TM. Geospatial analysis of neighborhood environmental stress in relation to biological markers of cardiovascular health and health behaviors in women: protocol for a pilot study. *JMIR Res Protoc.* 2021;10(7):e29191. doi: 10.2196/29191.

Abstract Publications:

- Ortiz-Chaparro E, Neally S, Vijayakumar N, Curlin K, Tamura K, Turner B, **Gray V**, Tirado B, Mitchell V, Collins B, Saxena A, McCoy J, Osei Baah F, Baumer Y, Powell-Wiley T. Associations between neighborhood walkability and proinflammatory cytokines related to cardiovascular disease risk in African American women. Society of Behavioral Medicine 42nd Annual Meeting and Scientific Sessions; April 12-16, 2021. [Virtual poster presentation]

- **Gray V**, Turner B, Gutierrez-Huerta C, Neally S, Curlin K, Vijayakumar N, Ortiz-Chaparro E, Tirado B, Mitchell V, Collins B, Baumer Y, Powell-Wiley T. Social isolation associates with the expression of NKp46 on natural killer cells through a relationship partially mediated by RANTES in African-American women. American Heart Association EPI/Lifestyle Scientific Sessions; May 20-21, 2021. [Virtual poster presentation]

- Ortiz-Chaparro E, Neally S, Vijayakumar N, Curlin K, Tamura K, Turner B, **Gray V**, Tirado B, Mitchell V, Collins B, Saxena A, McCoy J, Osei Baah F, Baumer Y, Powell-Wiley T. Associations between neighborhood walkability, cytokines and monocytes related to cardiovascular disease risk in African American women. New England Science Symposium; April 23–24, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- Student National Medical Association, Annual Medical Education Conference, Dr. Wilbert C. Jordan Research Forum; April 2-3, 2021.
- Harvard Medical School 20th Annual New England Science Symposium; April 23-24, 2021.
- American Heart Association, EPI/Lifestyle Scientific Sessions; May 20-21, 2021.

Awards:

- Kaiser Permanente Northern California Medical Student Scholarship for Demonstrated Commitment to Underserved Communities, 2021

Stephanie Guang

School: Warren Alpert Medical School of Brown University
Mentor: Rajeshwari Sundaram, Ph.D., Senior Investigator, Biostatistics and Bioinformatics Branch
Institute: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Research Project Title: Identifying Prolonged Second Stage Labor using Machine Learning Techniques

Management of prolonged second stage of labor remains a long-standing challenge. Prolonged labor is dependent on many dynamic antepartum and intrapartum factors; however, no clinically useful tools exist to assess individualized risk. We used machine learning models to accurately classify prolonged second stage and predict its duration with respect to clinically relevant timepoints.

Predictive models were trained using data from the Consortium on Safe Labor, which abstracted electronic medical record data at 12 sites in the United States. The second stage of labor was analyzed as both a binary outcome according to ACOG guidelines and multiclass outcome with second stage duration hourly increments of one, two, three, and four hours after complete cervical dilation.

The mean duration of second stage of labor was 0.85 hours (SD 1.02). Of the 103,415 births included in this analysis, 3,519 (3.5%) had prolonged second stage of labor beyond ACOG guidelines (>1-3 hours depending on parity and epidural use). For binary classification, the model with the highest discriminative ability was gradient boosting (C statistic = 0.87), followed by random forest model (C statistic = 0.85). Deep Neural Network (DNN) (C statistic = 0.81) had moderate discriminative ability and logistic regression had the weakest classification performance (C statistic = 0.77). For multiclass classification, both gradient boosting (C statistic =0.82) and random forest (C statistic =0.82) had superior discriminative ability. DNN (C statistic =0.79) and logistic regression (C statistic =0.79) had lower performance metrics. Features with high variable importance included parity, station at full dilation, epidural use, dilation on admission, maternal age, estimated fetal weight, and contractions on admission.

These findings demonstrate the utility of machine learning in predicting prolonged second stage of labor using data available to the obstetric provider, to create individualized predictions and support clinical decision-making during labor.

Full Length Publications:

- **Guang S**, Grantz K, Saha A, Gleason J, Peddada S, Sundaram R. Identifying prolonged second stage of labor using machine learning techniques. [In preparation]

Nitasha Gupta

School: Renaissance School of Medicine at Stony Brook University
Mentor: Jung-Min Lee, M.D., Lasker Clinical Research Scholar, Women's Malignancies Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)

Research Project Title: Targeting Cell Cycle Checkpoint Pathways as a Therapeutic Strategy in PARP Inhibitor–Resistant Ovarian Cancer with *BRCA* Mutation

High-grade serous ovarian cancer (HGSOC) is the most lethal gynecologic malignancy in the US. Roughly 50% of HGSOCs are deficient in homologous recombination repair (*e.g.*, *BRCA1/2* mutations), which is associated with increased responsiveness to PARP inhibitors (PARPis), although emerging resistance to PARPis is a pressing clinical problem. Cell cycle checkpoints (*e.g.*, CHK1) are upregulated in PARPi-resistant preclinical and clinical models, and targeting these pathways may overcome PARPi resistance.

In our phase II trial of CHK1 inhibitor (CHK1i) monotherapy in 22 heavily pretreated *BRCA*-mutant HGSOC patients, there was a response rate of 11% (1 complete response [CR] and 1 partial response [PR]) in the evaluable cohort (n=18), and only 6% among those with prior PARPi use (n=17). Response to CHK1i was not correlated with clinical characteristics like prior number of therapies (p=0.09), PARPi-free interval (p=0.36), or duration on PARPi (p=0.96). Through exploratory analyses utilizing pre-treatment fresh core biopsies and blood samples and employing various methods including RNAseq, whole exome sequencing, cfDNA, and immunohistochemistry, we aim to characterize the resistance mechanisms in this cohort and identify potential biomarkers of CHK1i sensitivity and resistance.

Preliminary RNAseq analysis reveals that overexpression of cell cycle-related pathways, like E2F targets and G2/M checkpoint pathways, as well as downregulation of epithelial-to-mesenchymal transition and metabolic pathways are associated with clinical benefit (CR + PR + stable disease ≥ 6 months). In addition, the PARPi-naïve CR patient demonstrated upregulation of the immunoreactive subtype of HGSOC, associated with enhanced T-cell activation, tumor-infiltrating lymphocytes, and better prognosis, whereas the mesenchymal HGSOC subtype, associated with poor prognosis, was upregulated among those with lack of clinical benefit in the PARPi-resistant setting. Ongoing biomarker analyses will provide novel insights into potential genomic and transcriptomic signatures associated with clinical benefit or resistance to CHK1i in *BRCA*-mutant patients with and without prior PARPi use.

Full Length Publications:

- **Gupta N**, Lampert E, Lee JM. Carving a niche for immunotherapy in ovarian cancer. *Oncotarget* 2021 Jan 5; 12(1):4–7. doi: 10.18632/oncotarget.27864.
- **Gupta N**,* Huang TT,*Horibata S, Lee JM. Cell cycle checkpoints and beyond: exploiting new strategies of ATR/CHK1/WEE1 pathway inhibition for PARP inhibitor–resistant cancer treatment. *Cancers* 2021 [https://www.mdpi.com/journal/cancers/special_issues/cell_cycle_proteins_cancer_therapy#planned] **Equal contribution*

Abstract Publications:

- Huang, TT, Nair, JR, **Gupta, N**, Yamamoto, TM, Bitler, BG, Lee, JM. Different treatment schemes cause distinct PARP inhibitor resistance mechanisms in *BRCA2*-mutant ovarian cancer cells. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Oct 7-10, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Association for Cancer Research Annual Meeting; Apr. 10-15, 2021 and May 17-21, 2021.
- American Society of Clinical Oncology Annual Meeting; June 4-8, 2021.
- American Association for Cancer Research NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Oct 7-10, 2021.

Ashley D. Hadjis

School: Virginia Commonwealth University School of Medicine
Mentor: Christopher Kanakry, M.D., Lasker Clinical Research Scholar, Experimental Transplantation and Immunotherapy Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)

Research Project Title: Relative Impact of Various Chemotherapeutics Given Early Post-Transplant on T-cell Responses and Graft-versus-Host Disease in Murine MHC-Haploidentical Hematopoietic Transplantation

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for malignant and non-malignant diseases, but access to HCT traditionally has been limited by availability of human leukocyte antigen (HLA)-matched donors. The administration of post-transplantation cyclophosphamide (PTCy) early after HCT can effectively limit alloreactivity, allowing HLA-partially mismatched donors to be used as safely as use of fully HLA-matched donors.

PTCy mitigates graft-versus-host disease (GVHD) by inducing functional impairment of alloreactive T cells and preferential recovery of $CD4^+$ regulatory T cells (T_{regs}). Specifically, PTCy is associated with reduced proliferation of alloreactive $CD4^+$ effector T cells (T_{effs}) at day +7 and preferential recovery of T_{regs} at day +21. T cells survive PTCy via expression of two major drug resistance pathways: aldehyde dehydrogenase and ABC transporters.

Using a T-cell replete, MHC-haploidentical, murine HCT model we investigated the relative efficacy of five other chemotherapeutics (methotrexate, bendamustine, paclitaxel, vincristine, and cytarabine), that vary in mechanisms of metabolism and drug resistance, to mitigate GVHD.

PTCy was superior to all other chemotherapeutics in ameliorating clinical GVHD, while methotrexate and cytarabine were partially effective. At day +7 PTCy, methotrexate, bendamustine, and paclitaxel all significantly reduced histopathological GVHD ($p<0.0001$, $p<0.0001$, $p=0.0322$, $p=0.0454$) compared with vehicle-treated controls, but by day +21 significant reduction was seen only with PTCy ($p=0.0003$).

Flow cytometric analysis of blood and splenic lymphocytes revealed that only PTCy effectively reduced alloreactive T_{eff} proliferation at day +7 ($p=0.0008$, $p=0.0491$) and facilitated preferential T_{reg} recovery at day +21 ($p<0.0001$, $p<0.0001$). Methotrexate and cytarabine did not reduce alloreactive T_{eff} proliferation at day +7, but did facilitate preferential T_{reg} recovery by day +21 (MTX: $p<0.0001$, $p<0.0001$; Ara-C: $p<0.0001$, $p=0.0015$).

These results suggest that the effects of PTCy are unique and further support reduced alloreactive T_{eff} proliferation at day +7 and preferential T_{reg} recovery at day +21 as potential biomarkers of optimal GVHD prevention.

Full Length Publications:

- **Hadjis AD**, Nunes NS, Khan SM, Fletcher RE, Eckhaus MA, Kanakry CG. The relative impact of various chemotherapeutics given early post-transplant on T cell responses and graft-versus-host disease on murine MHC-haploidentical hematopoietic transplantation. [In preparation]

Virtual Professional Meetings:

- Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR Digital Experience; Feb 8-12, 2021.

John C. Hancock

School: University of Utah School of Medicine
Mentor: Mark Gilbert, M.D., Chief, Neuro-Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: The Role of Vaccines in the Treatment of Glioblastoma

The use of immunotherapies for the treatment of malignant brain tumors is a topic that has garnered considerable excitement in recent years. However, despite many immunotherapy clinical trials aimed at treating glioblastoma multiforme (GBM), very few have demonstrated a significant survival benefit. Several factors for this have been identified, one of which is that GBMs are immunologically "cold," implying that the cancer does not induce a strong T cell response. It is postulated that this is why clinical trials using an immune checkpoint inhibitor alone have not demonstrated efficacy.

While it is well established that anti-cancer T cell responses can be facilitated by the presentation of tumor-specific antigens to the immune system, treatment-related death of GBM cells and subsequent release of molecules have not been shown to be sufficient to evoke an anti-tumor immune response effective enough to have a significant impact. To overcome this limitation, vaccines can be used to introduce exogenous antigens at higher concentrations to the immune system to induce strong tumor antigen-specific T cell responses. In our review, we described vaccination strategies that are under investigation to treat GBM, categorizing them based on their target antigens, form of antigens, vehicles used, and pairing with specific adjuvants.

We reviewed the concept of vaccine therapy in combination with immune checkpoint inhibitors, as it is hypothesized that this approach may be more effective in overcoming the immunosuppressive milieu of GBM. Clinical trial design and the need for incorporating robust immune monitoring into future studies were also discussed. We believe that the integration of evolving technologies of vaccine development, delivery, and immune monitoring will further enhance the role of these therapies and will likely remain an important area of investigation for future treatment strategies for GBM patients.

Full Length Publications:

- Frederico SC*, **Hancock JC*** (co-first authors), Brettschneider E, Ratnam NM, Gilbert MR, Terabe M. Making a cold tumor hot: the role of vaccines in the treatment of glioblastoma. *Front Oncol*. May 2021;11(1591). doi: 10.3389/fonc.2021.672508

Virtual Professional Meetings:

- American Association for Cancer Research Virtual Conference: Tumor Immunology and Immunotherapy; Oct. 19–20, 2020.
- Society for NeuroOncology Annual Meeting and Clinical Trials Course; Nov. 17–21, 2020.

Austin T. K. Hoke

School: University of North Carolina School of Medicine
Mentors: Nyall London, M.D., Ph.D., Principal Investigator, Sinonasal and Skull Base Tumor Program; Carter Van Waes, M.D., Ph.D., Chief, Head and Neck Surgery Branch
Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)

Research Project Title: Modeling Chordoma Combination Immunotherapy with Natural Killer Cells and IL-15

Chordoma is a rare bone tumor derived from notochord remnants that affects the axial skeleton. It is resistant to chemo- and radiation therapy, and rarely curable by surgical resection. High rates of locoregional recurrence and distant metastases lead to poor prognosis. Immunotherapy may offer more promising outcomes.

Previous work showed that chordomas express PD-L1 and EGFR, rendering them targetable by antibodies against PD-L1 (N-601, novel structural analog of avelumab) and EGFR (cetuximab). N-601 and cetuximab are humanized IgG1 antibodies that mediate antibody-dependent cellular cytotoxicity (ADCC) with natural killer (NK) cells. N-803 is a clinical grade IL-15 superagonist that stimulates and expands T cells and NK cells, with proven clinical efficacy against various malignancies. No studies have explored the role of anti-PD-L1, anti-EGFR, IL-15 superagonism, or combinatory approaches with NK cells in chordoma.

In preclinical *in vitro* models of chordoma, the presence of N-601 and cetuximab increased the cytotoxicity of NK cells against chordoma cells by 6.2- and 9.3-fold, respectively ($p<0.0001$). Treatment of NK cells with N-803 increased their cytotoxicity 13.6-fold ($p<0.0001$), which was further enhanced by addition of N-601 or cetuximab. PD-L1-specific chimeric antigen receptor (CAR) engineered NK cells were also effective against chordoma cells, and their efficacy was further increased by upregulation of PD-L1 on tumor cells through exposure to IFNγ.

Using flow cytometry, we isolated a cancer stem cell (CSC) population within a chordoma cell line and found that CSCs expressed significantly more NK cell activating ligand B7-H6 (CSC % positivity 72, MFI 350; non-CSC % 6.9, MFI 25) and PD-L1 (CSC % positivity 63.8, MFI 1033; non-CSC % 6.1, MFI 835) than non-CSCs. We found that chordoma CSC are preferentially vulnerable to NK cell killing in the presence of anti-PD-L1 antibody (N-601) and IL-15 superagonist (N-803).

This is the first study evaluating combinatory immunotherapy approaches with NK cells in chordoma and warrants further investigation in a controlled clinical trial.

Full Length Publications:

- Gunti S, **Hoke A**, Vu K, London N. Organoid and spheroid tumor models: techniques and applications. *Cancers.* 2021 Feb 19;13(4):874. doi: 10.3390/cancers13040874.
- **Hoke A**, Malfitano M, Zanation A, Ebert C, Senior B, Kimple A, Thorp B. Postoperative pain management and perceived patient outcomes following endoscopic pituitary surgery. *The Laryngoscope.* [Under review]
- Hoke A, Padget M, Fabian K, Nandal A, Gallia G, Bilusic M, Soon-Shiong P, Hodge J, London N. Combinatorial natural killer cell based immunotherapy approaches selectively target chordoma cancer stem cells. *JCI Insight.* [Under review]

Abstract Publications:

- **Hoke A**, Padget R, Fabian K, Hodge J, London N. Modeling chordoma combination immunotherapy with natural killer cells and IL-15. John B. Graham Student Research Day, University of North Carolina School of Medicine; Apr. 16, 2021. [Virtual oral presentation]
- Lando M, Moskovitz A, Pancholy B, Noel J, **Hoke A**, Iwata A, Puccinelli C, Friduss M. The head and neck surgeon's role in the management of hypercalcemic crisis due to primary hyperparathyroidism. American Head and Neck Society 10th Annual International Meeting; Jul. 22-25, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- International Chordoma Foundation Meeting; July 16-17, 2020.
- American Head and Neck Society 10th Annual International Meeting; July 22-25, 2021.

Awards:

- John B. Graham Student Research Day, University of North Carolina School of Medicine; Best Translational Research Oral Presentation Award. April 16, 2021.
- Best Pre-Doctoral Talk, Annual NIDCD Research Retreat, May, 2021.

Mahdieh Hosseini

School: Lewis Katz School of Medicine at Temple University
Mentor: Mark Hallett, M.D., Chief, Human Motor Control Section
Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research Project Title: Characterizing M2 Muscarinic Acetylcholine Receptor Binding in Patients with Cervical Dystonia

Dystonia is a disorder characterized by involuntary muscle contractions that cause slow repetitive movements or abnormal postures. Cervical dystonia (CD) is a form of focal dystonia that affects the muscles of the neck and shoulders. Several lines of evidence including animal models and human imaging studies suggest that cholinergic neurotransmission is implicated in the striatum of patients with cervical dystonia. However, the exact role of muscarinic receptors remains unclear in the pathophysiology of CD.

The goal of this study was to assess a novel M2-selective radioligand, [18F]FP-TZTP, as a potential marker of M2 muscarinic receptors using positron emission tomography (PET). An additional goal was to compare distribution of M2 muscarinic acetylcholine receptor binding in the basal ganglia of patients with primary CD compared to healthy volunteers.

Twelve patients with CD and 12 age- and sex-matched healthy volunteers were enrolled and completed the study. M2 muscarinic acetylcholine receptor mapping was performed using high resolution PET with [18F]FP-TZTP as the radioligand. A two-parameter multilinear reference tissue model (MRTM2) was used to calculate the normalized distribution volume of the radioligand (VT*). The MRTM2 assumes equal regional cerebral blood flow between the two study groups in the input region. Therefore, the medial orbitofrontal cortex was selected as the input region, rather than the cerebellum, as previously published. VT* values in the healthy volunteer group were consistent with prior reports, suggesting that the MRMT2 method can be used with different input regions, other than the cerebellum.

Further between-group comparisons for regions of interest (ROI), including striatum, thalamus, amygdala, and cerebellum, are ongoing for assessment of M2 muscarinic acetylcholine receptor binding in patients with primary CD.

In conclusion, [18F]FP-TZTP PET is a potential non-invasive tool for assessment of M2 cholinergic receptor binding in cervical dystonia, which can provide insight into the pathophysiology of cervical dystonia.

Full Length Publications:

- **Hosseini M**, Kassavetis P, Defazio G, Hallett M. Blink rate in blepharospasm. *Mov Disord Clin Pract.* [Under review]
- Kassavetis P, **Hosseini M**, Mente K, Waugh R, Shamim E, Dieckmann W, Hallett M, Horovitz S. Muscarinic M2 cholinergic receptors in cervical dystonia. [In preparation]

Abstract Publications:

- **Hosseini M**, Kassavetis P, Hallett M. Sensory tricks and blink rate in patients with blepharospasm. American Neurological Association Annual Meeting; Oct. 2021 [Virtual poster presentation]

Virtual Professional Meetings:

- International Parkinson and Movement Disorder Society Congress; Sep. 2020
- American Neurological Association Annual Meeting; Oct. 2020
- Pennsylvania Neurological Society's Annual Meeting; Oct. 2020
- American Academy of Neurology Annual Meeting; April 2021

Jack D. Jeskey

School: Lake Erie College of Osteopathic Medicine - Bradenton
Mentor: Kenneth Kraemer, M.D., Senior Investigator, Laboratory of Cancer Biology and Genetics
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)

Research Project Title: Complex Phenotypes in Trichothiodystrophy Patients with *XPD (ERCC2)* Mutations

Trichothiodystrophy (TTD), Cockayne syndrome (CS) and Cerebro-Oculo-Facial-Skeletal syndrome (COFS) are rare, autosomal recessive disorders with defective nucleotide excision repair (NER). Overlaps of different DNA repair disorders in the same patient have been reported, including xeroderma pigmentosum (XP)/CS complex and XP/TTD. We describe 7 TTD patients in 6 families with *XPD (ERCC2)* mutations and additional clinical features of CS or COFS. The XPD protein functions as a helicase in the NER pathway and also as a component of the basal transcription factor, TFIIH.

All 7 patients presented with major features of TTD ("tiger tail" banding on polarized microscopy, skin abnormalities, short stature and developmental delay). Four TTD patients (TTD406BE and TTD407BE, 9 yo (died, 19 yo) and 7 yo (died, 20 yo) sisters; TTD519BE, 15 yo boy (died, 17 yo); and XP624BE, 5 yo boy) also had CS features, including deep-set eyes and postnatal growth failure. TTD406BE, TTD407BE, and TTD519BE had CS-type pigmentary retinopathy. Three patients (TTD373BE, 13 mo girl with early death; TTD522BE, 10 yo girl; and TTD633BE, 13 mo girl) also had features of COFS with microcephaly, congenital cataracts, facial dysmorphism and skeletal abnormalities. DNA sequencing revealed that each patient was a compound heterozygote with predicted deleterious mutations in *XPD (ERCC2).* Five of the patients shared a complex splice site mutation: L461V,V716_R730del. One novel mutation, D240G, was identified in TTD522BE.

Different *XPD (ERCC2)* repair/ transcription gene defects are associated with complex clinical phenotypes and may reflect interactions of different alleles or of modifier genes. Additional functions of the XPD protein may also be affected and contribute to clinical diversity. These findings may provide insight into genotype-phenotype associations in these patients.

Full Length Publications:

- Rizza ER, DiGiovanna JJ, Khan SG, Tamura D, **Jeskey JD**, Kraemer KH. Xeroderma pigmentosum: a model for human premature aging. *J Invest Dermatol.* 141(4S): 976-984. doi:10.1016/j.jid.2020.11.012
- **Jeskey JD,** Rizza ER, Sarihan M, Khan SG, Boyle J, Tamura D, Mendelsohn N, Brooks B, Merideth M, DiGiovanna JJ, Kraemer KH. Complex phenotypes in trichothiodystrophy patients with *XPD (ERCC2)* mutations. [In preparation]

Abstract Publications:

- **Jeskey JD,** Rizza ER, Sarihan M, Khan SG, Boyle J, Tamura D, Mendelsohn N, Brooks B, Merideth M, DiGiovanna JJ, Kraemer KH. Complex phenotypes in trichothiodystrophy patients with *XPD (ERCC2)* mutations. Society for Investigative Dermatology Annual Meeting, May 3-8, 2021. *J Invest Dermatol 141(S27).* doi:10.1016/j.jid.2021.02.17
- Ho A, Rizza ER, **Jeskey JD**, Folarin S, Tamura D, Khan SG, Zhou X, DiGiovanna JJ, Evans C, Kraemer KH. A deep learning classifier for the analysis of tiger tail banding in trichothiodystrophy. Society for Investigative Dermatology Annual Meeting, May 3-8, 2021. *J Invest Dermatol 141(S27).* doi:10.1016/j.jid.2021.02.602

Virtual Professional Meetings:

- Society of Investigative Dermatology Annual Meeting, May 3-8, 2021.

Jennifer L. Jess

School: Michigan State University College of Human Medicine
Mentor: Nirali Shah, M.D., Lasker Clinical Research Scholar; Head, Hematologic Malignancies Section, Pediatric Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Hematologic Toxicities Following CD22 CAR T-cell Therapy

Hematologic toxicities including coagulopathy, endothelial activation and cytopenias are seen with chimeric antigen receptor (CAR) T-cell therapies for hematologic malignancies and may be associated with cytokine release syndrome (CRS) and neurotoxicity.

The goal of our study was to characterize the hematologic toxicities seen in patients receiving CD22 CAR T-cells for relapsed/refractory CD22+ hematologic malignancies (NCT02315612). The main objective was to characterize the hematologic toxicities associated with CRS. Secondary analysis included correlation of hematologic toxicities with neurotoxicity. A coagulopathy cohort was identified in subjects with evidence for bleeding, or abnormal coagulation parameters, including elevated D-dimer and prothrombin time and hypofibrinogenemia.

Sixty-five subjects were enrolled; 62 received CD22 CAR T-cell infusions and 43 patients achieved complete remission as documented on day 28 bone marrow evaluation. Grade 3-4 neutropenia and thrombocytopenia were seen in 65% of patients at day 28. Fifty-three subjects with CRS were evaluated for hematologic toxicities. Eighteen patients were coagulopathic, 16 of whom had clinical manifestations of bleeding. Bleeding was primarily mucosal, and 12 subjects had more than one manifestation of bleeding, the majority of which resolved following CRS resolution. Coagulopathic patients had higher peak ferritin, D-dimer, PT/INR, LDH, tissue factor, prothrombin fragment F1+2 and s-VCAM-1. Neurotoxicity manifestations were relatively mild; single-cell analysis revealed that CD22 is expressed in mature oligodendrocytes, but not in neurovascular cells or oligodendrocyte precursor cells (OPCs).

With an increasing incidence of CD19-negative relapse following CD19 CAR T-cell approaches, CD22 CAR T-cells are becoming increasingly important in the treatment of hematologic malignancies. Our study characterizes hematologic toxicities with CD22 CARs and demonstrates endothelial activation and mucosal bleeding manifestations, with limited neurotoxicity. Systematic characterization of the antigen-specific toxicity profile of novel CAR T-cell constructs will be important for future clinical development.

Full Length Publications:

- Shalabi H, Martin S, Yates B, Wolters P, Kaplan C, Smith H, Sesi C, **Jess J**, Toledo-Tamula, MA, Struemph K, Delbrook CP, Mackall C, Lee D, Shah N. Comprehensive analysis of neurotoxicity following CD19/28z CAR T-cells in children and young adults with B-cell malignancies. *Neuro-Oncology.* [In press]

Abstract Publications:

- **Jess J**, Yates B, Dulau-Florea A, Cullinane A, Shalabi H, Lozier J, Shah N. Hematologic toxicities and coagulopathy following CD22 CAR T-cells. PTCTC/ASPHO Annual Meeting. April 20-23, 2021. [Virtual oral presentation]
- **Jess J**, Yates B, Dulau-Florea A, Cullinane A, Shalabi H, Lozier J, Shah, N. Hematologic toxicities and coagulopathy following CD22 CAR T-cells. Children's Cancer Foundation,5th Annual Research Symposium. June 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Society of Pediatric Hematology/Oncology Conference; April 20-23, 2021.
- Children's Cancer Foundation, 5th Annual Research Symposium; June 2, 2021.

Anas U. Khan

School: University of Alabama School of Medicine
Mentor: Kareem Zaghloul, M.D., Ph.D., Chief, Functional and Restorative Neurosurgery Section
Institute: National Institute of Neurological Disorders and Stroke (NINDS)
Research Project Title: The Role of Neuronal Primary Cilia in Metabolism and Epilepsy

Historically, primary cilia were thought to play a critical role in development. More recent evidence suggests that they function as signaling antennae in mature cells as well. In neurons, there is now evidence that traumatic injury and epileptiform activity alter cilia morphology in certain areas of the hippocampus. Additionally, knockdown of a ciliary protein Arl13b increases excitatory activity. In other cell types, one of the principle signaling cascades in cilia, the Sonic hedgehog (Shh) pathway, has been shown to play a role in glycolysis regulation. Epileptiform activity has also been shown to upregulate Shh release and pathway activation in neurons. After investigating whether epileptiform activity alters cilia morphology in mixed primary rat cortical cultures, and finding no effect, we asked the question whether seizures alter the metabolic profile of neurons via the primary cilia without changing morphology. We hypothesized that such a process might be in effect due to modulation of Shh signaling, for the reasons cited above. Our experimental plan is to induce seizure-like activity in mixed glial/neuronal cell cultures and reaffirm enhanced glycolytic activity without a concomitant increase in oxidative phosphorylation. We will then attempt to establish that this change is due to increased Shh pathway activity by inhibiting or knocking out/down the Smoothened receptor, a Class Frizzled (Class F) G protein-coupled receptor that is a component of the hedgehog signaling pathway. Finally, we will demonstrate that this process requires the presence of functional primary cilia by repeating these experiments after selectively knocking down proteins required for ciliary function.

Nabila R. Khondakar

School: State University of New York Downstate College of Medicine
Mentor: Peter Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)

Research Project Title: Use of Multiparametric MRI-Targeted Biopsy to Reclassify Patients Eligible for Active Surveillance on Systematic Biopsy

Very low-risk prostate cancer is managed with active surveillance (AS), which involves monitoring for signs of cancer progression and reduces morbidity associated with definitive treatment. Although guidelines increasingly allow for active surveillance in men with both Grade Group 1 and Grade Group 2 cancers, they do not specify which biopsy method should be used. Biopsy method is important to consider, as the standard systematic biopsy misses a substantial fraction of clinically significant cancer.

The objective of this study was to evaluate whether MRI-targeted biopsy resulted in more accurate classification of prostate cancer patients eligible for AS. We queried our institutional database of patients who underwent radical prostatectomy. Patients were included if they received a combined MRI-targeted and systematic biopsy, and had a diagnosis on systematic biopsy of either Grade Group 1, Grade Group 2, or no cancer. Upgrading was determined by comparing Grade Group on wholemount pathology to Grade Group on systematic and targeted biopsies. A total of 806 patients who underwent radical prostatectomy between June 2007 and January 2021 were identified. A total of 501 patients underwent combined biopsy, among whom 353 were diagnosed with ≤ Grade Group 2 on systematic biopsy. Of these 353 patients, 57 had no disease, 108 had Grade Group 1, and 188 had Grade Group 2 disease on systematic biopsy. The rate of upgrading to Grade Group ≥ 3 at prostatectomy was significantly higher after systematic than after targeted biopsy (22% vs 5%, $p < 0.0001$). Thus, approximately 1 in 5 patients eligible for AS based on the 12-core transrectal ultrasound (TRUS)-guided systematic biopsy portion of combined biopsy were found to have clinically significant disease with Grade Group ≥ 3 on wholemount histopathology. MRI-targeted biopsy may exclude patients previously eligible for active surveillance based on systematic biopsy results alone.

Full Length Publications:

- **Khondakar NR**, Ahdoot M, Daneshvar M, Gomella PT, Yerram N, Williams C, O'Connor LP, Parnes H, Merino M, Wood B, Choyke P, Turkbey B, Pinto PA. Use of multiparametric MRI targeted biopsy to reclassify patients eligible for active surveillance on systematic biopsy. [Under review]
- **Khondakar NR**, Owens-Walton J, Daneshvar M, Gomella PT, Williams C, O'Connor LP, Pinto PA. Emerging role for local therapy in oligometastatic prostate cancer. *Clin Adv Hematol Oncol.* 2021 Jul;(7):460-467.
- **Khondakar NR**, Daneshvar M, Williams C, O'Connor LP, Gomella P, Turkbey B, Pinto PA. Advances in multiparametric-MRI and PET-CT for prostate cancer: a narrative review. *BJU Int.* [Under review]
- Williams C*, **Khondakar NR***, Daneshvar MA, O'Connor LP, Gomella PT, Mehralivand S, Yerram NK, Egan J, Gurram S, Rompré-Brodeur A, Webster BR, Owens-Walton J, Parnes H, Merino MJ, Wood BJ, Choyke P, Turkbey B, Pinto PA. The risk of prostate cancer progression in active surveillance patients with bilateral disease detected by combined MRI-fusion and systematic biopsy. *J Urology*. 2021 Jun 28. doi: 10.1097/JU.0000000000001941.
- Williams C, **Khondakar N**, Pinto P, Turkbey B. The importance of quality in prostate multiparametric MRI. *Semin Roentgenol* [Under review]
- Ahdoot M*, Williams C*, Daneshvar MA, Hague C, Wilbur AR, Shih J, **Khondakar N**, Gomella P, Yerram N, Mehralivand S, Gurram S, Siddiqui M, Pinsky P, Parnes H, Merino M, Wood B, Turkbey B, Pinto PA. Why does MRI-targeted biopsy miss clinically significant prostate cancers? [Under review]
  **Equal contribution*

Abstract Publications:

- **Khondakar N**, Egan J, O'Connor L, Ahdoot M, Wiliams C, Daneshvar M, Yerram N, Owens-Walton J, Gurram S, Choyke P, Merino M, Wood B, Turkbey B, Pinto P. The significance of multiple negative biopsies in patients on AS. American Urologic Association 2021 Annual Meeting, Las Vegas, NV; Sep. 10, 2021 [Oral presentation]
- **Khondakar N**, Gurram S, Ahdoot M, Yerram N, Daneshvar M, Gomella P, O'Connor L, Williams C, Owens-Walton J, Merino M, Wood B, Turkbey B, Pinto P. MRI for risk stratification in patients with PSA less than four. American Urologic Association 2021 Annual Meeting, Las Vegas, NV**;** Sep. 10, 2021 [Oral presentation]
- **Khondakar N**, Ahdoot M, O'Connor L, Daneshvar M, Yerram N, Williams C, Owens-Walton J, Gurram S, Gomella P, Egan J, Mehralivand S, Merino M, Wood B, Turkbey B, Pinto P. Predictors of Gleason grade upgrading on wholemount pathology after MRI. American Urologic Association 2021 Annual Meeting, Las Vegas, NV; Sep. 10-13, 2021 [Poster presentation]
- **Khondakar N**, O'Connor LP, Williams C, Daneshvar M, Egan J, Yerram N, Webster B, Merino M, Choyke P, Wood B, Turkbey B, Pinto P. Bilateral disease and risk of prostate cancer progression in an active surveillance cohort. American Society of Clinical Oncology Genitourinary Cancers Symposium. *J Clin Oncol* 39; no. 6 suppl:206. Feb. 20, 2021
- Williams C, **Khondakar N**, Daneshvar M, et al. MRI-Targeted and systematic biopsy for detection of grade progression in patients on active surveillance for prostate cancer. Society of Women in Urology 2021 Annual Meeting; Jan. 22, 2021
- O'Connor L, Daneshvar M, Egan J, Williams C, **Khondakar N**, Wang A, Yerram N, Gurram S, Merino M, Choyke P, Wood B, Turkbey B, Pinto P. Presence of bilateral disease at time of active surveillance enrollment is associated with increased risk of pathologic progression. Society of Women in Urology 2021 Annual Meeting; Jan. 22, 2021
- Williams C, Daneshvar MA, Gomella PT, Yerram N, **Khondakar NR**, Merino MJ, Wood BJ, Choyke P, Turkbey B, Pinto PA. Does deferred prostatectomy for grade group 1 and 2 increase risk of adverse pathology? American Urologic Association, Mid-Atlantic Section Meeting. National Harbor, MD; Oct. 2021 [Poster presentation].

Virtual Professional Meetings:

- American Society of Clinical Oncology Genitourinary Cancers Symposium; Feb. 11–12, 2021 [Virtual]
- Society of Urologic Oncology 21st Annual Meeting; Dec. 3-5, 2020 [Virtual]
- Society of Women in Urology 10th Annual Clinical Mentoring Conference; Jan.

Allison R. Kumnick

School: University of Miami Miller School of Medicine
Mentor: Veronica Gomez-Lobo, M.D., Director, Pediatric and Adolescent Gynecology
Institute: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Research Project Title: Implications of Anti-Müllerian Hormone Levels in Female Childhood and Adolescent Cancer Survivors: A meta-analysis

There are an estimated 400,000 female childhood cancer survivors (CCSs) of childbearing age in the United States. Many chemotherapy and radiation therapies are gonadotoxic, increasing the likelihood of premature ovarian insufficiency and infertility. Anti-Mullerian hormone (AMH), one of the biomarkers used to assess ovarian reserve, may have a role in the care of CCSs.

The goal of this study was to investigate the association between AMH levels after treatment and their relationship with reproductive outcomes. We conducted a literature review and meta-analysis of 509 studies pertaining to AMH values in CCSs. Individual patient data from 14 institutions were analyzed. Data are described as mean (SD). Spearman rho and mixed models were used for analysis.

A total of 672 patients were represented with a median age of 23.3 (8.7) years at the time of AMH measurement. Median age at diagnosis was 11.2 (5.9) years with follow-up time of 12.2 (8.8) years. Controlling for age at study, AMH values [2.14 (2.31) ng/mL] were positively correlated with age at diagnosis (p=0.0061), as well as weakly inversely correlated with duration of follow-up (p=0.0464). Compared with leukemia, patients with neuroblastoma had significantly lower age-controlled AMH values (p=0.0178). For women 21+ years old, AMH was not different by history of pregnancy versus never pregnant (p=0.3313). An inverse correlation was noted between AMH and FSH (r_s= -0.522, p=0.0001), as expected.

In conclusion, this meta-analysis of 14 studies highlights both the utility and the limitations of AMH levels in children and adolescent girls with a history of cancer treatment. A limitation includes the cross-sectional nature of this study, and a prospective longitudinal investigation would be valuable. Nonetheless, our findings may be useful for practicing reproductive endocrinologists, pediatric gynecologists, and oncologists.

Full Length Publications:

- Maher J, **Kumnick A**, Sinaii N, Meacham L, Gomez-Lobo V. Implications of anti-Müllerian hormone levels in female childhood and adolescent cancer survivors: a meta-analysis. [Under review]
- **Kumnick A**, Hanfling S, Dowlut-McElroy T, Maher J, Gomez-Lobo V. An intersectional analysis of contraceptive types chosen among sexual minority women: a nationally representative study. [Under review]

Abstract Publications:

- **Kumnick A,** Sinaii N, Gomez-Lobo V, Maher J. Implications of anti-Mullerian hormone levels in female childhood cancer survivors: a meta-analysis. American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting; Apr. 30 - May 2, 2021. [Virtual poster presentation]
- Barrison L**, Kumnick A**, Gomez-Lobo V, Maher J. Disparities in seeking infertility care: data from the 2017-2019 CDC National Survey of Family Growth. Society for Reproductive Investigation 68th Annual Scientific Meeting; Jul. 6-9, 2021. [Virtual oral presentation]
- Alzamora M, K**umnick A,** Gomez-Lobo V, Maher J. Fertility intention, counseling and treatment in female cancer survivors. American Society for Reproductive Medicine Scientific Congress; Oct. 17-20, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting; Apr. 30 - May 2, 2021.
- Society for Reproductive Investigation 68th Annual Scientific Meeting; Jul. 6-9, 2021.

Vijay Letchuman

School: University of Missouri – Kansas City School of Medicine
Mentor: Daniel Reich, M.D., Ph.D.; Chief, Translational Neuroradiology Section, Neuroimmunology Branch
Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research Project Title: The Central Vein Sign Profile of Newly Developing T2 or Contrast-Enhancing Lesions on Magnetic Resonance Imaging in Patients with Multiple Sclerosis

The central vein sign (CVS), a central hypointensity within lesions on T2*-weighted magnetic resonance imaging (MRI), has been established as a sensitive and specific biomarker for the diagnosis of multiple sclerosis (MS) and occurs in the large majority of MS lesions studied using high-quality MRI protocols. We aimed to identify the CVS profiles of new white matter lesions developing in MS patients followed over time and to elucidate risk factors associated with the development of new lesions with CVS positivity (CVS+) and without CVS (CVS-).

In this retrospective longitudinal cohort study, adults from the NIH MS Natural History Study were evaluated. New T2 or contrast-enhancing lesions were identified via the radiology report or subtraction imaging. MS lesions were segmented using a deep learning-based method and manually corrected by a single rater. Each new lesion was evaluated for CVS by a single, trained rater.

A total of 154 MS subjects (68% female and 10 healthy controls) were included; 96 subjects had at least one new T2 or contrast-enhancing lesion, for a total of 233 CVS-eligible lesions. The median follow-up duration for cases with new lesion(s) was 3.1 (Q1–Q3: 0.7–6.3) years. Of the CVS-eligible lesions, 159 (68%) were CVS+. Of patients with new included lesions (62/96; 65%), 30 (48%) developed only CVS+, 12 (19%) only CVS-, and 20 (32%) developed both CVS+ and CVS- new lesions. Diabetes was more frequent in those who developed only CVS+ new lesions. Increased baseline CVS+ percentage was associated with increased (OR = 1.47, 95% CI = 1.1–1.9) and older age with decreased (OR = 0.48, 95% CI = 0.3–0.8) likelihood of any new CVS+ lesion development.

In summary, our study describes the MR imaging characteristics of newly developing T2 or contrast-enhancing lesions in patients with MS, along with risk factors associated with the development of new lesions.

Full Length Publications:

- **Letchuman V***, Al-Louzi O*, Manukyan S, Beck ES, Roy S, Ohayon J, Pham DL, Cortese I, Sati P, Reich DS. The central vein sign profile of newly developing T2 or enhancing lesions in multiple sclerosis: a 3-year longitudinal study. *Neurology.* [Under Review].
  **Equal contribution*

Abstract Publications:

- **Letchuman V***, Al-Louzi O*, Manukyan S, Beck ES, Roy S, Ohayon J, Pham DL, Cortese I, Sati P, Reich DS. The central vein sign profile of newly developing T2 or enhancing lesions in multiple sclerosis. AAP/ASCI/APSA Joint Meeting. April 2021. [Virtual poster presentation]
  **Equal contribution*

Virtual Professional Meetings:

- Association of American Physicians/American Society for Clinical Investigation/American Physician-Scientists Association Joint Meeting; April 8-10, 2021.
- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2021; February 25-27, 2021.

Awards:

- NINDS Clinical Research Excellence Award, 2021
- America's Committee for Treatment and Research in Multiple Sclerosis, Educational Grant, 2020
- Foundation of the Consortium of Multiple Sclerosis Centers, Medical Student Research Scholarship, 2021

Pashayar P. Lookian

School: Creighton University School of Medicine
Mentor: Zhengping Zhuang, M.D., Ph.D., Senior Investigator, Neuro-Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Immune Mobilizing Monoclonal T-cell Receptors (TCRs) Against Cancer (ImmTAC) Targeting the Carbonic Anhydrase IX Epitope in Glioblastoma

The goal of our study was to develop a new immunotherapeutic strategy for glioblastoma (GBM) using a bispecific fusion protein engineered to express a stable, high-affinity T-cell receptor (TCR) targeting carbonic anhydrase IX (CAIX), fused to a single chain variable antibody fragment (scFv) specific for the CD3 T-cell co-receptor (anti-CAIX/anti-CD3 ImmTAC). As CAIX is overexpressed in GBM relative to normal brain tissue, our hypothesis was that the anti-CAIX/anti-CD3 ImmTac construct would specifically bind to CAIX on GBM cells and increase cytotoxicity of anti-tumor lymphocytes through targeted co-stimulatory CD3 binding.

Efficacy was assessed in 3 GBM cell lines; U251, LN229, and T98G. The specificity of the anti-CAIX/anti-CD3 ImmTac construct was validated using naïve U251 and CRISPR/Cas CAIX knockout U251 cell lines. Tumor cells and human donor lymphocytes were co-cultured with anti-CAIX/anti-CD3 ImmTAC for 48 hours in the presence of anti-CAIX/anti-CD3 ImmTAC or a saline buffer control. Cytotoxicity was measured by lactate dehydrogenase (LDH) release assay.

The LDH release assay demonstrated that the anti-CAIX/anti-CD3 ImmTAC induced an increase in cytotoxicity of 20% in the naïve U251 (80% vs 60%, $p < 0.005$) and 40% in the T98G (80% vs 40%, $p < 0.0001$) cell lines compared to the respective controls. The basal level of cytotoxicity observed is likely attributable to co-culture of tumor cells and lymphocytes, resulting in non-specific activation and/or overstimulation. There was no significant increase in cytotoxicity for the LN229 cell line due to lower inherent CAIX expression. Similarly, in the CAIX knockout U251 cells, we saw loss of the enhanced cytotoxicity effect in the presence of anti-CAIX/anti-CD3 ImmTAC, when comparing naïve to CAIX knockout U251 cells (80% vs 58%, $p < 0.005$).

Our data demonstrate that anti-CAIX/anti-CD3 ImmTAC co-administered with donor lymphocytes showed a CAIX-specific and enhanced anti-GBM immune response through attraction and activation of T-cells to ImmTac-coated tumor cells.

Full Length Publications:

- **Lookian PP***, Zhao D*, Medina R, Wang H, Zenka J, Gilbert MR, Pacak K, Zhuang Z. Mannan-BAM, TLR ligands, anti-CD40 antibody (MBTA) vaccine immunotherapy: a review of current evidence and applications in glioblastoma. *Int J Mol Sci.* 22(7):3455. 2021.
  **Equal contribution*
- Bryant JP, Chandrashekhar V, Cappadonna A, **Lookian P,** Chandrashekhar V, Vortmeyer A, Heiss JD, Zhuang Z, Rosenblum J. Multimodal atlas of the murine inner ear: from embryo to adult. Front Neurol. 12:699674. doi: 10.3389/fneur.2021.699674.
- **Lookian P**, Chandrashekhar V, Cappadonna A, Bryant JP, Chandrashekhar V, Tunacao J, Smirniotopoulos J, Heiss JD, Zhuang Z, Rosenblum J. Tentorial venous anatomy of mice and men. *JCI Insight.* [Under review]
- Cappadona A, **Lookian P**, Knutsen R, Donahue D, Chandrashekhar V, Bryant JP, Zhao D, Chandrashekhar V, Kozel B, Heiss JD, Zhuang Z. Non-invasive in situ visualization of the murine cranial vasculature. *Cell Rep Methods.* [Under review]

Abstract Publications:

- Wang H, Medina R, Ye J**, Lookian PP**, Uher O, Zenka J, Gilbert MRR, Pacak K, Zhuang Z. An immunotherapeutic vaccine composed of irradiated whole tumor cells pulsed with Mannan-BAM, TLR ligands and anti-CD40 antibody induces potent immune response in preclinical GBM animal models. Society of Neurooncology Annual Meeting and Education Day. Nov. 18, 2021
- **Lookian PP**, Rosenblum JS, Bryant JP, Cappadonna A, Wang H, Chandrashekhar V, Smirniotopoulos J, Pacak K, Zhuang Z. Glomus tumors in EPAS1 gain-of-function mutation syndrome in patients and mouse models. American Academy of Neurological Surgeons Annual Scientific Meeting, Orlando, FL; Aug. 21–25, 2021. (Virtual poster presentation)
- Rosenblum JS, **Lookian PP**, Chandrashekhar V, Cappadonna A, Tunacao J, Bryant JP, Chandrashekhar V, Smirniotopoulos J, Zhuang Z, Heiss JD. Tentorial venous anatomy of mice and men. American Academy of Neurological Surgeons Annual Scientific Meeting, Orlando, FL; Aug. 21–25, 2021. (Virtual poster presentation)
- Chandrashekhar V, Rosenblum JS, **Lookian PP**, Bryant JP, Cappadonna A, Chandrashekhar V, Smirniotopoulos J, Zhuang Z, Heiss JD. Automated neurovascular segmentation, quantification, and morphometric analysis from *ex vivo* micro-CT. American Academy of Neurological Surgeons Annual Scientific Meeting, Orlando, FL; Aug. 21–25, 2021. (Virtual poster presentation)
- Bryant JP, Rosenblum J, **Lookian PP**, Munasinghe J, Donahue D, Cappadonna A, Zhuang Z, Heiss JD. *Ex vivo* 14T MR imaging of whole mouse brain. American Association of Neurological Surgeons Annual Scientific Meeting; Aug. 21-25, 2021.

Virtual Professional Meetings

- American Academy of Neurological Surgeons Annual Scientific Meeting, Orlando, FL; Aug. 21–25, 2021.

Wenting Ma

School: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Mentors: Andrew Mannes, M.D., Chief, Department of Perioperative Medicine
Michael Iadarola, Ph.D., Senior Research Scientist, Department of Perioperative Medicine Lab
Institute: NIH Clinical Center (CC)
Research Project Title: Identifying the Molecular Signatures of Clinical Pain Neurons within the Peripheral Nociceptive Afferent Pathway

Primary afferent neurons of the dorsal root ganglia (DRG) receive somatosensory and nociceptive inputs from the periphery and transduce pain signals to the spinal cord. Administration of opioid drugs interferes with such peripheral-to-central nociceptive signaling, resulting in marked analgesia.

Additionally, selective chemoaxotomy of the central projection of DRG neurons expressing TRPV1, a calcium-permeable ion channel that transduces thermal and inflammatory stimuli, generates profound pain relief in rats, canines, and humans. However, the exact molecular properties of DRG TRPV1+ neuronal subtypes responsible for clinically-relevant pain and pain control, require further elucidation. This study examined rat DRG neurons using high resolution multiplex fluorescent *in situ* hybridization using mRNA probes to explore co-localization of pain-transducing and analgesia-producing molecular markers. *Trpv1* did not co-colocalize with *Spp1*, a marker for large diameter proprioceptive neurons, validating that nociception and proprioception are governed by distinct neuronal populations. *Trpv1+* neurons were heterogeneous, expressing varying levels of *Trpv1* and analgesic markers. While the densely labeled *Trpv1+* neurons did not co-express the mu-opioid receptor, a major mediator of opioid analgesia, neurons sparsely labeled with *Trpv1* co-expressed *Oprm1*. This finding suggests that the medium/low *Trpv1*-expressing neurons represent a population of neurons primarily responsible for pain and pain relief. Moreover, co-localization of *Trpv1* and *Oprm1* explains the remarkable efficacy of opioid drugs at the cellular level of neurocircuitry. Additionally, the medium/low *Trpv1*-expressing neurons co-expressed other markers implicated in pathological pain states, such as *Trpm8*, which is involved in cold allodynia, as well as *Scn11a*, whose gain-of-function mutation leads to familial episodic pain. As such, this investigation provides unique evidence that a specific population of medium/low *Trpv1+* DRG neurons significantly contribute to both clinical pain *and* pain relief.

Full Length Publications:

- Mannes PZ, Wang TL, **Ma W**, Selzer J, Blanco C. Substance use policies in United States allopathic medical schools: A national study. [In press]
- Sapio MR, Nara P, **Ma W**, Cassidy M, Dougherty MK, Maric D, Iadarola MJ, Mannes, AJ. A rapid approach for the near-total removal of lipofuscin autofluorescence in human postmortem dorsal root ganglion. [Under review]
- Kim JJ, Sapio MR, Vazquezl FA, Maric D, Loydpierson AJ, **Ma W**, Zarate CA, Iadarola MJ, Mannes, AJ. Transcriptional activation, deactivation and rebound molecular patterns in cortex, hippocampus and amygdala in response to ketamine infusion. [Under review]

Virtual Professional Meetings:

- 2021 Annual NIH Pain Consortium Symposium on Advances in Pain Care; May 24-25, 2021

Victoria S. Maglaras

School: State University of New York at Buffalo School of Dental Medicine
Mentor: Niki Moutsopoulos, D.D.S., Ph.D., Senior Investigator, Oral Immunity and Infection Section
Institute: National Institute of Dental and Craniofacial Research (NIDCR)
Co-Mentor: Patricia Diaz, D.D.S., Ph.D., Empire Innovation Professor and Director, UB Microbiome Center, University at Buffalo School of Dental Medicine
Research Project Title: Characterization of Oral Microbial Communities in Patients with Leukocyte Adhesion Deficiency-1 through 16S Ribosomal RNA Sequencing

Leukocyte Adhesion Deficiency Type I (LAD1) is a rare autosomal recessive disorder resulting from mutations in the ITGB2 gene that encodes for the CD18 subunit of ᵦ2 integrins. This mutation results in defective leukocyte adhesion and transmigration of neutrophils into tissues. Affected individuals suffer from recurrent infections, cutaneous lesions and periodontal disease, which is present in over 50% of LAD1 patients.

LAD1-associated periodontitis starts at a young age (often childhood) and is very severe, presenting significant alveolar bone loss and premature loss of the primary and permanent dentition, despite standard periodontal disease treatment. It is thought that the tooth-adherent bacteria and their byproducts are what trigger the inflammatory response and tissue destruction in these patients. Therefore, it is important to characterize tooth-associated microbial communities in LAD1-associated periodontitis.

We performed 16S ribosomal RNA (rRNA) sequencing of tooth-associated microbial samples from LAD1 (n=6 patients/42 samples) and healthy (n=8 patients/24 samples) age/gender matched individuals. Data analysis revealed that the microbial communities of LAD1 patients are distinctly separate from those of healthy individuals, in terms of community composition. Furthermore, tooth-associated microbial communities in LAD1 were less rich (with fewer species present) compared with those of healthy subjects.

Investigation of the relative abundance of operational taxonomic unit (OTU)-species within the two communities revealed a large number (n=164) of species differentially present between health and LAD1. While classic periodontitis-associated species such as *P. gingivalis* and *T. denticola* were not detected in LAD1, unique species such as *Pseudomonas aeruginosa* were detected in LAD1 but not in health. Another feature of the LAD1 microbiome was the absence of classical health-associated bacteria, such as *Streptococcus spp.* and *Actinomyces spp*.

Future studies will investigate the functional potential of LAD1-associated communities, and the mechanisms by which they may trigger inflammatory responses.

Justin D. McCallen

School: Brody School of Medicine at East Carolina University
Mentor: Tim Greten, M.D., Head, Gastrointestinal Malignancy Section, Thoracic and GI Malignancies Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Defining Adenosine 2a Receptor as an Immunotherapy Target for Liver Cancer in Murine Models

Immune checkpoint inhibitors such as anti-PD1 show promising treatment benefits for liver cancer and have been approved as first line treatment, yet most patients are resistant to treatment. Adenosine is a well-recognized immunosuppressive metabolite, which can be excessively generated by tumor cells via hypoxia-induced exonuclease activity of CD73, a GPI-linked cell surface enzyme.

Subsequently, adenosine can impair anti-tumor T cell responses through adenosine 2a receptor (A2aR) signaling, and recently A2aR antagonists have shown efficacy as a novel immunotherapy. Liver cancers are hypoxic and adenosinergic, yet the potential of A2aR as an immunotherapy target for liver cancer is unexplored.

Utilizing flow cytometry, we characterized the adenosine profile of previously established mouse liver cancer cell lines to identify CD73-expressing cell lines. We assessed the efficacy of single-agent or combination anti-PD1 and A2aR antagonist (SCH 58261) in treating orthotopic CD73+ liver tumor. Flow cytometry analysis was used to characterize the liver and tumor immune cells following treatment.

A mouse cholangiocarcinoma cell line, SB1, was identified as CD73+. The presence of an intrahepatic SB1 tumor increased the expression of A2aR on hepatic T cells ($p=0.019$). In tumor-bearing mice, anti-PD1 treatment increased A2aR expression on hepatic, but not splenic, CD8+ T cells (hepatic: $p=0.036$; splenic: $p=0.206$), representing potential mechanisms of T cell impairment. The combination of A2aR antagonist and anti-PD1 significantly reduced the size of intrahepatic SB1 tumors ($p<0.0001$). Immunoprofiling of hepatic CD8+ T cells showed that mice treated with single-agent or combination anti-PD1 plus A2aR antagonist produced more IFNg and TNFa (anti-PD1: $p=0.003$; combination: $p=0.008$). Yet only the combination therapy yielded hepatic CD8+ T cells that contained significantly more cytolytic molecules, granzyme B and perforin ($p=0.018$).

This study demonstrates that A2aR antagonism can overcome anti-PD1-resistance of CD73+ liver tumor. The decrease in tumor size with combination treatment corresponded with greater production of inflammatory cytokines and cytolytic function by tumor-associated hepatic T cells.

Full Length Publications:

- Wabitsch S, McVey JC, Ma C, Ruf B, Kamenyeva O, **McCallen JD,** Diggs LP, Heinrich B, Greten TF. Hydroxychloroquine can impair tumor response to anti-PD1 in subcutaneous mouse models. *iScience*. 2020 Dec 26;24(1):101990. doi: 10.1016/j.isci.2020.101990.
- Wabitsch S, **McCallen JD**, Ma C, Greten TF. Evaluating the impact of hydroxychloroquine on mouse lymphocyte proliferation and cytokine production *in vivo* and *in vitro*. *STAR Protoc*. 2021 May 3;2(2):100517. doi: 10.1016/j.xpro.2021.100517.
- Wabitsch S, Tandon M, Ruf B, Zhang Q, **McCallen JD,** McVey JC, Ma C, Green BL, Diggs LP, Heinrich B, Greten TF. Anti-PD-1 in combination with MEK inhibition suppresses tumor growth and improves survival of intrahepatic cholangiocarcinoma in mice. *Cell Mol Gastroenterol Hepatol*. 2021 May 23:S2352-345X(21)00100-4. doi: 10.1016/j.jcmgh.2021.05.011.

Abstract Publications:

- **McCallen JD**, Ma C, Greten TF. An adoptive platelet transfer assay to study platelet-mediated immune regulation in NASH mice. Federation of Clinical Immunology Societies Annual Meeting; June 8-11, 2021. [Virtual oral presentation]

Travel to Professional Meetings:

- American Association of Cancer Research Annual Meeting; Apr. 9-14, 2021
- Federation of Clinical Immunology Societies Annual Meeting; June 8-11, 2021

Diana I. Nwokoye

School: Howard University College of Medicine
Mentor: Prashant Chittiboina, M.D., Neurosurgery Unit for Pituitary and Inheritable Disorders, Surgical Neurology Branch
Institute: National Institute of Neurological Disorders and Stroke (NINDS)

Research Project Title: PPP1R17, a Novel Tumor Suppressor Regulator, Promotes Tumorigenesis in Cushing's Disease

Sporadic pituitary adenomas occur in over 10% of the population. Hormone secreting adenomas including those causing Cushing's disease (CD) cause severe morbidity and early mortality. Mechanistic studies are hindered by a lack of *in vitro* models and transcriptomic maps of the human pituitary gland. We surgically procured and annotated en-route normal human pituitary gland tissue separately from CD adenomas derived from the same subjects. We created the first transcriptomic maps of the post-natal human pituitary gland at bulk and single cell resolution.

Syngeneic pairwise bulk RNAseq analysis revealed a 16-fold overexpression of Protein Phosphatase 1 Regulatory Subunit 17 (*PPP1R17*) in CD adenomas, compared to adjacent normal pituitary tissue (p=0.04, paired t-test; 3 sets of paired adenoma-normal tissue samples) . PPP1R17 is a potent inhibitor of the tumor suppressor Protein Phosphatase 2A (PP2A). We found that *PPP1R17* expression was restricted to the CD adenoma compartment in single cell (5 adenoma-normal pairs; 3 CD and 2 non-CD samples) and single nucleus (3 CD, 2 non-CD samples) RNAseq datasets (expression logfc 2 – 5). PP2A inhibitors with known tumorigenic activity including SET, PME-1 and CIP2A were not overexpressed in any compartments. We confirmed the formation PPP1R17 -PP2A complexes with co-immunoprecipitation experiments in a brain tumor cell line, a novel, normal corticotroph-enriched murine cell line (mCort) and a murine corticotroph tumor cell line (ATT20). Overexpression of *PPP1R17* in mCort and ATT20 resulted in increased phosphorylation of AKT (Ser473) and ERK (Thr202 and Tyr204); these kinases are involved in signaling pathways that regulate cell growth, proliferation and survival.

Our findings suggest that PPP1R17, acting through its inhibition of tumor suppressor PP2A, may promote activation of tumorigenic pathways and contribute to the etiology of Cushing's disease.

Full Length Publications:

- Bryant JP, **Nwokoye DI**, Cox MF, Mbabuike NS. The progression of diversity: black women in neurosurgery. *Neurosurg Focus*. 2021 Mar 1;50(3): E9. doi: 10.3171/2020.12.FOCUS20945.
- Mortazavi A, **Nwokoye D**, Asuzu D, Scott G, Mastorakos P, Chittiboina P. Multiple VHL related hemangioblastomas and holocord syrinx: identifying the causative lesion. *J Neurosurg: Case Lessons* [In press]
- Asuzu D, Alvarez R, Fletcher P, Mandal D, Johnson K, Wu W, Elkahloun A, Clavijo P, Clint A, Dragan M, Ray-Chaudhury A, **Nwokoye D**, Nieman L, Stratakis C, Stojilkovic S, Chittiboina P. Human pituitary transcriptome reveals apoptosis escape in sporadic adenomas. [Under review]

Abstract Publications:

- **Nwokoye D**, Asuzu D, Mandel D, Chittiboina P. PPP1R17, a novel tumor suppressor regulator, promotes tumorigenesis in Cushing's disease. Congress of Neurological Surgeons Annual Meeting; Oct. 16-20, 2021. [Submitted]
- **Nwokoye D,** Asuzu D, Scott G, Nieman L, Smart DeeDee, Chittiboina P. The effect of vorinostat on ACTH-producing pituitary adenomas in Cushing's disease. Congress of Neurological Surgeons Annual Meeting; Oct. 16-20, 2021. [Submitted]
- Celano D, **Nwokoye D**, Chittiboina P. Deep phenotyping reveals germline determinants of disease severity in Neurofibromatosis Type 2. Congress of Neurological Surgeons Annual Meeting; Oct. 16-20, 2021. [Submitted]
- Cierra H, **Nwokoye D**, Fossett D. Management of cervical fracture in the setting of ankylosing spondylitis: a case report. Congress of Neurological Surgeons Annual Meeting; Oct .16-20, 2021. [Submitted]
- Azusu D, Haynes C, **Nwokoye D**, Neiman L, Stratakis C, Chittiboina P. Post-operative cortisol dynamics in Cushing's disease patients predicts early remission after transsphenoidal surgery. Congress of Neurological Surgeons Annual Meeting; Oct 16-20, 2021. [Submitted]
- Clark V, Williams G, Kolade O, **Nwokoye D**, Clemmon J, Okorie N, Fossett D. Radiation-free intraoperative neuronavigation for lumbosacral pedicle screw placement. Congress of Neurological Surgeons Annual Meeting; Oct 16-20, 2021. [Submitted]

Erika N. Ortiz Chaparro

School: University of Puerto Rico School of Medicine
Mentor: Tiffany Powell-Wiley, M.D., Stadtman Investigator and Chief, Social Determinants of Obesity and Cardiovascular Risk Laboratory, Cardiovascular Branch
Institute: National Heart Lung and Blood Institute (NHLBI)

Research Project Title: Assessing Correlations between Inflammatory Mediators, Immune Cells, and the Built Environment in African American Women

Cardiovascular disease (CVD) is the leading cause of death worldwide and disproportionately impacts African Americans (AAs). AAs are also disproportionately exposed to under-resourced built environments, a factor that has been suggested to be associated with CVD. Many immune cells and cytokines have also been associated with CVD.

It is less well-known, however, how the built environment relates to inflammatory pathways. Using survey and laboratory data, our goal was to show if and how built environment associates with CVD-related cytokines and immune cells, specifically, monocytes.

Survey data and blood samples were obtained for a community-based cohort of AA women (N=40, age=59 [12] years) living in the Washington, DC metropolitan area. The Walk Score, an objective measure of neighborhood walkability, was used as a validated indicator of built environment. Serum cytokine levels were measured using Luminex technology and log-transformed. Monocyte subtypes were phenotyped using flow cytometry. We used linear regression models to determine relationships between Walk Score and both monocytes and cytokines, adjusting for body mass index, atherosclerotic CVD 10-year risk score, and neighborhood deprivation index, a neighborhood-level socioeconomic status measure.

Walk score was negatively associated with cytokines IL-15 (-0.34, p=0.03) and IP-10/CXCL10 (-0.36, p=0.02) and with total monocyte levels (-0.35, p=0.04). Therefore, as neighborhood walkability increased, IL-15, IP-10 and total monocyte levels decreased. Walk Score also trended toward a significant positive association with TGF-β (0.32, p=0.05) and classical monocytes (0.35, p=0.05), and a negative association with intermediate monocytes (-0.35, p=0.05). These results suggest an association between built environment and the level of CVD-related cytokines and monocytes. This highlights the importance of seeking connections between an individual's biology and their environment. Our findings also reinforce the notion that public health interventions targeting healthy behaviors and CVD risk should seek to impact the built environment of our communities.

Full Length Publications:

- Tamura K, Curlin K, Neally S, Vijayakumar N, Mitchell V, Collins B, Gutierrez Huerta C, Troendle J, Baumer Y, Osei Baah F, Turner B, Gray V,Tirado B, **Ortiz-Chaparro E**, Berrigan D, Mehta N, Vaccarino V, Zenk S, Powell-Wiley T. Geospatial analysis of neighborhood environmental stress in relation to biological markers of cardiovascular health and health behaviors in women: protocol for a pilot study. *JMIR Res Protoc.* 2021 Jul 22;10(7):e29191.
- Lee B, Powell-Wiley T, Ferguson M, Tamura K, Neally S, O'Shea K, Curlin K, Albarracin Y, Vijayakumar N, Morgan M, **Ortiz-Chaparro E**, Bartsch S, Osei Baah F, Wedlock P, Siegmund S, Randall S, Solano Gonzalez M, Domino M, Ranganath K, Hertenstein D, Syed R. Simulating the impact of a place-tailored digital health app promoting exercise classes on African-American women's physical activity and obesity. *J Med Internet Res.*[Under review]

Abstract Publications:

- **Ortiz-Chaparro E**, Neally S, Vijayakumar N, Curlin K, Tamura K, Turner B, Gray V, Tirado B, Mitchell V, Collins B, Saxena A, McCoy J, Osei Baah F, Baumer Y, Powell-Wiley T. Associations between neighborhood walkability and proinflammatory cytokines related to cardiovascular disease risk in African American women. Society of Behavioral Medicine 42nd Annual Meeting and Scientific Sessions; April 12–16, 2021. [Virtual poster presentation]
- Gray V, Turner B, Gutierrez-Huerta C, Neally S, Curlin K, Vijayakumar N, **Ortiz-Chaparro E**, Tirado B, Mitchell V, Collins B, Baumer Y, Powell-Wiley T. Social isolation associates with the expression of NKp46 on Natural Killer cells through a relationship partially mediated by RANTES in African-American women. American Heart Association EPI/Lifestyle Scientific Sessions; May 20-21, 2021. [Virtual poster presentation]

Virtual Professional Meetings

- American Medical Students Association Convention & Exposition; March 6-8, 2021.
- American Medical Association 2021 Medical Student Advocacy Conference; March 4–5, 2020.
- Society of Behavioral Medicine 42nd Annual Meeting and Scientific Sessions; April 12–16, 2021
- Harvard Medical School 20th Annual New England Science Symposium; April 23-24, 2021.

Awards

- Society of Behavioral Medicine Annual Meeting, Student Award for Outstanding Abstract Submission, 2021.

Jeunice S. Owens-Walton

School: Medical College of Georgia at Augusta University
Mentor: Mark Ball, M.D., Assistant Research Physician, Urologic Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Examining Minority Enrollment in Clinical Trials in Urologic Oncology

Racial/ethnic disparities affect outcomes across medicine, and the field of oncology is no exception. Proportionate representation in clinical trials is an important step towards addressing health and healthcare inequities. Given the paucity of existing data on this topic in urologic oncology, we sought to quantify the enrollment of minority patients in clinical trials studying prostate, kidney, and bladder/urothelial cancers.

We identified nationally registered clinical trials by querying the *ClincialTrials.gov* database for completed phase II and III interventional clinical trials in the US funded by the NIH, academic centers, or industry sponsors in prostate, kidney, and bladder cancers. The Surveillance, Epidemiology, and End Results (SEER) database was then queried for the US prevalence of prostate, kidney, and bladder cancer cases between 2007 and 2017. Representation Quotients (RQ) were calculated to describe the proportion of each racial/ethnic group enrolled in clinical trials over the proportion of persons from each group among national cancer cases by cancer type.

One-hundred and sixty-nine clinical trials met inclusion criteria. Aggregate RQs from 2000 to 2017 showed that White patients were continually overrepresented in trials for all cancer types. Black and Asian patients were poorly represented across all cancer types. When then stratified by 2-year increments, the RQs remained stable for all races, from 2000-2017. When stratified by ethnicity, Hispanic patients were underrepresented across all cancer types in the study period. When examining representation by funding source, we found that US government funded clinical trials proportionally enroll the most diverse patient populations compared to academic institutions and industry.

Clinical trials targeting prostate, kidney and bladder cancers continue to underrepresent racial/ethnic minority patients. Based on the incidence of these cancers within minority populations, there need to be improved and targeted efforts focused on creating racially and ethnically inclusive cancer research.

Full Length Publications:

- **Owens-Walton J**, Gurram S, Merino MJ, Linehan WM, Ball MW. Macronodular adrenal hyperplasia masquerading as an upper pole renal mass. *Urol Case Rep.* 2021 Feb 12;37:101603. doi: 10.1016/j.eucr.2021.101603.
- Williams C*, Khondakar NR*, Daneshvar MA, O'Connor LP, Gomella PT, Mehralivand S, Yerram NK, Egan J, Gurram S, Rompré-Brodeur A, Webster BR, Owens-Walton J, Parnes H, Merino MJ, Wood BJ, Choyke P, Turkbey B, Pinto PA. The risk of prostate cancer progression in active surveillance patients with bilateral disease detected by combined MRI-fusion and systematic biopsy. *J Urology.* 2021 Jun 28. doi: 10.1097/JU.0000000000001941.
- Khondakar NR, **Owens-Walton J**, Daneshvar M, Williams C, O'Connor L, Yerram NK, Pinto PA. Emerging role for local therapy in oligometastatic prostate cancer. *Clin Adv Haemotol Oncol.* 2021 Jul:19(7):460-467.
- **Owens-Walton J**, Pinto PA. Translational Urology: Handbook for Designing and Conducting Clinical and Translational Research. Elseiver Clinical and Translational Urology Research. Public Health, Chapter 101, Good questions. [Under review]
- **Owens-Walton J**, Williams C, Rompre-Brodeur A, Pinto PA, Ball MW. Minority enrollment in phase II and III clinical trials in urologic oncology. [Under review]

Abstract Publications:

- **Owens-Walton J**, Williams C, Rompré-Brodeur A, Pinto P, Ball MW. Examining minority enrollment in clinical trials in urologic oncology. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Oral presentation]
- **Owens-Walton J**, Okoro C, Rompré-Brodeur A, Merino M, Ball MW. Active surveillance in nonhereditary bilateral multifocal type I papillary renal cell carcinoma. American Urologic Association Annual Meeting, Las Vegas, NV ; Sep. 2021 [Poster presentation]
- Rompré-Brodeur A, **Owens-Walton J**, Gurram S, Gomella PT, Webster BR, Ryan B, Nielsen D, Ricketts C, Nix J, Bratslavsky G, Metwalli A, Gautam R, Malayeri AA, Merino MJ, Pinto PA, Srinivasan R, Ball MW, Linehan WM, Management of hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated renal cell carcinoma. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Poster presentation]
- Egan J, Gurram S, **Owens-Walton J**, Li, Lineham WM, Ball MW. Predicting renal functional outcomes after partial nephrectomy: a comparison of nephrometry systems. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Poster presentation]

Abstract Publications (continued)

- Williams C, Daneshvar MA, Wu Y, **Owens-Walton J**, Yerram NK, Gomella PT, O'Connor LP, Khondakar NR, Ahdoot MA, Negussie A, Xu S, Turkbey B, Merino MJ, Boctor E, Wiskin J, Wood BJ, Pinto PA. Prostate ultrasound tomography: correlation with MRI and whole mount histopathology. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Poster presentation]
- Williams C, Daneshvar M, Khondakar N, **Owens-Walton J**, O'Connor LP, Yerram N, Gomella PT, Ahdoot M, Webster BR, Choyke P, Turkbey B, Merino M, Wood B, Pinto P. Utility of MRI and targeted biopsy to diagnose local cancer recurrence after prostatectomy. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Poster presentation]
- Khondakar N, Ahdoot M, O'Connor L, Daneshvar M, Yerram N, Williams C, **Owens-Walton J**, Gurram S, Gomella P, Egan J, Mehralivand S, Merino M, Wood B, Turkbey B, Pinto P. Predictors of Gleason grade upgrading on wholemount pathology after MRI. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Poster presentation]

- Khondakar N, Egan J, O'Connor L, Ahdoot M, Wiliams C, Daneshvar M, Yerram N, **Owens-Walton J**, Gurram S, Choyke P, Merino M, Wood B, Turkbey B, Pinto P. The significance of multiple negative biopsies in patients on active surveillance. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Oral presentation]

Virtual Professional Meetings

- Society of Urologic Oncology 21st Annual Meeting, Dec. 2-4, 2020.
- Society of Women in Urology 10th Annual Clinical Mentoring Conference, Jan. 22, 2021.
- American Society of Clinical Oncology Genitourinary (GU-ASCO), Feb. 11-13, 2021.

Awards:

- Donald M. Mode Urology Research Symposium. Best Student Presentation, Second Place 2021. Medical College of Georgia Department of Urology.

Sriram S. Paravastu

School: University of Missouri- Kansas City School of Medicine
Mentor: Pamela G. Robey, Ph.D., Senior Investigator, Skeletal Biology Section
Institute: National Institute of Dental And Craniofacial Research (NIDCR)
Research Project Title: Articular Cartilage Repair by Human Bone Marrow Stromal Cells on Hyaluronic Acid-Coated Fibrin Microbeads

Osteoarthritis is often disabling; affected cartilage rarely heals, leading to progressive dysfunction. Effective treatments are lacking. Subcutaneously transplanted naïve human bone marrow stromal cells (hBMSC) are able to form stable cartilage in conjunction with hyaluronic acid-coated fibrin microbeads (FMBs). We investigated the ability of hBMSC/FMB constructs to generate native cartilage-like tissue in articular cartilage defects in immunocompromised rats.

hBMSCs from surgical bone waste were grown in culture. Articular cartilage defects were created in immunocompromised SRG rat distal femurs via microdrill injury. Defects were left unrepaired (sham), or filled with FMBs alone, hBMSCs attached to FMBs (FMBs+cells), or with a pellet created by incubating hBMSCs with FMBs for 10 days in chondrogenic medium. At 4 and 8 weeks, and 4 and 6 months post-surgery, femurs were harvested and paraformaldehyde-fixed, EDTA-decalcified for 30 days, paraffin-embedded, sectioned, and stained. A region of interest (ROI) was drawn surrounding the defect, and the percentage of the ROI staining positive for cartilage proteoglycan with safranin O (CP+ROI) was calculated. Second-harmonic generation microscopy (SHG) was used to evaluate histomorphometry.

Toluidine blue staining revealed cartilage formation in defects at 4- and 8-weeks in the FMBs+cells and pellet groups. CP+ROI in the 8-week FMBs+cells and pellet groups was 8.95% and 3.03%. A comparable healthy rat CP+ROI was 58.43%. CP+ROI in the 6-month FMBs+cells and pellet group defect areas was 3.11% and 1.67%. There was negligible CP+ROI in all FMBs alone and sham groups. SHG showed that from sham to FMB alone to pellet to FMBs+cells groups, the organization of collagen fibrils began to more closely approximate healthy rat cartilage at 8 weeks.

At early timepoints, there is evidence of cartilage formation in drilled articular cartilage defects in both the FMBs+cells and pellet groups, demonstrating the potential for our method to regenerate articular cartilage.

Full Length Publications:

- Jallouk AP, **Paravastu S**, Weilbaecher K, Aft RL. Long-term outcome of neoadjuvant zoledronic acid therapy in locally advanced breast cancer. *Breast Cancer Res Treat.* 2021 May; 187(1):135-144. doi:10.1007/s10549-021-06100-2

Abstract Publications:

- **Paravastu SS**, Mui BW, Gadomski SJ, Merling R, Kuznetsov S, Robey PG. Articular cartilage regeneration in rats using human bone marrow stromal cells. Osteoarthritis Research Society International (OARSI) 2021 World Conference; April 29-May 3, 2021. (Virtual oral presentation)

Virtual Professional Meetings:

- Osteoarthritis Research Society International (OARSI) 2021 World Conference; April 29-May 3, 2021.

Nidhi H. Patel

School: University of Miami Miller School of Medicine
Mentor: Nehal Mehta, M.D., Senior Investigator, Section of Inflammation and Cardiometabolic Diseases
Institute: National Heart, Lung, Blood Institute (NHLBI)

Research Project Title: Heightened Leukopoietic Activity Associates with Systemic Inflammation and Subclinical Atherosclerosis; Results from Two Observational Studies

In stable patients without chronic inflammatory conditions, higher splenic leukopoietic activity predicts major adverse cardiovascular events (MACE). Psoriasis is an immune-mediated inflammatory disease with increased risk of myocardial infarction. Preclinical studies in psoriasis models show an association between chronic inflammation and leukopoiesis. We sought to test the hypothesis that leukopoietic activity is heightened in psoriasis, and that higher leukopoiesis associates with systemic inflammation and atherosclerotic disease measures in this cohort.

Multimodality imaging and biomarker assays were performed in 240 participants (210 with psoriasis and 30 healthy). Leukopoietic activity (spleen and bone marrow (BM) uptake) and arterial inflammation were obtained using fluorodeoxyglucose positron emission tomography/ computed tomography (FDG PET/CT). Coronary artery characteristics including non-calcified burden (NCB) and lipid rich necrotic core (LRNC) were quantified using dedicated software for CT angiography. Next, in a longitudinal study of 441 individuals without psoriasis, we examined the relationship between leukopoietic activity and arterial inflammation, and subsequent MACE.

Splenic and BM activity were increased in psoriasis (vs healthy volunteers) and significantly associated with proatherogenic lipids, and systemic and arterial inflammation. Higher splenic activity associated with higher total coronary burden (β=0.33; $p<0.001$), NCB (β=0.36; $p<0.001$), and LRNC (β=0.36; $p<0.001$) in adjusted models. Similar associations were seen for BM activity in adjusted models (β=0.36; β=0.39; β=0.26; respectively, all $p<0.001$). Further, arterial inflammation mediated the association between splenic and BM activity and NCB in psoriasis by 44% and 43% respectively. Concordantly, in individuals without psoriasis, arterial inflammation mediated 74% of the relationship between splenic activity and MACE.

In psoriasis, there was evidence of heightened leukopoiesis which associated with coronary artery disease and which was partly mediated by arterial inflammation. Further, this leukopoietic-arterial axis appears to contribute to MACE among individuals without inflammatory conditions. Accordingly, these findings provide insights into atherogenic mechanisms in psoriasis and in the general population.

Full Length Publications:

- **Patel NH**, Osborne M, Teague H, Parel P, Svirydava M, Sorokin AV, Teklu M, Manyak G, Zhou W, Pantoja C, Scott C, Playford M, Kapoor P, Rodante J, Keel A, Chen M, Tawakol A, Mehta NN. Heightened leukopoietic activity associates with systemic inflammation and subclinical atherosclerosis; results from two observational studies. *Circ Cardiovasc Imaging.* [Under review]
- **Patel NH**, Dey A, Sorokin AV, Teklu M, Petrole R, Zhou W, Mehta NN. Chronic inflammatory diseases and coronary heart disease: insights from cardiovascular CT. *J Cardiovasc Comput Tomogr.* 2021 Jun 24: S1934-5925(21)00086-1. doi: 10.1016/j.jcct.2021.06.003.
- Manyak G, **Patel NH**, Teklu M, Mehta NN. Inflammation and cardiometabolic diseases: lessons learned from psoriasis. *Int J Cardiol Diab* (2021). [In press]
- Manyak G, **Patel NH**, Dey A, Svirydava M, Parel P, Teague H, Sorokin A, Teklu M, Zhou W, Rodante J, Keel A, Playford M, Mehta NN. Chronic inflammation in psoriasis promotes visceral adipose tissue association with lipid-rich necrotic core through atherogenic myeloid score. *Arterioscler Thromb Vasc Biol.* [Under review]
- Zhou W, Dey A, Manyak G, Teklu M, **Patel NH**, Teague H, Mehta NN. The application of molecular imaging to advance translational research in chronic inflammation. *J Nucl Cardiol.* 2020 Nov 26. doi: 10.1007/s12350-020-02439-z.
- Teklu M, Zhou W, Kapoor P, **Patel NH**, Dey A, Sorokin A, Manyak G, Teague H, Erb-Alvarez J, Sajja A, Abdelrahman K, Reddy A, Uceda D, Lateef SS, Shanbhag SM, Scott C, Prakash N, Svirydava M, Parel P, Rodante J, Keel A, Siegel E, Chen M, Bluemke D, Playford M, Gelfand J, Mehta NN. Metabolic syndrome and its factors are associated with noncalcified coronary burden in psoriasis: an observational cohort study. *J Am Acad Dermatol. 2021* May;84(5):1329-1338.
- Gonzalez A*, Teklu M*, Sorokin A, Prussick R, Gonzalez-Cantero J, Martin-Rodriguez J, **Patel NH**, Manyak G, Teague H, Rodante J, Keel A, Perez-Hortet C, Sanchez-Moya AI, Jiminez N, Ballester A, Solis J, Fernandez-Friera L, Barderas MG, Gonzalez-Calvin JL, Jaen P, Playford M, Dey A, Gelfand J, Mehta NN. Subclinical liver disease is associated with subclinical atherosclerosis in psoriasis: results from two observational studies. *J Invest Dermatol.* [In press]
- Teklu M, Zhou W, Kapoor M, **Patel NH**, Playford M, Sorokin A, Dey A, Teague H, Abdelrahman K, Manyak G, Erb-Alvarez J, Shanbhag S, Rodante J, Keel A, Lockshin B, Chen M, Gelfand J, Bluemke D, Wenger N, Mehta NN. Sex differences in subclinical coronary atherosclerosis in psoriasis by coronary computed tomography angiography. *JACC Cardiovasc Imaging.* [In press]

Full Length Publications (continued)

- Teklu M, Zhou W, Kapoor P, **Patel NH**, Playford M, Sorokin A, Dey A, Teague H, Manyak G, Rodante J, Keel A, Chen M, Bluemke D, Mehta NN. Abdominal subcutaneous adipose tissue negatively associates with subclinical coronary artery disease in men with psoriasis. *Am J Prev Cardiol*. [Under review]
- Zhou W, Teklu M, Bui Vy, Manyak G, Kapoor P, Dey A, Sorokin A, **Patel NH**, Teague H, Playford M, Erb-Alvarez J, Rodante J, Keel A, Shanbhag S, Hsu LY, Bluemke D, Chen M, Carlsson M, Mehta NN. The relationship between systemic inflammation and increased left ventricular mass is partly mediated by noncalcified coronary artery disease burden in psoriasis. *Am J Prev Cardiol*. [Under review]

Virtual Professional Meetings:

- American Heart Association Scientific Sessions; Nov. 13-15, 2020.

Casey M. Paton

School: University of Rochester School of Medicine
Mentor: Neal Young, M.D., Chief, Hematology Branch
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research Project Title: Identifying Somatic Mutations Associated with Morbidity in Hematologic Conditions

Aplastic anemia is a marrow failure syndrome in which hematopoietic progenitors do not produce sufficient numbers of erythrocytes, leukocytes, and megakaryocytes to sustain the body. Aplastic anemia can transition to myeloid malignancy. The disproportionate propagation of distinct hematopoietic clones is a hallmark of aplastic anemia. Somatic mutations identified in these clones by DNA sequencing can provide information on the dynamics and clinical correlates of the condition.

By sequencing the blood of 660 patients and comparing the genomic data with clinical patient outcomes, we identified specific somatic mutations and strengthened existing evidence for their association with risk of cancer or death.

Patients were divided into those with clonal evolution (n=95) and those without (n=566). The clonal evolution group was then further divided into those with High Risk (HR, n=59) or Low Risk (LR, n=36) evolution. The HR group contained distinct karyotypes: monosomy 7, deletion 7p, inversion 7, and complex changes, while the LR group contained its own distinct karyotypes: deletion 13q, deletion 5q, and trisomy 8. The HR group was more likely to possess somatic mutations in the genes RUNX1, SETBP1, or U2AF1. The LR group was more likely to possess somatic mutations in the genes BCOR or BCORL1. Both groups were observed to have mutations in the ASXL1 and DNMT3A genes.

We then sought to define predictive clinical indicators for risk of clonal evolution. We found that having both age greater than 37 and absolute neutrophil count greater than 870/uL at time of diagnosis were associated with a statistically higher risk of clonal evolution. These indicators will be useful for clinical management in future cases.

Together, these findings emphasize the role that somatic mutations play in the development of clonal evolution in aplastic anemia. They also strengthen the association between the somatic mutation RUNX1 and increased evolution risk.

Full Length Publications:

- **Paton C**, Mathews L, Groarke E, Rios O, Lotter J, Patel B, Young NS. COVID-19 infection in patients with severe aplastic anaemia. *Brit J Haematol.* 2021 Apr;193(5):902-905. doi: 10.1111/bjh.17415.

Abstract Publications:

- Groarke E, Patel B, Shalhoub R, Gutierrez-Rodrigues F, Desai P, Leuva H, Paton C, Young NS. Chromosomal aberrations and myeloid neoplasia following immunosuppression therapy for severe aplastic anemia: a retrospective cohort study. American Society of Hematology 63rd Annual Meeting; Dec. 11-14, 2021. [Submitted]

Virtual Professional Meetings:

- American Society of Hematology 62nd Annual Meeting; Dec. 2-10, 2020.
- European Hematology Association Annual Meeting; June 11, 2020.

Christian J. Peoples

School: Drexel University College of Medicine
Mentor: Mark Gilbert, M.D., Chief, Neuro-Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: High-affinity Natural Killer Cells and Avelumab: a Novel Combination Immunotherapy to Drive Antibody-dependent Cellular Cytotoxicity in Recurrent, High-grade Meningioma

High-grade meningiomas (grade II and III) are rare central nervous system tumors with malignant characteristics and a poor prognosis. Gross total resection is the optimal first step of treatment for both low and high-grade meningiomas, although additional treatment such as radiation is needed for the high-grade tumors. However, despite these measures, tumor recurrence is common in high grade tumors and there are no established treatments for this situation.

Immunotherapy may be an important treatment to consider. Immune checkpoint inhibitor therapy has been effective in other cancers, often strongly correlating with tumor expression of programmed death-ligand 1 (PD-L1). Importantly, PD-L1 expression correlates with grade of meningioma and although considered a brain tumor, meningioma is outside the blood-brain barrier. Preclinical testing of avelumab, a fully human anti-PD-L1 monoclonal antibody, in combination with high-affinity natural killer cells (haNK, the NK-92 human cell line engineered to express the high affinity CD16 V158 FcγRIIIa receptor) in meningioma-bearing mouse models, showed dramatic efficacy. Specifically, avelumab binds to PD-L1 receptors on tumors cells, disrupting the tumor's mechanism of exhausting host immune cells. Avelumab-coated tumor cells also serve as a target for haNK cells, which express Fc receptors that bind with high affinity to avelumab. We have designed a phase 1 clinical trial to identify the maximum tolerated dose and safety profile of avelumab in combination with haNK cells, which will enable a subsequent phase 2 efficacy study. Irradiated haNK cells are not patient specific, enabling widespread use. The phase 1 study will test increasing doses of the haNK cells to establish the optimal dosing. Additionally, 6-month progression-free survival, overall survival and patient outcomes measures using the MD Anderson Symptom Inventory for Brain Tumors (MDASI-BT) will be collected for preliminary efficacy data. In summary, this clinical trial, based on strong preclinical data, uses state of the art immunotherapy for a patient population with a rare disease.

Virtual Professional Meetings:

- American Association of Cancer Research: Tumor Immunology and Immunotherapy; Oct. 19–20, 2020.
- Society for Neuro-Oncology 2021 Meningioma Day: Current Management Strategies and Future Directions; May 15, 2021..

David K. Peprah

School: Yale School of Medicine
Mentors: Emily Chew, M.D., Director, Division of Epidemiology and Clinical Applications, Clinical Trials Branch; Tiarnan Keenan, M.D., Ph.D., Staff Clinician, Clinical Trials Branch
Institute: National Eye Institute
Research Project Title: Diabetes and Diabetic Retinopathy in African-born Blacks: a Cross-sectional Study

We performed a cross-sectional analysis of the prevalence of diabetes mellitus (DM) and diabetic retinopathy (DR) among 265 African-born blacks living in the Washington D.C. metropolitan area (male 62%, age 39.7±10.2y (mean±SD), BMI 27.8±4.5 kg/m2), who self-reported as healthy. Participants underwent oral glucose tolerance test (OGTT), comprehensive eye exams, spectral domain optical coherence tomography (OCT) and fundus photography.

Hemoglobin A1c (HbA1c), glycated albumin (GA) and fructosamine levels were determined. Allostatic load score (number of physiologic parameters for which the subject fell into highest risk quartiles) was calculated and visceral adiposity assessed with abdominal CT. Normal glucose tolerance (NGT) was documented in 49.1% (130/265), pre-DM in 40.0% (106/265), and newly-diagnosed DM in 10.2% (27/265). Retinopathy was present in 1.5% (4/265) overall: 18.5% (3/27) in those with DM, 1.0% (1/104) with pre-DM, and 2.3% (3/130) with NGT. The 3 NGT cases with retinopathy had hypertension and were excluded from analysis. On univariate analysis of diagnostic testing modalities, significant associations with DR were found in fasting glucose ($p<0.002$), 2h glucose from the OGTT ($p=0.010$), and fructosamine ($p=0.025$); no associations were found with HbA1c or GA ($p=0.089$ and 0.142, respectively). Higher allostatic load score and visceral adipose tissue were associated with DR ($p=0.025$ and 0.049, respectively). Additional ocular evaluations showed that 34.7% of participants had a cup/disc ratio $\geq$ 0.5 (normal 0.3), while mean intraocular pressure was 15±3 (normal 10-21) mmHg. Mean visual acuity was 20/25 for those without retinopathy and 20/36 for those with retinopathy ($p=0.037$). Retinal thickness by OCT demonstrated no differences among those with and without abnormal glycemic status. In conclusion, the combined prevalence of DM and pre-DM was high (50.2%) in this African-origin population, and DR was present in 18.5% with DM. In addition, a relatively large proportion of subjects had elevated cup/disc ratios, without an associated increase in intraocular pressure.

Full Length Publications:

- Le J, **Peprah D**, Agrón E, Keenan T, Clemons T, Chew E. Associations between age-related eye diseases and Charles Bonnet syndrome: Age-Related Eye Disease Study 2 Report Number 26. *Ophthalmology*. [In press]

Abstract Publications:

- **Peprah D**, Hwang C, Agrón E, Sumner A, Chew E. Diabetes and diabetic retinopathy in African-born blacks: a cross-sectional study. Association for Research in Vision and Ophthalmology; May 1-7, 2021. [Virtual poster presentation]
- Vitale S, Agrón E, Bhandari S, **Peprah D**, Farrell M, Clemons T, Keenan T, Domalpally A, Chew E. Does cataract surgery increase the risk of future development of late AMD? A nested case-control study from the AREDS2 and AREDS2 follow-on studies. Association for Research in Vision and Ophthalmology; May 1-7, 2021. [Virtual poster presentation]
- Broadhead G, Agrón E, **Peprah D**, Keenan T, Clemons T, Lawler T, J. A. Mares; E. Y. Chew. Dietary nitrate consumption and risk of progression in age-related macular degeneration. Association for Research in Vision and Ophthalmology; May 1-7, 2021. [Virtual presentation]
- Bhandari S, Agrón E, Vitale S, **Peprah D**, Farrell M, Clemons T, Keenan T, Domalpally A, Chew E. Cataract surgery and the risk of progression to late age-related macular degeneration: The Age-Related Eye Disease Study 2. Association for Research in Vision and Ophthalmology; May 1-7, 2021. [Virtual presentation]
- Thavikulwat A, Keenan T, Christakis P, **Peprah D**, Zonderman A, Evans M, Chew E. Retinal photography in a cohort of urban middle-aged adults. Association for Research in Vision and Ophthalmology; May 1-7, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Academy of Ophthalmology Virtual Annual Meeting. Nov. 13-15, 2020.
- Association for Research in Vision and Ophthalmology; May 1-7, 2021.

Emmanuel M. Quaye

School: University of Michigan Medical School
Mentor: Rebecca Brown, M.D., Lasker Clinical Research Scholar, Section on Translational Diabetes and Metabolic Syndromes, Diabetes Endocrinology and Obesity Branch
Institute: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Research Project Title: Leptin Decreases Energy Expenditure Despite Increased Thyroid Hormone in Patients with Lipodystrophy

Leptin is an adipokine that signals energy sufficiency. In rodents, leptin deficiency decreases energy expenditure (EE), which is corrected following leptin replacement. In humans, data are mixed regarding leptin-mediated effects on EE.

Using lipodystrophy as a human model of leptin deficiency and replacement, we conducted a non-randomized crossover study of 25 patients with lipodystrophy to determine the effects of metreleptin, a recombinant human leptin analog, on EE. We hypothesized that metreleptin treatment in patients with lipodystrophy would increase EE, neuroendocrine mediators of energy expenditure, sympathetic nervous system activity, and blood pressure. The initiation cohort consisted of 17 patients without prior exposure to metreleptin, studied before and after 14 days of parenteral metreleptin. The withdrawal cohort consisted of 8 previously metreleptin-treated patients, studied before and after 14 days of metreleptin withdrawal. We assessed 24-hour energy expenditure (TEE), resting energy expenditure (REE), autonomic nervous system activity (heart rate variability, HrV), plasma free T3, free T4, epinephrine, norepinephrine, and dopamine.

In the initiation cohort, TEE and REE decreased by 5.0% (121 ± 152 kcal/day; p=0.006) and 5.9% (120 ± 175 kcal/day; p=0.02). Free T3 increased by 19.4% (40 ± 49 pg/dL; p=0.01). No changes in catecholamines or HrV were observed. In the withdrawal cohort, free T3 decreased by 8.0% (p=0.04), free T4 decreased by 11.9% (p=0.002), and norepinephrine decreased by 34.2% (p=0.03), but no changes in EE, epinephrine, dopamine, or HrV were observed.

Metreleptin initiation decreased EE in patients with lipodystrophy, but no changes were observed after metreleptin withdrawal. Thyroid hormone was higher during metreleptin administration in both initiation and withdrawal cohorts. Decreased EE after metreleptin in lipodystrophy may result from reductions in energy-requiring metabolic processes (e.g., gluconeogenesis) that counteract increases in EE via adipose tissue-specific neuroendocrine and adrenergic signaling.

Full Length Publications:

- Grover A,* **Quaye E***(equal contribution), Brychta RJ, Christensen J, Startzell MS, Meehan CA, Valencia A, Marshall B, Chen KY, Brown RJ. Leptin decreases energy expenditure despite increased thyroid hormone in patients with lipodystrophy. *J Clin Endocrinol Metab*. 2021 April 23. doi: 10.1210/clinem/dgab269.
- **Quaye E**, Chacko S, Chung ST, Brychta RJ, Chen KY, Brown RJ. Energy expenditure due to gluconeogenesis in insulin resistance. [In preparation]

Abstract Publications:

- **Quaye E**, Grover A, Brychta RJ, Christensen J, Startzell MS, Meehan CA, Valencia A, Marshall B, Chen KY, Brown RJ. Leptin decreases energy expenditure despite increased thyroid hormone in patients with lipodystrophy. Endocrine Society Annual Meeting; March 20-23, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- Endocrine Society Annual Meeting; March 20-23, 2021.

Sheridan L. Reed

School: Michigan State University – College of Human Medicine
Mentor: Bradford J. Wood, MD., Director, NIH Center for Interventional Oncology
Institute: Clinical Center (CC) and National Cancer Institute (NCI)

Research Project Title: Safe from COVID-19: Development of a Novel Device to Protect against Asymptomatic Transmission due to Nebulized Medications, Intrahospital Transport, and in Imaging Suites

It has become increasingly recognized during the SARS CoV-2 pandemic that asymptomatic transmission is a major driver of outbreaks. Available isolation devices attempt to contain viral particles inside the device to decrease transmission; however, they have high costs and have been found to increase specific risks to healthcare workers.

We propose a novel filtration device that protects nearby patients and the surrounding environment (imaging suites), from serving as potential sources of exposure by reducing viral load to the nearby environment.

Using benchtop phantom studies, particle concentration was measured inside and outside the device, at both the filter covering the face of the phantom and the Velcro-sealed waist. Coughing was simulated inside the device by using pulsatile nebulized saline salts. Efficacy was measured using a "Derived Fit Factor" (dFF), the inverse of the Fit Factor defined by OSHA guidelines for mask respirators. While Fit Factor itself is designed to measure mask seals for protection of the wearer, the "derived Fit Factor" works as a surrogate measure of "source control." For particles 0.5 um in size, with the device fitted to 200 mmHg of suction and 1L/min of oxygen flow, the dFF remained above 100 for 100% and 52.3% of experiment duration for the filter and waist, respectively. For the same parameters, the dFF remained above 500 for 95.2% and 28.6% of experiment duration for the filter and waist. OSHA mandates a dFF above 100 for half-face respirators and 500 for full-face respirators.

As part of device development and validation, wearer vital signs were measured over time, and similar reverse fit tests were deployed. Pressure gradient across the device was also measured for varying oxygen flow rates and suction pressures. Future directions for the study include clinical trial testing in volunteer populations, as well as tolerability and detailed safety studies.

Full Length Publications:

- Flores M, Dayan I, Roth H, Zhong A, Harouni A, Gentili A, Abidin A, Liu A, Costa A, Wood B, Tsai CS, Wang CH, Hsu CN, Lee CK, Ruan C, Xu D, Wu D, Huang E, Kitamura F, Lacey G, Corradi GCA, Shin HH, Obinata H, Ren H, Crane J, Tetreault J, Guan J, Garrett J, Park JG, Dreyer K, Juluru K, Kersten K, Rockenbach MABC, Linguraru M, Haider M, AbdelMaseeh M, Rieke N, Damasceno P, Silva PMCE, Wang P, Xu S, Kawano S, Sriswa S, Park SY, Grist T, Buch V, Jantarabenjakul W, Wang W, Tak WY, Li X, Lin X, Kwon F, Gilbert F, Kaggie J, Li Q, Quraini A, Feng A, Priest A, Turkbey B, Glicksberg B, Bizzo B, Kim BS, Tor-Diez C, Lee CC, Hsu CJ, Lin C, Lai CL, Hess C, Compas C, Bhatia D, Oermann E, Leibovitz E, Sasaki H, Mori H, Yang I, Sohn JH, Murthy KNK, Fu LC, de Mendonça MRF, Fralick M, Kang MK, Adil M, Gangai N, Vateekul P, Elnajjar P, Hickman S, Majumdar S, McLeod S, **Reed S**, Graf S, Harmon S, Kodama T, Puthanakit T, Mazzulli T, Lavor VL, Rakvongthai Y, Lee YR, Wen Y. Federated learning used for predicting outcomes in SARS-COV-2 patients. *Res Sq* [Preprint]. 2021 Jan 8:rs.3.rs-126892. doi: 10.21203/rs.3.rs-126892/v1.
- Pritchard WF, Karanian JW, Jung C, Bakhutashvill I, **Reed SL**, Froelke BR, Barnes T, Wood BJ, Walsh BK, Mannes AJ. Miniature 3D printed pressure-driven ventilator maintains respiratory homeostasis in swine with induced acute pulmonary injury. [Under review]

Virtual Professional Meetings:

- Society for Interventional Oncology Annual Meeting, Feb. 3-6, 2021.
- Society for Interventional Radiology Annual Meeting, Mar. 20-26, 2021.

Awards:

- Society for Interventional Oncology 2021 Resident and Fellows Scholarship

Shahyan U. Rehman

School: Rutgers Robert Wood Johnson Medical School
Mentor: Jonathan Hernandez, M.D., Chief, Surgical Oncology Program
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Using an *ex vivo* Model to Evaluate the Efficacy of Targeting XPO7/SLK in Cholangiocarcinoma and Ovarian Cancer

Cholangiocarcinoma (CCA) and ovarian cancer (OC) are primarily epithelial cancers associated with poor patient outcomes. Our lab recently used immunohistochemistry (IHC) to define that cytoplasmic localization of exportin-7, a nuclear transport protein, identifies subpopulations of CCA and OC patients with particularly poor survival (n= 504).

We demonstrated that XPO7 exists in cytosol complexed to the serine/threonine kinase SLK. shRNA-mediated knockdown of XPO7 or SLK in CCA and OC cell lines prevented tumor organoid formation, and reduced tumor formation following tumor xenograft transplantation of cell lines into immunocompromised mice. We then demonstrated that the kinase inhibitor tivozanib is a direct SLK antagonist (IC50= 81.8 nM). Tivozanib reduced tumor organoid formation *in vitro* and induced tumor regression *in vivo* in murine xenografts. These findings reveal a novel XPO7:SLK signaling axis that promotes tumor formation and progression, and identifies a translatable potential therapy for these tumors.

To further our translational efforts with XPO7:SLK directed therapy, we used our SMART System (**S**urgically-resected **M**esothelium Cont**A**ining Unalte**R**ed **T**umor Microenvironment, Patent Application No. PCT/US2021/021525) to evaluate tivozanib in CCA and OC. Peritoneal metastases from patients with CCA and OC were maintained *ex vivo* for four days; experimental groups were treated with tivozanib and compared to untreated (control) tumor. IHC was used to determine cytoplasmic XPO7 status (positive vs negative). Cleaved caspase-3 and terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) were used as cell death markers. In both cancer types, XPO7 positivity correlated with increased cell death in response to tivozanib (58.27 vs 13.51 mean positive cells per 40X field, $p = 0.0045$). Conversely, negative cytoplasmic XPO7 staining correlated with cell death similar to control, as determined by cleaved caspase-3 and TUNEL staining (17.28 vs 9.979 mean positive cells per 40X field, $p > 0.05$).

Cytoplasmic expression of XPO7 by IHC unveils patients who may be candidates for drugs that target the SLK kinase. The SMART System is a novel translational model that can accelerate bench to bedside science.

Full Length Publications:

- Khan T, Verbus E, **Rehman S,** Chun Y, Hernandez J. The role of liver resection in patients with liver and unresectable lung colorectal metastases (LUNA). *Ann Surg Oncol*. 2021 May 13. doi: 10.1245/s10434-021-10109-8
- Ross A, Khan T, **Rehman S,** Nash G, Hernandez J. Early post-operative intraperitoneal vs hyperthermic intraperitoneal chemotherapy after optimal cytoreductive surgery for CRC with isolated peritoneal metastasis (ICARuS). *Ann Surg Oncol*. 2021 May 25. doi: 10.1245/s10434-021-10110-1

Abstract Publications:

- Khan T, Rossi A, Verbus E, Teke M, Saif A, **Rehman S**, Hong H, Luna A, Sinha S, Remmert K, Hewitt S, Blakely A, Davis J, Hernandez J. Cytoplasmic expression of XPO7 distinguishes a subset of ovarian carcinoma vulnerable to SLK inhibition. Society of Surgical Oncology International Conference on Surgical Cancer Care; March 18-19, 2021.
- Verbus EA, Rossi AJ, Khan T, Teke M, Saif A, **Rehman S,** Hong H, Luna AJ, Sinha S, Remmert K, Padget M, Blakely AM, Davis JL, Hodge JW, Hernandez JM. The use of an *ex vivo* tumor-bearing tissue perfusion model to investigate the effects of a novel immunotherapeutic agent. Society of Surgical Oncology International Conference on Surgical Cancer Care; March 18-19, 2021.

Virtual Professional Meetings:

- Society of Surgical Oncology International Conference on Surgical Cancer Care; March 18-19, 2021.

Marisa M. Salazar

School: Mayo Clinic Alix School of Medicine
Mentor: Thomas Nutman, M.D., Chief, Laboratory of Parasitic Diseases
Institute: National Institute of Allergy and Infectious Diseases (NIAID)
Research Project Title: Molecular Diagnostics for Monitoring Human Lymphatic Filariasis (LF) using Circulating Cell-Free Nucleic Acids in Body Fluids

Detecting parasitic circulating cell free nucleic acids (ccfDNA/ccfRNA) in plasma is a promising approach for sensitive and specific detection of active helminth infection, including *Wuchereria bancrofti* (Wb). Ccf nucleic acids, given their short half-lives, may be better biomarkers for assessing infection status than more traditional approaches, such as circulating antigen.

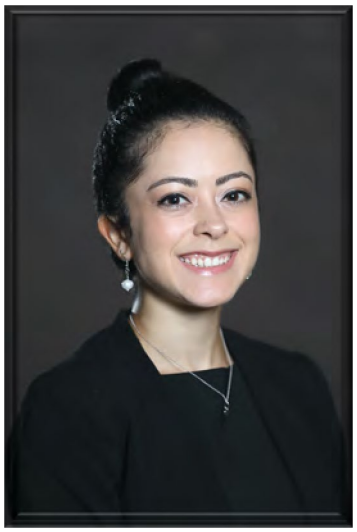
To identify potential Wb RNA targets, we performed Plasma-RNAseq using plasma from 10 Wb microfilaria-positive (mf-positive) individuals and 10 healthy blood bank donors, and used bioinformatic tools to ensure specificity. Six targets were identified that were specific to *Wb* and/or *Brugia malayi (Bm),* the causative agents of lymphatic filariasis (LF), and not found in *Loa loa (Ll)* or *Onchocerca volvulus (Ov),* closely related filarial parasites. These targets were compared to the previously-described DNA-based targets WbLDR and WbTR1 using newly optimized qPCR assays. After optimizing primer/probe combinations using genomic DNA or RNA from Wb or Bm, we demonstrated that ccfDNA and ccfRNA can be detected in Wb-infected individuals. Because the DNA-based assays appeared to be more sensitive than RNA-based targets, we next assessed the utility of the most sensitive ccfDNA qPCR assay as a biomarker of active Wb infection. Thus, we extracted ccfDNA from 250 mL of plasma from individuals with Wb infection from Cook Islands (n=71), India (n=19), Mali (n=13), Guyana (n=2), and Haiti (n=1). Of all the mf-positive individuals, 71% were positive for ccfDNA using WbTR1 qPCR; as expected, endemic uninfected controls and those with *Mansonella perstans* and/or *Ll* were negative. To understand the kinetics of Wb-specific ccfDNA following treatment, we assessed ccfDNA longitudinally following definitive treatment. In a small number of patients (n=2), we demonstrated, in time-course analyses, that patients had undetectable levels within a year of definitive treatment. Results from different Wb treatment regimens are underway. In conclusion, ccfDNA/RNA detection in LF holds promise for assessment of infection and treatment response in Wb and Bm infection.

Abstract Publications:

- **Salazar MM,** Bennuru S, Nutman TB. Molecular diagnostics for monitoring human lymphatic filariasis (LF) using circulating cell-free nucleic acids in body fluids. *Molecular Helminthology* 2021; June 2-4, 2021. [Virtual oral presentation]

Virtual Professional Meetings:

- American Society of Tropical Medicine and Hygiene 69th Annual Meeting, Nov. 15-19, 2020



Verónica A. Santana-Ufret

School: Wayne State University School of Medicine
Mentor: Anna María Nápoles, Ph.D., Scientific Director, NIMHD
Institute: National Institute on Minority Health and Health Disparities (NIMHD)

Research Project Title: ACEs High: The Impact of Adverse Childhood Experiences and Post Traumatic Stress Disorder on Chronic Inflammation in a Study of Urban Adults

Adverse childhood experiences (ACEs) and post-traumatic stress disorder (PTSD) are associated with poor health outcomes; dysregulated inflammation is a potential driver of this association. ACEs are traumatic events in childhood (0-17 yrs) that include physical, emotional, and sexual abuse, physical and emotional neglect, and different forms of household dysfunction as defined by the CDC. Roughly two-thirds of Americans experience ACEs.

PTSD is a syndrome that can develop following severe trauma such as actual or threatened death, serious injury, or sexual violation. In the U.S., PTSD has a lifetime prevalence of approximately 8% and is associated with a history of ACEs. We used the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study to investigate the chronic inflammatory effects of ACEs and PTSD. HANDLS is a 20-year study of 2,200 African American and 1,522 white adults aged 30-64 from diverse socioeconomic backgrounds residing in Baltimore City. We built linear mixed-effect regression models that assessed the effects of ACEs alone or combined with PTSD on inflammatory trajectories as stratified by race and sex using data spanning 2003-2017. Inflammation was quantified using the Cumulative Inflammation Index, which combines a neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio, and uric acid levels to create a z-score. In the aggregated HANDLS population, high ACE count was associated with a flatter inflammatory trajectory; however, disaggregation of the data by race, sex, and ACE type revealed that ACEs impacted inflammatory trajectories differentially based on race and sex, with African American men and white women showing steeper inflammatory trajectories in response to ACE exposure. PTSD similarly impacted inflammatory trajectories differentially based on race and sex. Collectively, these data show that different types of trauma have nuanced inflammatory effects across the lifespan of a diverse urban population and that race and sex must be considered in research on ACEs, PTSD, and chronic inflammation.

Full Length Publications:

- Nápoles AM, Stewart AL, Strassle PD, Quintero S, Bonilla J, Alhomsi A, **Santana-Ufret V**, Maldonado AI, Perez-Stable EJ. Racial/ethnic disparities in intent to obtain a COVID-19 vaccine: a nationally representative survey. *Prev Med*. [Under review]
- **Santana-Ufret V**, Maldonado AI, Quintero S, Nápoles AM. Racial/ethnic differences in the impact of adverse childhood experiences on chronic inflammation in a study of urban adults. [In preparation]

Abstract Publications:

- **Santana-Ufret V**, Maldonado AI, Nápoles AM. The complex interplay between adverse childhood experiences, post-traumatic stress disorder, and systemic inflammation in a longitudinal study of urban adults. International Society for Traumatic Stress Studies; Nov. 2-5, 2021. [Poster presentation]

Evan B. Selzer

School: Sidney Kimmel Medical College at Thomas Jefferson University
Mentor: Brian Brooks, M.D., Ph.D., Chief, Ophthalmic Genetics and Visual Function Branch
Institute: National Eye Institute (NEI)

Research Project Title: Suprachoroidal Viral Gene Therapy to Target Rat Retinal Pigment Epithelium

Modulation of gene expression in the retinal pigment epithelium (RPE) has been shown to therapeutically impact a variety of retinal degenerative diseases. AAV gene therapy provides a promising platform for the treatment of ocular genetic diseases. The current standard for AAV delivery to the RPE is subretinal injection. However, the surgical risks associated with this procedure create the need for alternative ways of delivering gene therapy to the pigmented layer of the retina.

An AAV vector designed to target the RPE (RPE-AAV) was engineered to express green fluorescent protein (eGFP) and administered to Sprague Dawley rats via suprachoroidal injection. Various injections containing 3-6 uL of vector at concentrations between 3.9 - 9.75 x 10^9 gc/uL were placed under the sclera into the suprachoroidal space. Once the rats recovered from injection, they were followed with fundus examination and photography. The animals then underwent enucleation, and the pattern of immunofluorescent labeling was recorded.

Rats showed eGFP expression on fundus examination one week post-injection. By two weeks, the area of eGFP expression reached maximal retinal coverage with about 1/5 of the retina showing florescence. Cryosections of eGFP-transduced eyes revealed co-localization of eGFP signal with staining for the RPE-specific RPE-65 protein. No eGFP expression was detected in adjacent photoreceptor cells co-stained with rhodopsin, indicating specificity of RPE-AAV transduction to the RPE.

Our results validate the ability of the RPE-AAV to strongly and specifically target the RPE upon suprachoroidal injection in a rat model. Replacement of the eGFP gene in the RPE-AAV vector with genes of therapeutic interest thus holds promise for turning this technique into a platform for testing and ultimately administering RPE gene therapy. The combination of RPE-AAV with suprachoroidal delivery has the potential to transform ocular gene therapy administration.

Full Length Publications:

- **Selzer EB**, Blain D, Hufnagel RB, Lupo PJ, Mitchell LE, Brooks BP. Evidence for environmental causes of uveal coloboma. *Surv Ophthalmol.* [Under review]

Virtual Professional Meetings:

- Advance: Research Career Development Conference of the Association for Research in Vision and Ophthalmology (ARVO); Feb. 25 - 26, 2021

Gauri G. Shastri

School: University of California, San Diego School of Medicine
Mentor: Philip Shaw, M.B. B.Ch., Ph.D., Senior Investigator, Social and Behavioral Research Branch
Institute: National Human Genome Research Institute (NHGRI)
Research Project Title: Relationship between Physical Age and Epigenetic Age in Attention-Deficit Hyperactivity Disorder (ADHD)

Genome-wide DNA methylation values change with age, providing a possible means of calculating the biological age of the donor of a biospecimen. Thus, mathematical algorithms, known as "epigenetic clocks," have been developed that use methylation values at a set of CpG sites to estimate epigenetic age. These clocks have demonstrated accelerated epigenetic aging in multiple neuropsychiatric diseases including schizophrenia, post-traumatic stress disorder, and major depressive disorder.

Attention-deficit hyperactivity disorder (ADHD) poses an important neurodevelopmental disease process in which to study epigenetic aging. This is because positive epigenetic age acceleration could be attributed to cumulative stress, while negative epigenetic age acceleration could be explained by developmental immaturity.

In the present study, we applied four different epigenetic clocks to estimate epigenetic age in blood (N= 127), saliva (N= 174), and post-mortem brain specimens (N= 111) from ADHD and neurotypical individuals. After determining the clock that performed best in each biospecimen type, mixed model linear regression analysis was used to explore whether a diagnosis of ADHD or symptom scores of inattention or hyperactivity-impulsivity were a significant determinant of epigenetic age at study entry, or rate of epigenetic aging (using longitudinal data).

Epigenetic age correlated significantly with chronological age across our biospecimens, reinforcing the validity of the epigenetic clock algorithms. However, neither the diagnosis of ADHD nor number of ADHD symptoms emerged as significant determinants of epigenetic aging in either the blood or saliva samples or the post-mortem brain samples at study entry. Furthermore, for those with biospecimens acquired over time, ADHD did not contribute significantly to the rate of epigenetic aging.

Thus, our study directly challenges the universality of applying epigenetic aging in psychiatric disease, despite its growing popularity in the field.

Full Length Publications:

- Shaw P, Blizzard S, **Shastri GG**, Kundzicz P, Curtis B, Ungar L, Koehly L. A daily diary study into the effects on mental health of COVID-19 pandemic-related behaviors. *Psychol Med.* [Under review]

Virtual Professional Meetings:

- Machine Learning in Genomics: Tools, Resources, Clinical Applications and Ethics; April 13-14, 2021.
- 12th Annual Julius Axelrod Neuroscience Symposium; Apr. 16, 2021.
- National LGBTQ Health Conference; May 20-21, 2021.

Sarah Silverstein

School: Rutgers New Jersey Medical School
Mentor: Carsten Bönnemann, M.D., Chief, Neurogenetics Branch, NINDS
David Adams, M.D., Ph.D., Deputy Director of Clinical Genomics, Office of the Clinical Director, NHGRI
Institute: National Human Genome Research Institute (NHGRI) and National Institute of Neurological Disorders and Stroke (NINDS)

Research Project Title: From Precision Diagnosis to Precision Treatment: Splice Altering Variants in Neuromuscular Disease

The genetic etiology of childhood-onset neuromuscular diseases remains unknown in a third of cases, despite extensive gene panel and exome sequencing evaluation. In order to detect pathogenic intronic variants missed by traditional techniques, we employed whole transcriptomic sequencing (WTS) alongside whole genome sequencing to better characterize non-coding variants.

Additionally, we employed other tools, including a novel graph aligner, for reanalysis of genome data. This combination of techniques allowed us to pinpoint a genetic etiology in patients who had previously eluded genetic diagnosis.

One case we diagnosed involved a variant in the nebulin gene, *NEB*. Nebulin is a structural protein found exclusively in skeletal muscle and is a well-known cause of congenital myopathies. Using WTS, we identified a splice-active variant that causes skipping of exon 144. *NEB* exon 144 expression is mutually-exclusive with exon 143, so that our patient lacked all isoforms containing exon 144. Since muscles contain varying balances of these two isoforms, we were able to correlate the relative abundance of exon 144 with the patient's MRI findings. Muscles which usually show higher exon 144 expression showed more severe disease on MRI in our *NEB*-mutant, exon 144 non-expressing patient.

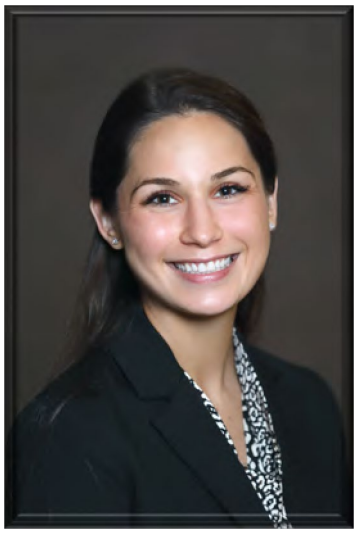
To translate these findings into novel treatments, we are employing anti-sense oligonucleotide (PMO) strategies to knock down splice-active variants. Since muscle cells can be difficult to grow in the lab, we designed a cell system by taking patient fibroblasts and transfecting them with a lentivirus plasmid containing MyoD transcription factor, which can induce muscle-specific gene expression in the presence of doxycycline. Using this system, we treated cells from a patient with a recessive desminopathy caused by a novel splice acceptor variant. Our goal is to utilize this cell system to test treatment strategies not only for our desminopathy patient, but also to establish a model that furthers the ease of designing personalized treatment for intronic variants in other patients.

Abstract Publications:

- **Silverstein S**, Syeda S, Foley R, Meilleur K, Leach M, Uapinyoying P, Chao K, Donkervoort S, Bonnemann C. Utilization of RNA sequencing to diagnose and to provide mechanistic insight into *NEB*-related myopathy. Muscular Dystrophy Association Annual Meeting; March 15-18, 2021. [Virtual Poster Presentation]

Virtual Professional Meetings:

- World Muscle Society Congress; September 28-October 2, 2020
- Muscular Dystrophy Association Annual Meeting; March 15-18, 2021



Ulana L. Stasula

School: University of Illinois College of Veterinary Medicine
Mentors: John Tisdale, M.D., Director, Cellular and Molecular Therapeutics Branch; Robert Donahue, V.M.D., Collaborative Investigator, Cellular and Molecular Therapeutics Branch
Institute: National Heart, Lung, and Blood Institute (NHLBI)
Research Project Title: Use of Groβ with Plerixafor to Mobilize Hematopoietic Stem Cells in the Nonhuman Primate Model

Hematopoietic stem cell (HSC) transplantation using a mobilized, apheresis-harvested graft is associated with increased efficiency of cell collection, improved cell quality, and better patient outcomes compared with marrow-derived grafts.

Granulocyte colony-stimulating factor (G-CSF) and plerixafor (a CXCR4 antagonist) are standard agents used alone and in combination to mobilize HSCs from marrow into the circulation, but poor mobilization responses can occur, necessitating multiple apheresis procedures. Importantly, G-CSF administration can also precipitate pain crises in sickle cell patients. Groβ, a CXCR2 agonist, has recently been evaluated in animal models to mobilize HSCs and no adverse effects were identified.

We sought to determine if co-administration of Groβ and plerixafor could effectively mobilize CD34+ HSCs in nonhuman primates. Nine rhesus macaques received 0.5 mg/kg Groβ SQ alone (n=9), 1 mg/kg plerixafor SQ alone (n=9), or Groβ plus plerixafor with plerixafor administered 30 minutes prior to Groβ (n=9). Serial blood samples were collected for flow cytometric analysis. Mean(SD) peak CD34+ counts were 33(16)/uL (Groβ alone), 231(99)/uL (plerixafor alone), and 365(353)/uL (combination), representing an increase of 1.1(0.8)-fold (Groβ), 8.9(3.0)-fold (plerixafor), and 29(44)-fold (combination) in circulating CD34+ cells, compared to baseline unstimulated counts. Peak mobilization occurred at 0.9(0.4) hours (Groβ), 4.7(1.0) hours (plerixafor), and 3.2(1.6) hours (combination). The CD34+CD45RA+ subset mobilized by 45 minutes, reaching a plateau at 4-6 hr. The CD34+CD45RA+CD117+CD90-subset, representing an immature CD34+ progenitor cell population, had the fastest and highest relative mobilization peak. Whereas G-CSF mobilization is associated with an early, paradoxical neutropenia, this effect was not observed for either agent.

Our results demonstrate that Groβ plus plerixafor is a rapid, effective HSC mobilization regimen, resulting in a synergistic 29-fold increase in CD34+ cell numbers in nonhuman primates. Groβ plus plerixafor may prove to be an optimal mobilization regimen in humans. Studies to determine Groβ plus plerixafor safety and efficacy are ongoing in human subjects.

Virtual Professional Meetings:

- American Association for Laboratory Animal Science (AALAS) National Meeting; Oct. 17-21, 2020.

Meron Teklu

School: Northwestern University Feinberg School of Medicine
Mentor: Nehal Mehta, M.D., Senior Investigator, Section of Inflammation and Cardiometabolic Diseases
Institute: National, Heart, Lung, and Blood Institute (NHLBI)
Research Project Title: Sex Differences in Subclinical Atherosclerosis in Psoriasis by Coronary Computed Tomography Angiography

Patients with psoriasis have a higher risk of myocardial infarction, especially young patients with severe disease. Sex differences in psoriasis and in burden of subclinical coronary atherosclerosis are understudied. Thus, we aimed to elucidate potential sex differences in subclinical coronary atherosclerosis in psoriasis.

At baseline visit, 268 participants (804 arteries) with psoriasis underwent coronary computed tomography angiography to quantify noncalcified, fibrofatty and fibrous coronary burden and low-dose CT to quantify visceral adipose tissue. Following one-year of observation, 194 participants (582 arteries) returned.

Of the 268 participants, 104 (39%) were women. Men had a worse cardiometabolic profile, including higher visceral adipose tissue (mean $\pm$ SD) (18,798 $\pm$ 9,048 cc vs 10,543 $\pm$ 6,985 cc; p<.001) and higher noncalcified (1.3 $\pm$ 0.47 mm^2 vs 0.96 $\pm$ 0.38 mm^2; p<.001), fibrofatty (0.22 $\pm$ 0.15 mm^2 vs 0.13 $\pm$ 0.13 mm^2; p<.001) and fibrous (0.98 $\pm$ 0.35 mm^2 vs 0.76 $\pm$ 0.22 mm^2; p<.001) coronary burden. Male sex was associated with noncalcified (β=0.31; p<.001), fibrofatty (β=0.23; p<.001) and fibrous (β=0.27; p<.001) burden independent of traditional cardiovascular risk factors and hs-CRP. In adjusted mediation analysis, visceral adipose tissue mediated 49%, 63% and 36% of the association between sex and noncalcified, fibrofatty and fibrous burden, respectively. At one year follow-up, women improved noncalcified (0.95 $\pm$ 0.33 mm^2 to 0.86 $\pm$ 0.34 mm^2; p=.02) and fibrous burden (0.79 $\pm$ 0.25 mm^2 to 0.70 $\pm$ 0.27 mm^2; p=.02) while men did not change noncalcified burden, improved fibrous burden to a lesser extent (1.0 $\pm$ 0.40 mm^2 to 0.95 $\pm$ 0.35 mm^2; p=.03) and worsened fibrofatty burden (0.20 $\pm$ 0.13 mm^2 to 0.23 $\pm$ 0.16 mm^2; p=.02).

In conclusion, male sex was associated with a higher burden of coronary atherosclerosis beyond traditional risk factors compared to females. Over time, men with psoriasis had less favorable progression of atherosclerosis. Coronary artery disease characteristics were partly mediated by visceral adipose tissue suggesting the need for further study of these relationships.

Full Length Publications:

- **Teklu M**, Zhou W, Kapoor P, Patel N, Dey AK, Sorokin AV, Manyak GA, Teague HL, Erb-Alvarez JA, Sajja A, Abdelrahman KM, Reddy AS, Uceda DE, Lateef SS, Shanbhag SM, Scott C, Prakash N, Svirydava M, Parel P, Rodante JA, Keel A, Siegel EL, Chen MY, Bluemke DA, Playford MP, Gelfand JM, Mehta NN. Metabolic syndrome and its factors are associated with noncalcified coronary burden in psoriasis: an observational cohort study. *J Am Acad Dermatol*. 2021 May;84(5):1329-1338.
- **Teklu M**, Mehta NN. FDG-PET in ischemic strokes of unknown origin: Have we found the needle in the haystack? *J Nucl Cardiol*. 2021 Apr 6. doi: 10.1007/s12350-021-02598-7.
- Zhou W, Dey A, Manyak G, **Teklu M**, Patel N, Teague H, Mehta NN. The application of molecular imaging to advance translational research in chronic inflammation. *J Nucl Cardiol*. 2020 Nov. doi: 10.1007/s12350-020-02439-z.
- **Teklu M**, Zhou W, Kapoor P, Patel N, Playford MP, Sorokin AV, Dey AK, Teague HL, Abdelrahman KM, Manyak GA, Erb-Alvarez JA, Shanbhag SM, Rodante JA, Keel A, Lockshin B, Chen MY, Gelfand JM, Bluemke DA, Wenger NK, Mehta NN. Sex differences in subclinical coronary atherosclerosis in psoriasis by coronary computed tomography angiography. *JACC Cardiovasc Imaging*. [In press]
- **Teklu M**, Gonzalez-Cantero A, Sorokin A, Prussick R, González-Cantero J , Martin-Rodriguez JL, Patel N, Parel PM, Manyak GA, Teague HL, Rodante JA, Keel A, Pérez-Hortet C, Sanchéz-Moya AI, Jiménez N, Ballester A, Solis J, Fernandez-Friera L, Barderas MG, Gonzalez-Calvin JL, Jaen P, Playford MP, Dey AK, Gelfand JM, Mehta NN. Subclinical liver disease is associated with subclinical atherosclerosis in psoriasis: results from two observational studies. *J Invest Dermatol.* [In press]
- **Teklu M**, Zhou W, Kapoor P, Patel N, Playford MP, Sorokin AV, Dey AK, Teague HL, Manyak GA, Rodante JA, Keel A, Chen MY, Bluemke DA, Khera AV, Mehta NN. Abdominal subcutaneous adipose tissue negatively associates with subclinical coronary artery disease in men with psoriasis. *Obesity*. [Under review]
- Zhou W, **Teklu M**, Bui V, Manyak GA, Kapoor P, Dey AK, Sorokin AV, Patel N, Teague HL, Playford MP, Erb-Alvarez JA, Rodante JA, Keel A, Shanbhag SM, Hsu LY, Bluemke DA, Chen MY, Carlsson M, Mehta NN. The effect of chronic inflammation and visceral adiposity on left ventricular mass in psoriasis: a prospective observational study. *Am J Prev Cardiol*. [Under review]
- Patel N, Dey AK ,Sorokin AV, **Teklu M**, Zhou W, Mehta N. Chronic inflammatory diseases and coronary heart disease: Insights from cardiovascular CT. *J Cardiovasc Comput Tomogr*. [Under review]

Full Length Publications (continued)

- Patel N, Osborne M, Teague H, Parel PM, Svirydava M, Sorokin AV, **Teklu M**, Manyak GA, Zhou W, Pantoja C, Scott C, Playford MP, Kapoor P, Rodante J, Keel A, Chen M, Tawakol A, Mehta NN. Heightened leukopoietic activity associates with systemic inflammation and subclinical atherosclerosis; results from two observational studies. *Circ Cardiovasc Imaging*. [Under review]
- Manyak GM, Patel N, **Teklu M**, Mehta NN. Inflammation and cardiometabolic diseases: lessons learned from psoriasis. *Intern J Cardodiab.* [Under review]

Abstract Publications

- **Teklu M**, Zhou W, Patel N, Manyak GA, Dey AK, Lateef SS, Uceda DE, Abdelrahman KM, Rodante JA, Keel A, Machado T, Scott C, Kapoor P, Sorokin AV, Teague HL, Playford MP, Chen MY, Mehta NN. Metabolic syndrome and its factors associate with noncalcified coronary burden in chronic inflammation: results from a prospective observational study. American Heart Association EPI, Lifestyle Annual Meeting. May 20-21, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Heart Association EPI, Lifestyle Annual Meeting. May 20-21, 2021

Elizabeth H. Theng

School: University of Missouri - Kansas City School of Medicine
Mentors: Michael Collins, M.D., Chief, Skeletal Disorders and Mineral Homeostasis Section
Carlos Ferreira, M.D., Head, Skeletal Genomics Unit
Institute: National Institute of Dental and Craniofacial Research (NIDCR)

Research Project Title: Hip Geometry Variation in Biallelic Ectonucleotide Pyrophosphatase/ Phosphodiesterase 1 (ENPP-1) Deficient Patients

ENPP-1 is an important regulator of skeletal and soft tissue mineralization. Rare biallelic loss of ENPP-1 leads to generalized arterial calcification of infancy (GACI), characterized by vascular, joint, and organ calcification, hypophosphatemic rickets/osteomalacia, and skin and retinal findings. Heterozygous ENPP-1 deficiency has been described in early-onset osteoporosis and an ENPP-1 polymorphism was found to be strongly associated with variation in hip geometry, as measured by DEXA hip structural analysis (HSA). However, the overall skeletal phenotype of ENPP-1-deficiency is not well characterized in affected individuals. HSA provides surrogate information about mechanical strength, offering a non-invasive and clinically accessible tool to assess hip geometry. Parameters include cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), subperiosteal width (SPW), endocortical width (ECW), cortical thickness (CT), section modulus (Z), and buckling ratio (BR)—each measured in the narrow neck (NN), intertrochanteric (IT), and femoral shaft (FS) regions.

HSA by DEXA was assessed in 7 homozygous ENPP-1-deficient patients (age range 5-56 years) and in 73 sex- and age-matched controls. All ENPP-1-deficient patients were hypophosphatemic, of which 2 were receiving treatment. Given the small sample size, standardized test statistics (*t*-scores) were derived for 21 hip geometry parameters; comparisons between groups were performed using the Mann-Whitney test. Multiple comparisons were corrected with a false discovery rate (FDR) q-value threshold set at 0.15.

Compared with controls, ENPP-1-deficient patients had significant changes in structural and derived measures of strength. Increases were seen in NN SPW, NN ECW, and FS SPW, which are correlated with bone fragility. In contrast, the increases seen in FS CSA, FS Z, FS CSMI, and NN CSMI are associated with improved bone strength. These findings suggest that ENPP-1 influences bone structure and strength, supporting previous findings and contributing to the nascent body of literature studying the impact of ENPP-1 on skeletal homeostasis.

Full Length Publications:

- **Theng EH**, German A, Pan KS, Isaac S, Boyce AM, Collins MT. Periorbital inflammation associated with craniofacial fibrous dysplasia: report of three cases and review of the literature. *Bone.* 2021 Aug 17. doi.org/10.1017/j.bone.2021.116157.
- Ovejero, D, Hartley IR, Fernandez de Castro Diaz, **Theng EH**, Li XB, Gafni RI, Collins MT. PTH and FGF23 Exert interdependent and synergistic effects on renal phosphate handling: evidence from patients with hypoparathyroidism and hyperphosphatemic familial tumoral calcinosis treated with synthetic human PTH 1-34. [Under review]

Abstract Publications:

- **Theng EH**, Oshegbo G, Tran W, Gafni RI, Ferreira, CR. Hip geometry variation in homozygous ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP-1) deficient patients. Endocrine Society ENDO Annual Meeting; Mar. 21-23, 2021. [Virtual poster presentation]

Virtual Professional Meetings:

- American Society for Bone and Mineral Research; Sept 11-15, 2020.
- Endocrine Society ENDO Annual Meeting; Mar. 21-23, 2021.

Cheyenne Williams

School: University of Pennsylvania Perelman School of Medicine
Mentor: Peter Pinto, M.D., Head, Prostate Cancer Section, Urologic Oncology Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Prostate Ultrasound Tomography: A Rad-Path Surgery Study to Investigate a Novel Method for Diagnosis

With recent technical developments, state-of-the-art ultrasound tomography (UT) is now able to provide submillimeter-resolution imaging for tissue characterization and malignancy detection. Compared to conventional pulse-echo ultrasound (US) imaging, UT provides quantitative US transmission that characterizes speed of sound and constructs speckle-free, refraction-corrected 360-degree-compounded reflection images. Given the success of UT in demonstrating accuracy for diagnosing breast cancers in patterns consistent with MRI, we sought to define the feasibility of UT for prostate cancer imaging. In this preliminary *ex vivo* study, UT and speed of sound are explored as potential novel opportunities to differentiate between benign and malignant prostate tissue.

Fresh whole prostate glands were collected immediately from patients undergoing radical prostatectomy for biopsy-confirmed prostate cancer. Within 30 minutes of extraction, each specimen was scanned in an echolucent, polyacrylamide gel phantom in the QT Ultrasound Breast Scanner. UT images were processed, then wholemount histopathology, pre-operative MRI, and UT images were manually segmented by expert genitourinary radiologists and pathologists, and all three modalities were then co-registered using both rigid and deformable elastic registration, based on prostate boundaries and anatomic landmarks. Localization of lesions identified by pre-operative MRI and wholemount pathology was then correlated and mapped in 3 dimensions with tri-planar UT images.

Forty consecutive prostate specimens were scanned with UT. Multi-modality correlation, 3D elastic co-registration, and fusion display of MRI, wholemount histopathology and *ex vivo* UT reflection sequences demonstrated co-localization of signal abnormalities on each modality where pathology-proven Gleason 6-9 tumors were present.

Development of hardware and software solutions to mechanically co-register a transrectal US with a trans-bladder US will enable translational steps towards assessment of narrow-angle ultrasound tomography for *in vivo* prostate imaging. Further data are required to validate, corroborate, and define performance metrics for this novel imaging approach applied to prostate cancer imaging.

Full Length Publications:

- **Williams C**, Daneshvar MA, Pinto PA. Emerging role of multiparametric MRI in detection of clinically significant prostate cancer. *Curr Opin Oncol*. 2021;33(3):244-251. doi: 10.1097/CCO.0000000000000717.
- Khondakar NR, Owens-Walton J, Daneshvar MA, **Williams C**, O'Connor LP, Yerram NK, Pinto PA. Emerging role for local therapy in oligometastatic prostate cancer. *Clin Adv Haemotol Oncol.* 2021 Jul;19(7):460-467.
- **Williams C***, Khondakar NR,* Daneshvar MA, O'Connor LP, Gomella PT, Mehralivand S, Yerram NK, Egan J, Gurram S, Rompré-Brodeur A, Webster BR, Owens-Walton J, Parnes HL, Merino MJ, Wood BJ, Choyke PL, Turkbey B, Pinto PA. The risk of prostate cancer progression in active surveillance patients with bilateral disease detected by combined MRI-fusion and systematic biopsy. *J Urology.* 2021 Jun 28. doi: 10.1097/JU.0000000000001941.
- **Williams C**, Khondakar NR, Pinto PA, Turkbey B. The importance of quality in prostate multiparametric MRI. *Semin Roentgenol* [Under review]
- **Williams C,** Gomella PT, Pinto PA. Case series in translational urology. In "Translational Urology: Handbook for Designing and Conducting Clinical and Translational Research." Ed. Siddiqui M. Amsterdam: Elsevier. Chapter 35. [Under review]
- **Williams C,** Gomella PT, Daneshvar MA, Khondakar NR, O'Connor LP, Egan J, Yerram NK, Gurram S, Choyke PL, Wood BJ, Merino MJ, Parnes HL, Turkbey B, Pinto PA. Risk of adverse pathology after deferred prostatectomy for grade group 1 and 2 prostate cancer. [Under review]
- Ahdoot MA*, **Williams C,*** Daneshvar MA, Hague C, Wilbur AR, Shih J, Khondakar NR, Gomella PT, Yerram NK, Mehralivand S, Gurram S, Siddiqui M, Pinsky PF, Parnes HL, Merino MJ, Wood BJ, Turkbey B, Pinto PA. Why does MRI-targeted biopsy miss clinically significant prostate cancers? [Under review]
- Khondakar NR, Daneshvar MA, **Williams C**, O'Connor LP, Gomella PT, Turkbey B, Pinto PA. Advances in multiparametric-MRI and PET-CT for prostate cancer: a narrative review. *BJU Int.* [Under review]
- Khondakar NR, Ahdoot MA, Daneshvar MA, Gomella PT, Yerram NK, **Williams C**, O'Connor LP, Parnes H, Merino M, Wood BJ, Choyke P, Turkbey B, Pinto PA. Use of multiparametric MRI-targeted biopsy to reclassify patients eligible for active surveillance on systematic biopsy. [Under review]
- Owens-Walton J, **Williams C,** Rompre-Brodeur A, Pinto PA, Ball MW. Minority enrollment in phase II and III clinical trials in urologic oncology. [Under review]

Abstract Publications:

- **Williams C**, Ahdoot MA, Daneshvar MA, Gomella PT, Owens-Walton J, Khondakar NR, O'Connor LP, Yerram NK, Mehralivand S, Merino MJ, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Why does MRI-targeted biopsy miss clinically significant cancers? American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Oral presentation]

Abstract Publications (continued)

- **Williams C**, Daneshvar MA, Yerram NK, Kim S, Fujiwara S, Rinaldi L, Baek S, O'Connor LP, Kim Q, Gomella PT, Khondakar NR, Ahdoot MA, Owens-Walton J, Merino MJ, Wood BJ, Choyke PL, Turkbey B, Hager G, Pinto PA. Identification of chromatin signatures predictive of prostate cancer progression. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Oral presentation]
- **Williams C**, Daneshvar MA, Khondakar NR, Owens-Walton J, O'Connor LP, Yerram NK, Gomella PT, Ahdoot MA, Webster BR, Choyke PL, Turkbey B, Merino MJ, Wood BJ, Pinto PA. Utility of MRI and targeted biopsy to diagnose local cancer recurrence after prostatectomy. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Poster presentation]
- **Williams C**, Daneshvar MA, Wu Y, Owens-Walton J, Yerram NK, Gomella PT, O'Connor LP, Khondakar NR, Ahdoot MA, Negussie A, Xu S, Turkbey B, Merino MJ, Boctor E, Wiskin J, Wood BJ, Pinto PA. Prostate ultrasound tomography: correlation with MRI and whole mount histopathology. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Poster presentation]
- **Williams C,** Yerram NK, Daneshvar MA, O'Connor LP, Egan J, Gomella PT, Owens-Walton J, Khondakar NR, Ahdoot MA, Merino MJ, Wood BJ, Choyke PL, Turkbey B, Pinto PA. Prostate lesion growth velocity on consecutive MRIs predicts grade progression. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Poster presentation]
- Khondakar NR, Ahdoot MA, O'Connor LP, Daneshvar MA, Yerram N, **Williams C**, Owens-Walton J, Gurram S, Gomella P, Egan J, Mehralivand S, Merino M, Wood B, Turkbey B, Pinto PA. Predictors of Gleason grade upgrading on wholemount pathology after MRI. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Poster presentation]
- Khondakar NR, Egan J, O'Connor LP, Ahdoot M**, Williams C**, Daneshvar MA, Yerram NK, Owens-Walton J, Gurram S, Choyke PL, Merino MJ, Wood BJ, Turkbey B, Pinto PA. The significance of multiple negative biopsies in patients on active surveillance. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Oral presentation]
- O'Connor LP, Gomella PT, Daneshvar MA, **Williams C,** Khondakar NR, Owens-Walton J, Yerram NK, Gurram S, Ahdoot MA, Varble N, Xu S, Turkbey B, Pinto PA, Wood BJ. Transperineal ultrasound with transperineal needles for MRI fusion prostate biopsy: demonstration of novel technique. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021. [Oral presentation]
- Owens-Walton J, **Williams C,** Rompre-Brodeur A, Pinto P, Ball MW. Examining minority enrollment in clinical trials in urologic oncology. American Urologic Association Annual Meeting, Las Vegas, NV; Sep. 2021 [Oral presentation]
- **Williams C**, Khondakar NR, Daneshvar MA, O'Connor LP, Egan J, Yerram NK, Rompre-Brodeur A, Owens-Walton J, Merino MJ, Choyke PL, Wood BJ, Turkbey B, Pinto PA. MRI-guided fusion biopsy of the prostate resection bed among post-radical prostatectomy patients with rising PSA. Genitourinary Cancer Symposium, American Society of Clinical Oncology; *J Clin Oncol* 39, no. 6 suppl (Feb. 20, 2021):208. [Poster presentation]
- Egan J, **Williams C,** Khondakar NR, O'Connor LP, Daneshvar MA, Yerram NK, Merino MJ, Choyke PL, Wood BJ, Turkbey B, Pinto PA. Considerations for active surveillance in select Gleason grade group 2 patients: a preliminary study. Genitourinary Cancer Symposium, American Society of Clinical Oncology; *J Clin Oncol* 39, no. 6 suppl (Feb. 20, 2021):207. [Virtual poster presentation]
- Khondakar NR, O'Connor LP, **Williams C,** Daneshvar MA, Egan J, Yerram NK, Webster B, Merino MJ, Choyke PL, Wood BJ, Turkbey B, Pinto PA. Bilateral disease and risk of prostate cancer progression in an active surveillance cohort. Genitourinary Cancer Symposium, American Society of Clinical Oncology; *J Clin Oncol* 39, no. 6 suppl (Feb. 20, 2021):206. [Virtual poster presentation]
- **Williams C,** Yerram NK, Khondakar NR, Long L, O'Connor LP, Wang A, Ahdoot MA, Lebastchi A, Gurram S, Zeng J, Chalfin HJ, Harmon S, Mehralivand S, Merino MJ, Parnes HL, Choyke PL, Shih J, Wood BJ, Turkbey B, Pinto PA. MRI-targeted and systematic biopsy for detection ofgrade progression in patients on active surveillance for prostate cancer. Society of Women in Urology Annual Meeting; Jan. 2021 [Virtual oral presentation]
- O'Connor LP, Daneshvar MA, Egan J, **Williams C,** Khondakar NR, Yerram NK, Webster B, Merino MJ, Choyke PL, Wood BJ, Turkbey B, Pinto PA. Presence of bilateral disease at time of active surveillance enrollment is associated with increased risk of pathologic progression. Society of Women in Urology Annual Meeting. Jan. 2021. [Virtual oral presentation]
- Wiskin J, **Williams C**, Turkbey B, Xu S, Toubaji A, Daneshvar MA, Boctor E, Wu Y, Klock J, Wood BJ, Pinto PA. Prostate imaging with ultrasound tomography. IEEE International Ultrasonics Symposium; Sep. 11-16, 2021.
- **Williams C,** Daneshvar MA, Gomella PT, Yerram N, Khondakar NR, Merino MJ, Wood BJ, Choyke P, Turkbey B, Pinto PA. Does deferred prostatectomy for grade group 1 and 2 increase risk of adverse pathology? American Urologic Association, Mid-Atlantic Section Meeting. National Harbor, MD; Oct. 2021 [Poster presentation].

Virtual Professional Meetings:

- Society of Women in Urology 10th Annual Clinical Mentoring Conference; Jan. 22, 2021.
- Genitourinary Cancer Symposium, American Society of Clinical Oncology Annual Meeting; Feb. 11-13, 2021.

Awards

- Donald M. Mode Urology Research Symposium. Best Student Presentation, Second Place 2021. Medical College of Georgia Department of Urology.

Keval B. Yerigeri

School: Northeast Ohio Medical University
Mentor: Raffit Hassan, M.D., Chief, Thoracic and Solid Tumor Immunotherapy Section, Thoracic and GI Malignancies Branch
Institute: National Cancer Institute, Center for Cancer Research (NCI/CCR)
Research Project Title: Inflammatory Biomarkers as Prognostic Indicators for Malignant Mesothelioma

Mesothelioma is an aggressive tumor of mesothelial cells most commonly originating in the pleura or peritoneum, with a primary risk factor of asbestos exposure. Soluble mesothelin-related protein (SMRP) is currently the only FDA-approved diagnostic biomarker; megakaryocyte potentiating factor (MPF) has equivalent diagnostic performance. Prognostic markers to inform clinical decisions are not available. In addition to SMRP and MPF, we explored CRP, CA125, neutrophil-to-lymphocyte ratio, fibrinogen, and platelet count as prognostic indicators.

Of 448 mesothelioma patients with previously collected tumor bio-specimens and SMRP and MPF data, 405 were selected based on confirmed pleural/peritoneal mesothelioma, available inflammatory biomarker data, and applicable informed consent. Labmatrix and BTRIS software were used to collect biomarker values and CRIS was used to extract disease status (new, active, or surveillance) and histology. Subjects were separated into quartiles per biomarker; overall survival (OS) was calculated from date of protocol consent using Kaplan-Meier estimates. Quartiles were combined into 2-3 groups after initial data analysis.

Median OS for patients in the lowest quartile of SMRP values (0 - 1.685 nmol/L) was 3.7 years compared to 0.7 years in the highest quartile (9.71 - 400) and 1.3 years in the middle 50% (global $p < 0.0001$). For CA125, median OS was 1.7 years for the lower half versus 0.9 years for the higher half of values. Similarly, for neutrophil-to-lymphocyte ratio, median OS was 2.5 years for the upper half compared to 0.7 years for the lower half. C-reactive protein correlated with a median OS of 5.1 years in the lowest quartile (0 - 3.64 mg/dL) versus 0.5 years in the highest quartile (62.1 - 300), and results were similar for fibrinogen.

Inflammatory biomarkers provide significant prognostic information and are easy to access with routine labs. Future steps include developing a prognostic scoring model with cumulative biomarker values, for greater precision.

Full Length Publications:

- **Yerigeri K,** Hasan R. Inflammatory biomarkers as prognostic indicators for malignant mesothelioma. [In preparation]

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Rajit Banerjee
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