NIH MEDICAL RESEARCH SCHOLARS PROGRAM

2023-2024 RESEARCH COMPENDIUM

NIH National Institutes of Health
Clinical Center

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 10-12-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 molecular biology to artificial intelligence for image reconstruction, 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 seminars 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.

"Through the MRSP we look to inspire a new generation of physician scientists who will turn discoveries into health. I can't wait to see what these exceptional young people accomplish."
– NIH DIRECTOR MONICA M. BERTAGNOLLI, M.D.

MEDICAL RESEARCH SCHOLARS PROGRAM FUNDING

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 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.

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.

MRSP Scholars celebrate the holiday season with cheer

Meet and Greet event with MRSP Scholar and author Abhinav Suri for the release of his book "Practical AI for Healthcare Professionals: Machine Learning with Numpy, Scikit-learn, and TensorFlow"

NIH MRSP Scholars Ashley Golbus, Sahit Menon, Gustavo Serrano-Berrios, Jack Victory, and David Zarrin finish 2nd in the NIH 38th annual Institute Challenge Relay and finished 2nd out of 103 teams. Team Name: Run DMC (Da MRSP Crew)

MRSP ACADEMIC CURRICULUM

JOURNAL CLUBS

This conversational series focuses on the patient population participating in clinical protocols at the NIH Clinical Center. MRSP Scholars have the opportunity to engage with both research physicians as well as patients.

PROCESS OF DISCOVERY

This seminar series covers 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, including institute directors, scientific and clinical directors, as well as established principal investigators from the intramural institutes.

CLINICAL TEACHING ROUNDS

This conversational series focuses on the patient population participating in clinical protocols at the NIH Clinical Center. MRSP Scholars have the opportunity to engage with both research physicians as well as patients.

GREAT TEACHERS

This colloquia focuses on nationally renowned clinician-scientists who are invited to the NIH as part of the Clinical Center Grand Round series.

PROFESSIONAL DEVELOPMENT

Professional development is an important aspect of continuing career growth and success. The MRSP professional development sessions assist participants to gain sustainable skills with long-term benefits.

2023-2024 SUMMARY RESEARCH ACHIEVEMENTS AND SCHOLARLY OUTPUT

During the 2023-2024 MRSP year, the scholars celebrated many research accomplishments, as shown by the number of manuscripts they produced (Figure 1); the number of scholars who were first authors on published manuscripts (Figure 2); the number of scholars who presented their work at professional meetings (Figure 3); and the number of scholars who attended professional meetings, (Figure 4). Specifically, **28** scholars (**54%**) produced a total of **74** manuscripts for peer-reviewed publication, including 36 articles that were published or in press in peer-reviewed journals and **38** papers under review. MRSP scholars were first authors on (**64%**) of published manuscripts. Forty-eight scholars (**92%**) attended 125 professional meetings where they presented a total of 138 abstracts; **19** scholars (**32%**) received awards for outstanding research achievement. Two scholars were invited to spend a second year at NIH as an intramural research training awardee, and two additional scholars were accepted into the NIH Oxford-Cambridge PhD Program and will pursue further research at NIH as doctoral candidates.

FIGURE 1.
COMPLETION OF 74 MRSP MANUSCRIPTS

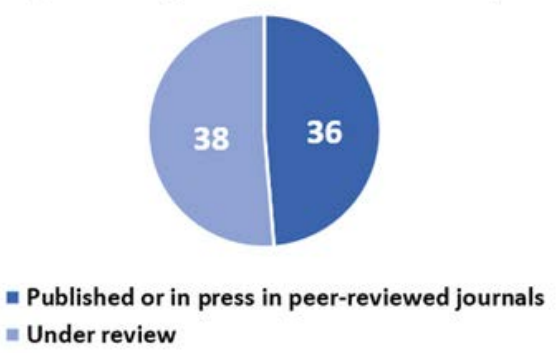


FIGURE 2.
AUTHOURSHIP OF MANUSCRIPTS

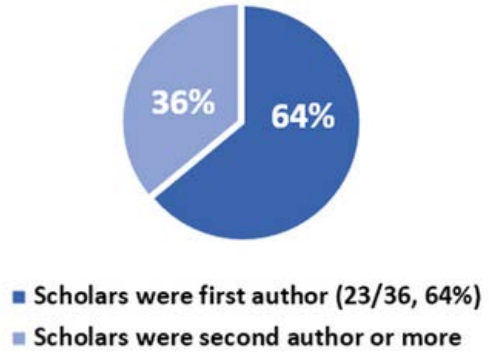


FIGURE 3.
PRESENTATIONS AT SCHOLARLY MEETINGS
n=TOTAL ABSTRACTS

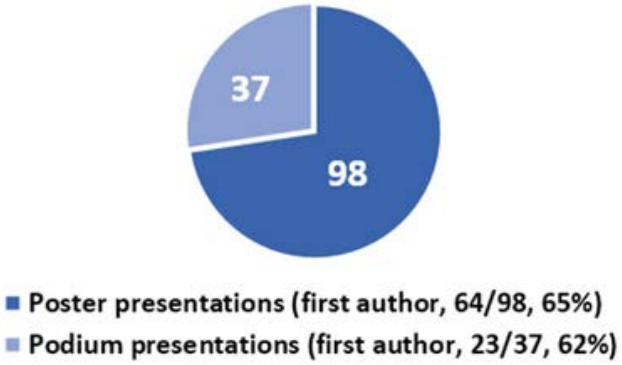
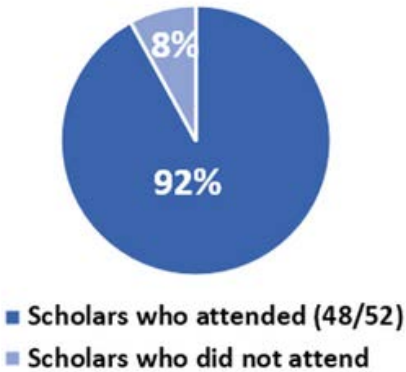


FIGURE 4.
ATTENDANCE AT PROFESSIONAL MEETINGS



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*Equal contribution

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PUBLICATIONS

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*Equal Contribution

Kenigsberg AP, Nemirovsky DR, Mason JB, Hesswani C, Koller CR, **Azar WS**, Parikh S, **Gelikman DG**, Mena E, Lindenberg L, **Schuppe KC**, et al. Is focal therapy overutilized: an evaluation of continued eligibility for focal therapy of prostate cancer in an active surveillance cohort. *Urology*. [Under review].

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AWARDS AND HONORS

- Knights Templar Eye Foundation Travel Grant Award, Association for Research in Vision and Ophthalmology, 2023 Annual Meeting
- Retina Research Foundation/Joseph M. and Eula C. Lawrence Travel Grant, Association for Research in Vision and Ophthalmology, 2024
- Best Poster Award, American Urological Association 2024 Annual Meeting
- Best Poster, American Urological Association 2024 Independent Practice Research Symposium
- Top 10 Abstract Award, Engineering and Urology Society 2024 Annual Meeting
- New England Student Urology Symposium, Best Abstract & Oral Presentation Award, 2024
- Pennsylvania Academy of Dermatology Travel Grant, 2023
- Vicky H. Whittemore Travel Award, International TSC 2023 Research Conference
- American Medical Association, Physician of Tomorrow Scholarship, 2024
- American Society of Clinical Oncology, Conquer Cancer Medical Student Scholarship, 2024
- Best Poster, Cancer Biology Section of American Head & Neck Society at Combined Otolaryngology Spring Meetings, 2024
- Second Place Poster Award, American Otological Society, Combined Otolaryngology Spring Meetings, 2024
- H.O.W. - Hearing the Ovarian Cancer Whisper - Dr. Robert C. Knapp Medical Student Award
- Young Investigator Award, Pediatric Transplant and Cellular Therapy Consortium, 2024
- Outstanding Poster Award, Pediatric Transplant and Cellular Therapy Consortium, 2024
- Jane-Nugent Award, Neurosurgical Society of the Virginias, 2024
- Best Overall Abstract, Brown University Student Neurosurgery and Neurology Research Conference, 2024
- ACTRIMS Neurology Residents Summit in Multiple Sclerosis, Travel Award
- Best Basic Science Poster and Abstract, Metropolitan DC Thoracic Society, 2024 Annual Meeting
- Best Clinical Case Report, Metropolitan DC Thoracic Society 2024 Annual Meeting
- Certificate of Merit, American Roentgen Ray Society, 2024
- Cum Laude Educational Exhibit Award. Radiological Society of North America, 2023
- Medical Student Travel Grant. Radiological Society of North America, 2023
- Conference on Retroviruses and Opportunistic Infections, New Investigator Scholarship, 2024
- Finalist, Elevator Pitch Competition, NIH Graduate Student Research Symposium, 2024
- Finalist, NHLBI Three Minute Talk Competition (3rd place), 2024
- Finalist, NINDS Three Minute Talk Competition (3rd place), 2024
- Best Oral Presentation and Travel Grant Award, Annual CCR Fellows and Young Investigators Colloquium, NCI/CCR, Rockville, MD, 2024
- Best Poster Prize, Student Category, NCI POB Research Round-up, May 2024

MAAME-ANIMWAH AMOAKO
Duke University School of Medicine

MENTORS

Janet E. Hall, M.D., Clinical Director, Chief
Skand Shekhar, M.D., Assistant Research Physician

Clinical Research Branch, Reproductive Physiology and Pathophysiology Laboratory, National Institutes of Environmental Health Sciences (NIEHS)

An Analysis of Thyroid Hormone Disparities in Healthy Black and White Young Women

Studies have found lower levels of thyroid stimulating hormone (TSH) in black compared to white individuals who are clinically euthyroid. There are no data on racial or ethnic differences in total T4 (TT4), fT3, or reverse T3 (rT3) in reduced energy states in normal weight women.

Ten healthy white women age 23.5 ± 2.7 yr (mean ± SD) and 6 healthy black women age 23.0 ± 2.1 yr were prescribed two 5-day dietary interventions (45 kcal/kg LBM neutral energy availability (NEA) diet and a 20 kcal/kg LBM deficient energy availability (DEA) diet) initiated in the early follicular phase of the menstrual cycle. Frequent blood sampling over 8 hours was initiated at 08:00 hour on 5th day of diet, with TSH assessed every 10 min, TT3, rT3 and TT4 every 60 min, and FT3, FT4 at the beginning and end of sampling. Liquid chromatography-tandem mass spectrometry (LC-MS) was used for all thyroid hormones except TSH and TBG, measured using ELISA. Findings were analyzed using ANOVA and presented as mean and standard error.

Age, weight, BMI, and percentage fat mass were not different. Baseline TSH values differed between black and white participants, with no difference in the fT4, fT3, TT4, TT3, and rT3. TSH levels with NEA diet were significantly lower in black participants ($p<0.0001$), with no difference with DEA diet. TT4, fT4, fT3, and rT3 levels were not different between black and white participants with NEA or DEA diets. TT3 levels with NEA diet were significantly lower for black participants ($p=0.03$), with no difference with DEA diet ($p=0.30$).

We show that black participants have significantly lower fasting levels of TSH and TT3 compared to white participants with an NEA diet. Further, our findings suggest a difference in sensitivity to DEA given that differences with NEA diet were not found with DEA diet.

ABSTRACTS

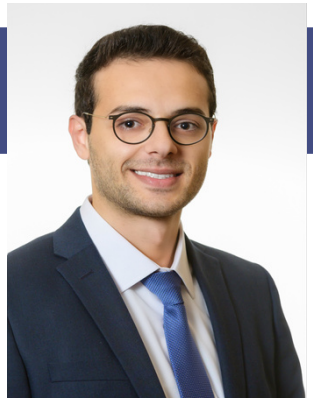
- **Amoako M**, Okunbor JI, Lunn S, Baffoe-Bonnie A, Olunuga E, Grace MR, Dotters-Katz SK. Exploring mood checks as an early touch point for analyzing breastfeeding cessation in high-risk obstetric patients. Student National Medical Association (SNMA), Annual Medical Education Conference (AMEC), Wilbert Jordan Research Forum, New Orleans, LA; Mar. 29, 2024. [Poster]
- Olunuga E, Okunbor JI, **Amoako M**, Lunn S, Baffoe-Bonnie A, Grace MR, Dotters-Katz SK (2024, March 29). The relationship between indication for 1-week postpartum mood check with need for intervention. SNMA AMEC Wilbert Jordan Research Forum, New Orleans, LA.; Mar. 29, 2024 [Poster]

PROFESSIONAL MEETINGS

- Student National Medical Association, Annual Medical Education Conference, New Orleans, LA; Mar. 27-31, 2024.

WILLIAM S. AZAR

Georgetown University School of Medicine



MENTOR

Peter Pinto, M.D., Head
Prostate Cancer Section, Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

A Novel LLM-Mediated Data Extraction Tool: A Comparative Study in Patients who Underwent Radical Prostatectomy

The integration of large language models (LLMs) into healthcare promises to transform medical research. We developed and evaluated a LLM-powered data extraction tool, the National Institutes of Health (NIH) Integrated Data Analysis Platform (NIDAP) Text Extraction Program (NTEP).

We included 369 patients enrolled in a clinical trial and built a ground-truth dataset with 4,797 datapoints for 13 variables from radical prostatectomy pathology reports. We compared this manually curated dataset with one generated by NTEP, which utilizes custom-built LLM prompts for data extraction from electronic health record (EHR) documents. Prompt engineering was conducted, and minor processing and formatting adjustments were made to the NTEP-generated dataset for statistical comparison.

Extraction accuracy was assessed using Cohen's Kappa (κ) for binary and categorical variables and mean squared error (MSE) with Pearson's correlation coefficient for continuous and discrete variables. The LLM achieved a κ-score of 1 for binary variables surgical margin status, lymph node involvement, and seminal vesicle invasion, indicating perfect agreement with the ground-truth dataset. For extraprostatic extension, lympho-vascular invasion, and perineural invasion, the κ-score was 0.99. For categorical variables, the κ-score was 1 for case number and pathologist name, and 0.99 for Gleason sum. For discrete variables, the LLM correctly identified all positive lymph nodes but miscalculated the total number of lymph nodes dissected for one patient, resulting in a MSE of 0.0027 and a Pearson's coefficient of 0.99. For continuous variables, the LLM matched prostate dimensions perfectly but missed the prostate weight in one case (0.27% of the dataset). Overall, the LLM correctly identified 99.8% of datapoints.

Our tool, NTEP, shows high accuracy in extracting binary, numerical, and categorical variables from radical prostatectomy pathology reports, showcasing the effectiveness of LLMs in healthcare data management and their potential to replace manual data extraction from EHRs.

PUBLICATIONS

- Gelikman DG, Mena E, Lindenberg L, **Azar WS**, Rathi N, Yilmaz EC, Harmon SA, Schuppe KC, Hsueh JY, Huth H, Wood BJ, Gurram S, Choyke PL, Pinto PA, Turkbey B. Reducing false-positives due to urinary stagnation in the prostatic urethra on 18F-DCFPyL PSMA PET/CT with MRI. *Clin Nucl Med*. 2024 Jul 1;49(7):630-636. PMID: 38651785.
- Kenigsberg AP, Nemirovsky DR, Mason JB, Hesswani C, Koller CR, **Azar WS**, Parikh S, Gelikman DG, Mena E, Lindenberg L, Azar WS, Schuppe KC, et al. Is focal therapy overutilized: an evaluation of continued eligibility for focal therapy of prostate cancer in an active surveillance cohort. *Urology*. [In review]
- Gelikman DG, **Azar WS**, Yilmaz EC, Lin Y, Shumaker L, Fang AM, Harmon SA, Huang EP, Parikh SH, Hyman JA, Schuppe KC, Nix JW, Choyke PL, Gurram S, Wood BJ, Rais-Bahrami S, Pinto PA, Turkbey B. A PI-RADS v2.1-based predictive model for clinically significant prostate cancer. *J Urol*. [In review]

- **Azar WS**, Junkin D, William Nicholas, Hesswani C, Koller CR, Schuppe KC, Parikh SH, Nethala D, Kenigsberg AP, Mendhiratta N, Sandeep Gurram, Peter A. Pinto. A novel LLM-mediated data extraction tool: a comparative study in patients who underwent radical prostatectomy. NEJM AI. [In review]

ABSTRACTS

- **Azar WS**, Koller CR, Parikh SH, Hesswani C, Schuppe KC, Azari SS, Kenigsberg AP, Mendhiratta N, Nethala D, Hyman J, Noun J, Siva J, Gelikman DG, Merino M, Parnes HL, Wood BJ, Turkbey B, Gurram S, Xu S, Pinto PA. Is it time to abandon the transrectal probe in prostate biopsy? American Urological Association Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster]
- **Azar WS**, Hesswani C, Schuppe KC, Koller CR, Parikh SH, Azari S, Kenigsberg AP, Mendhiratta N, Nethala D, Merino MJ, Turkbey B, Pinto PA, Gurram S. Is it time we include high-risk MRI features in nomograms to calculate the risk of lymph node invasion prior to radical prostatectomy? Urological Society for American Veterans, San Antonio, TX; May 5, 2024. [Podium]
- **Azar WS**, Hesswani C, Schuppe KC, Koller CR, Parikh SH, Kenigsberg AP, Mendhiratta N, Nethala D, Pinto PA, Gurram S. Does location of positive margins after radical prostatectomy affect risk of biochemical recurrence? Urological Society for American Veterans, San Antonio, TX; May 5, 2024. [Poster]
- **Azar WS**, Junkin DM, Williams N, Parikh SH, Hesswani C, Schuppe KC, Koller CR, Nethala D, Mendhiratta N, Kenigsberg AP, Gurram S, Pinto PA. A novel LLM-mediated data extraction tool: a comparative study in patients who underwent radical prostatectomy. Engineering and Urology Society Annual Meeting, San Antonio, TX; May 5, 2024. [Poster].
- Parikh SH, Hesswani C, **Azar WS**, Koller CR, Schuppe KC, Kenigsberg AP, Mendhiratta N, Azari S, Nethala D, Enders J, Wu Y, Boctor E, Klock J, Wood BJ, Gurram S, Turkbey B, Pinto PA. A new look: the promising use of 3-dimensional quantitative transmission ultrasound tomography for the detection of prostate cancer an ex vivo study. American Urological Association Annual Meeting, San Antonio, TX; May 2-6, 2024 [Poster]
- Schuppe KC, Kenigsberg AP, **Azar WS**, Hesswani C, Parikh SH, Koller C, Azari S, Gelikman DG, Mendhiratta N, Nethala D, Merino M, Turkbey B, Gurram S, Pinto PA. The impact of magnetic resonance imaging-detected zonal location on prostate cancer recurrence: implications for preoperative risk stratification. American Urological Association Annual Meeting, San Antonio, TX; May 2-6, 2024 [Poster]
- Schuppe KC, Koller C, Parikh S, Hesswani C, **Azar WS**, Azari S, Kenigsberg AP, Rathi N, Hyman J, Gelikman DG, Mendhiratta N, Nethala D, Gurram S, Merino M, Choyke P, Turkbey P, Pinto PA. Does pre-prostatectomy magnetic resonance imaging reduce racial disparities in oncologic outcomes for African American patients: a propensity score-matched analysis. American Urological Association Annual Meeting, San Antonio, TX; May 2-6, 2024 [Poster]
- Hesswani C, Yilmaz EC, Harmon SA, Gelikman DG, Koller CR, Parikh SH, Schuppe KC, **Azar WS**, Kenigsberg AP, Azari S, Gurram S, Turkbey B, Pinto PA. Evaluation of a biparametric MRI AI algorithm for the detection of prostate cancer using spatial annotations on wholemount prostate pathology. American Urological Association Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster]
- Parikh SH, Hesswani C, Schuppe KC, Koller CR, **Azar WS**, Gelikman DG, Kenigsberg AP, Mendhiratta N, Nethala D, Azari S, Hyman JA, Wood BJ, Gurram S, Madan RA, Karzai F, Pinto PA. Effect of novel neoadjuvant androgen signaling inhibitors prior to robotic radical prostatectomy on pathological or short-term survival outcomes. Urological Society for American Veterans, San Antonio, TX; May 5, 2024. [Podium]

- Schuppe KC, Kenigsberg AP, **Azar WS**, Hesswani C, Parikh SH, Koller CR, Gelikman DG, Azari S, Mendhiratta N, Nethala D, Merino M, Turkbey B, Gurram S, Pinto PA. Beyond the bulge: the correlation between extracapsular extension on multi-parametric magnetic resonance imaging with pathological findings and long-term oncologic outcomes following robot-assisted radical prostatectomy. Urological Society for American Veterans, San Antonio, TX; May 5, 2024. [Poster]
- Parikh S, Hesswani C, Schuppe K, Koller C, **Azar WS**, Gelikman DG, Kenigsberg AP, Mendhiratta N, Azari S, Nethala D, Hyman JA, Madan RA, Turkbey B, Karzai F, Gurram S, Pinto PA. The impact of novel neoadjuvant androgen signaling inhibitors on robotic radical prostatectomy: a propensity score-matched comparison of intraoperative and short-term outcomes. Urological Society for American Veterans, San Antonio, TX; May 5, 2024. [Poster]
- Azari S, Parikh SH, Blake Z, Koller CR, **Azar WS**, Hesswani C, Schuppe KC, Kenigsberg AP, Nethala D, Merino M, Parnes HL, Gurram S, Turkbey B, Wood BJ, Xu S, Pinto PA. Totally transperineal ultrasound MRI fusion-guided transperineal prostate biopsy in patients with no rectum. Engineering and Urology Society Annual Meeting, San Antonio, TX, San Antonio, TX; May 5, 2024 [Poster]
- Mason JB, Azari S, Kenigsberg AP, Blake Z, Nemirovsky DR, Koller C, **Azar WS**, Parikh SH, Schuppe KC, Hesswani C, Mendhiratta N, Nethala D, Mezhiritsky V, Merino M, Choyke PL, Parnes HL, Gurram S, Turkbey B, Wood BJ, Pinto PA. Focal therapy eligibility: an evaluation of initial and continued candidacy for focal therapy in a grade group 2 active surveillance cohort. Engineering and Urology Society Annual Meeting, San Antonio, TX; May 5, 2024 [Poster]
- Azari S, Mason JB, Kenigsberg AP, Koller C, Parikh S, **Azar WS**, Schuppe KC, Siva J, Hesswani C, Blake Z, Mendhiratta N, Nemirovsky DR, Siva, Charles Hesswani, Nethala D, Mezhiritsky V, Merino M, Wood BJ, Choyke PL, Parnes HL, Gurram S, Turkbey B, Pinto PA. Impact of PI-RADS 5 lesions on active surveillance for grade group. Society of Urological Oncology Annual Meeting, Washington, DC; Nov. 28-Dec. 1, 2023. [Poster]

PROFESSIONAL MEETINGS

- Focal Therapy Society Annual Meeting, Washington, DC; Sep. 7-9, 2023.
- Advances in Management of Prostate, Kidney, and Bladder Cancers, MedStar Health, Washington, DC; Sep. 23-24, 2023.
- Society of Urological Oncology Annual Meeting, Washington, DC; Nov. 28-Dec. 1, 2023.
- American Society of Clinical Oncology Genitourinary Cancers Symposium, San Fransisco, CA; Jan. 25-27, 2024.
- Urology Resident's Day, Mid-Atlantic Section of the American Urological Association, Linthicum, MD; Feb. 24, 2024.
- American Urological Association Annual Meeting, including the Urological Society for American Veterans and the Engineering and Urology Society Annual Meeting, San Antonio, TX; May 2-6. 2024.

AWARDS

- Best Poster Award, American Urological Association Annual Meeting, 2024
- Top 10 Abstract Award, Engineering and Urology Society, AUA Annual Meeting, 2024

DEVIN K. BARZALLO

Case Western Reserve University School of Medicine

MENTORS

Joel Moss, M.D., Ph.D., Senior Investigator
Critical Care Medicine & Pulmonary Branch, National Heart, Lung, & Blood Institute (NHLBI)

Thomas Darling, M.D., Ph.D., Chair
Department of Dermatology, Uniformed Services University of the Health Sciences

Sclerotic Bone Lesions May Distinguish Patients with Mosaic or Germline Tuberous Sclerosis Complex from Those with Sporadic Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a cystic lung disease presenting sporadically (S-LAM) or in Tuberous Sclerosis Complex (TSC). TSC is characterized by hamartomas in multiple organs, including the skin (facial angiofibromas). Both conditions arise from mutations in TSC1 or TSC2. TSC patients exhibit germline (mutation on one allele in all cells) or mosaic (mutation in only some cells) disease. Germline TSC patients present with symmetrically distributed facial angiofibromas (Sym-AF), while some mosaic patients also display Sym-AF. Conversely, mosaic patients with a lower variant allele frequency (VAF), indicative of fewer affected cells, often present with asymmetrically distributed facial angiofibromas (Asym-AF).

We reported that S-LAM patients had few or no sclerotic bone lesions (SBLs), whereas TSC-LAM patients had multiple SBLs. SBLs are regions of bone characterized by increased density. This was based on a clinical and not a genetic diagnosis of TSC. We aim to elucidate the number of SBLs in patients classified as S-LAM, mosaic TSC-LAM (Asym-AF or Sym-AF), and germline TSC-LAM.

We analyzed 95 adult LAM patients, 46 of whom had S-LAM and the remainder TSC-LAM, including germline (23 patients), mosaic with Asym-AF (n=9), and mosaic with Sym-AF (n=17). The median total number of SBLs was 1 (IQR: 1-3) for S-LAM, 3 (IQR: 0-8) for Asym-AF, 13 (IQR: 5.75-28.25) for Sym-AF, and 29 (IQR: 14.5-89.75) for germline TSC patients. The median number of TSC-associated mucocutaneous findings significantly increased from Asym-AF (2, IQR=2-4), to symmetrical angiofibroma mosaic (5, IQR=4-6), to germline TSC (6, IQR=6-7), and correlated with the number of SBLs (R=0.3819, p=0.013).

Our findings suggest that SBLs may serve as a clinical marker for identifying mosaic TSC, particularly in cases of adult-onset S-LAM where conventional diagnostic criteria may be equivocal. The sequential increase in SBL burden aligns with the progression of other TSC manifestations and underscores the potential diagnostic value of SBLs in refining disease management.

ABSTRACTS

- **Barzallo DK**, Burke K, Raiciulescu S, Olsen C, Moss J, Darling T. Features of tissue regeneration in periungual fibromas associated with tuberous sclerosis complex. Society of Investigative Dermatology, Dallas, TX (2024). [Poster]
- **Barzallo DK**, Moss J, Darling T. Navigating tuberous sclerosis complex: dermatological insights and evolving concepts. American Academy of Dermatology, San Diego, CA (2024). [Poster]
- **Barzallo DK**, Zhang X, Wang J, Cartron A, Jones A, Julien-Williams P, Wu H, Wilkerson M, Dalgard C, Moss J, Darling T. Ultraviolet signature mutations in TSC skin tumors are increased in sun-exposed body sites, reinforcing recommendations for good sun protection. International TSC Alliance Meeting, Washington, DC (2023). [Podium]

PROFESSIONAL MEETINGS

- International Tuberous Sclerosis Alliance, Research Conference, Washington DC; Sep. 7-9, 2023.
- Latino Medical Student Association, National Conference, Atlanta, GA; Sep. 14-17, 2023.
- Pennsylvania Academy of Dermatology, Hershey Park, PA; Sep. 21-23, 2023.
- Medical Organization of Latino Advancement; Chicago, IL; Oct. 13-15, 2023.
- American Public Health Association; Atlanta, GA; Nov. 13-15, 2023.
- Skin of Color Society, Washington DC; Dec. 12, 2023.
- American Academy of Dermatology, San Diego, CA; Mar. 8-12, 2024.
- Society of Investigative Dermatology, Dallas, TX; May 15-18, 2024.

AWARDS

- Pennsylvania Academy of Dermatology Travel Grant, 2023
- Vicky H. Whittemore Travel Award for International TSC Research Conference, 2023
- Medical Organization of Latino Advancement Scholarship, 2023
- National Medical Foundation, Health Equity Leadership, APHA Travel Grant
- American Medical Association, Physician of Tomorrow Scholarship, 2024
- American Society of Clinical Oncology, Conquer Cancer Medical Student Scholarship, 2024

GITANJALI L. BHUSHAN

Penn State College of Medicine

MENTOR

Leah Katzelnick, Ph.D., MPH, Stadtman Investigator

Viral Epidemiology and Immunity Unit, National Institute of Allergy and Infectious Diseases (NIAID)

Antigenic Cartography Using Hamster Sera Identifies SARS-CoV-2 JN.1 Evasion Seen in Human XBB.1.5 Booster Sera

The rapid evolution of SARS-CoV-2 variants and complex population immunity from different combinations of SARS-CoV-2 variant infections and COVID-19 vaccinations presents challenges for determining updates to vaccine antigens. Analyses such as antigenic cartography allow for characterization of antigenic differences among emerging variants using primary infection sera; sera recovered following infection by a single variant. However, increasing population immunity makes human primary infection sera difficult to obtain.

We generated hamster primary infection sera spanning ancestral to Omicron JN.1 SARS-CoV-2 variants and measured pseudovirus neutralizing antibody titers against a large panel of variants. Neutralizing antibody titers in human and hamster primary infection sera were compared and antigenic differences were analyzed through antigenic maps. We constructed antibody landscapes of complex human sera which allowed us to visualize how various vaccination and infection histories affect antibody titer magnitude and recognition of distinct variants.

We found that neutralization titers and breadth of matched human and hamster pre-Omicron variant primary infection sera correlate well and generate similar antigenic maps. The hamster antigenic map shows modest antigenic drift among XBB sub-lineage variants, with JN.1 and BA.4/BA.5 variants within the XBB cluster, but with five to six-fold antigenic differences between these variants and XBB.1.5. Analysis of complex human sera showed that an XBB.1.5 booster immunization increased neutralization titers and breadth more than immunizations with only ancestral and bivalent COVID-19 vaccines, although a five-fold titer difference was still observed between JN.1 and XBB.1.5 variants. These findings suggest that the JN.1 is sufficiently antigenically divergent that antibody coverage could be improved with a matched vaccine antigen.

PUBLICATIONS

- Wang W*, **Bhushan GL***, Paz S, Stauft CB, Selvaraj P, Goguet E, Bishop-Lilly KA, Subramanian R, Vassell R, Lusvarghi S, Cong Y, Agan B, Richard S, Epsi NJ, Fries A, Fung CK, Conte MA, Holbrook MR, Wang TT, Burgess TH, Pollett SD, Mitre E, Katzelnick LC, Weiss CD. Antigenic cartography using hamster sera identifies SARS-CoV-2 JN.1 evasion seen in human XBB.1.5 booster sera. *NPJ Vaccines* [Under review] *Equal contribution

ABSTRACTS

- **Bhushan GL**, Wang W, Paz S, Stauft CB, Subramanian R, Goguet E, Lusvarghi S, Cong Y, Holbrook MR, Burgess T, Epsi N, Fries A, Agan B, Richard S, Mitre E, Wang T, Pollett S, Katzelnick L, Weiss CD. Antigenic characterization of SARS-CoV-2 variants using hamster and human sera and antibody landscapes of humans with diverse vaccination and infection histories. American Association of Immunologists, Chicago, IL; May 3-7, 2024. [Poster]

PROFESSIONAL MEETINGS

- Viral Sub-species Classification Workshop, Rockville, MD; April 8-10, 2024.
- Immunological Imprinting in SARS-CoV-2 Infection and Vaccination Workshop, Rockville, MD; April 25-26, 2024.
- American Association of Immunologists Annual Meeting, Chicago, IL; May 3-7, 2024.

UJWAL BODDETI

University of Maryland School of Medicine

MENTORS

Sara Inati, M.D., Head
Neurophysiology of Epilepsy Unit, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke (NINDS)

Kareem Zaghloul, M.D., Ph.D., Chief
Functional Neurosurgery Section, *Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke (NINDS)*

Multiunit Neuronal Sequences are Stereotyped During Preictal Period

Drug-resistant epilepsy outcomes have been largely stagnant over the past two decades. Although recent advances have greatly improved seizure control, there is still much work to be done. Our group has recently shown that neuronal firing activity is uniquely stereotyped across seizure events, suggesting that population neuronal activity may reveal patterns in seizure activity that have not yet been explored. Here, we show that preictal firing patterns begin to uniquely organize on a low-dimension neural manifold, up to 1-hr prior to seizure onset, suggesting a potential utility in advanced seizure prediction and intervention.

We obtained intracranial recordings from epilepsy patients implanted with Utah Intracortical Electrode Arrays, undergoing neuromonitoring at the NIH Clinical Center. We bandpass filtered signals (0.5-5 kHz) using a 4th-order Butterworth filter and subsequently smoothed signals using a Gaussian kernel (σ=25 ms). We detected baseline, preictal (< 1-hr from seizure), and seizure neuronal firing activity. We then used Uniform Manifold Approximation and Projection (UMAP) to reduce neural sequence information to a low-dimension embedding and represent them on a neural manifold.

We visualized neuronal sequences on a neural manifold and quantified similarity of preictal sequences to baseline and seizure, by measuring Euclidean distance of each sequence representation to baseline centroid. We find preictal sequences localize spatially near seizure sequences on the neural manifold, starting 1-hr prior to seizure onset, whereas baseline sequences are randomly distributed. Furthermore, preictal sequences deviate significantly from baseline centroid ($p<0.0001$), akin to seizure sequences ($p<0.0001$), suggesting that preictal neuronal firing patterns are similarly uniquely stereotyped.

These findings suggest that changes in neuronal firing activity may begin much earlier than electrographic seizure onset. Ultimately, our findings portend the possibility of predicting seizures well in advance, opening doors for significantly improving preexisting treatments, such as closed-loop neuromodulation, but also paving the way for novel therapeutics.

PUBLICATIONS

- **Boddeti U**,* Nusraty S,* Zaghloul K, Brown DA. Microglia in glioblastomas: molecular insight and immunotherapeutic potential. *Cancers (Basel)*. 2024 May 22;16(11):1972. PMID: 38893093. *Equal contribution
- Langbein J, **Boddeti U**, Xie Z, Ksendzovsky A. A scoping review of closed-loop neuromodulation for neuropsychiatric disorders. *BMJ Ment Health* [Under review]
- **Boddeti U**, Diamond J, McAfee D, Xie Z, Langbein J, Nusraty S, Bachani M, Ksendzovsky A, Zaghloul K. Evidence of seizure networks in a 4-aminopyridine model of epilepsy. [Under review]

ABSTRACTS

- **Boddeti U**, Diamond J, Ksendzovsky A, Inati S, Zaghloul K. Single-unit neuronal firing becomes increasingly synchronized during transition from preictal to seizure state. University of Maryland School of Medicine Medical Student Research Day, Baltimore, MD; Nov 28-29, 2023. [Podium]
- **Boddeti U**, Diamond J, Ksendzovsky A, Inati S, Zaghloul K. Preictal bursting activity may predict seizure onset. American Association of Neurological Surgeons Annual Meeting, Chicago, IL; May 3-6, 2024. [Podium presentation]. Also presented at Brown University Student Neurosurgery and Neurology Research Conference, Providence, RI; Jan. 6, 2024. [Podium]

PROFESSIONAL MEETINGS

- University of Maryland School of Medicine Medical Student Research Day, Baltimore, MD; Nov 28-29, 2023.
- Brown University Student Neurosurgery and Neurology Research Conference, Providence, RI; Jan. 6, 2024.
- Neurosurgical Society of the Virginias Annual Meeting, White Sulfur Springs, WV; Jan. 25-27, 2024.
- American Association of Neurological Surgeons Annual Meeting, Chicago, IL; May 3-6, 2024.

AWARDS

- Publication Recognition Award, University of Maryland School of Medicine, 2023
- Best Overall Abstract, Brown University Student Neurosurgery and Neurology Research Conference, 2024
- Jane-Nugent Award, Neurosurgical Society of the Virginias, 2024

PAUL G. BORGMAN III

Florida State University College of Medicine

MENTORS

Naomi Taylor, M.D., Ph.D., Head
Basic-to-Translational Oncology Section and Head, Immunology-Hematology Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Nirali Shah, M.D., Lasker Clinical Research Scholar, Head
Hematologic Malignancies Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Incidence of Pre-Existing B-Cell Aplasia in CAR T-Cell Clinical Trials at the NCI

B-cell aplasia, marked by low B-cell counts, is a typical outcome of B-cell targeted CAR T-cell therapy. It functions as a surrogate marker for persistence of functional CAR T-cells and post-treatment relapse risk assessment. However, data on the prevalence of pre-existing B-cell aplasia among patients entering CAR T-cell trials are scarce. Our study addresses this gap by examining the incidence of pre-existing B-cell aplasia and its relationship with pre-treatment characteristics and prior therapies in patients enrolled in CAR T-cell clinical trials at the NCI.

We retrospectively reviewed four different CAR T-cell clinical trials for acute lymphoblastic leukemia at the NCI. After determining the incidence of pre-existing B-cell aplasia, we sought to determine associations between presence of B-cell aplasia and other pre-treatment characteristics using Fisher's Exact test (alpha = 0.05). We used descriptive statistics to evaluate any relationships between presence of B-cell aplasia and types of prior therapies patients received.

In n=162 patients enrolled in NCI trials, 70.9% had pre-existing B-cell aplasia prior to CAR T-cell infusion. Among the entire cohort, 54.9% had undergone a prior hematopoietic stem cell transplant, and 65.4% had greater than M2 marrow involvement. Stratification by numbers of prior immunotherapies revealed the following: 73.3% (no prior immunotherapy), 64.6% (1 prior immunotherapy), and 78.4% (> 1 prior immunotherapy). Statistical analysis showed a significant association between B-cell aplasia and prior stem cell transplant (p=0.002).

Our study highlights the increased incidence of pre-existing B-cell aplasia among patients entering CAR T-cell clinical trials at the NCI. We observed a statistically significant relationship between receipt of a prior stem cell transplant and presence of B-cell aplasia. Our data suggest that B-cell aplasia is an uncertain surrogate for functional CAR T-cell persistence and marker for prediction of leukemic relapse, and needs further validation.

PUBLICATIONS

- Sahai I,* **Borgman P**,* Yates B, Rankin AW, Shah NN. Incidence of pre-existing B-cell aplasia in B-ALL: Implications for post-CAR T-cell monitoring. *Blood Advances*. [Under review] *Equal contribution

ABSTRACTS

- **Borgman P**, Yates B, Rankin AW, Shah NN. Incidence of pre-existing B-cell aplasia in chimeric antigen receptor T-cell clinical trials at the National Cancer Institute. NCI Pediatric Oncology Branch Research Round-Up, Bethesda, MD, May 2024.
- **Borgman P**, Kondo T, Chien C, Yates B, Wu X, Shah NN, Taylor N. Clonal expansion of CAR T-cells with a CAR transgene integration in the KMT2D locus. NCI Pediatric Oncology Branch Research Round-Up, Bethesda, MD, May 2024.

PROFESSIONAL MEETINGS

- NCI Pediatric Oncology Branch Research Round-Up, Bethesda, MD, May 2024.

GREGORY H. BOYEK

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MENTOR

Carston G. Bönnemann, M.D., Chief
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Correction of an Intronic Pseudoexon-Inducing Variant in Collagen-VI Related Muscular Dystrophy Using an Adenine Base Editor

Collagen VI-related dystrophies (COL6-RDs) are a group of genetic muscle diseases existing on a spectrum of severity that ranges from the severe Ullrich congenital muscular dystrophy (UCMD) to the milder Bethlem muscular dystrophy. Patients with UCMD exhibit neonatal onset weakness and hypotonia that prevents or causes loss of ambulation and progressive respiratory insufficiency. Patients with Bethlem muscular dystrophy exhibit proximal weakness and contractures but remain ambulatory into adulthood; intermediate phenotypes also exist.

Previous research described a recurrent, de novo deep intronic variant in intron 11 of COL6A1 (c.930+189C>T) that creates an in-frame pseudoexon insertion with a dominant negative mechanism of action. This COL6A1 pathogenic variant is now one of the most commonly identified causative variants in the COL6 genes causing the severe Ullrich presentation when in full heterozygosity. Among our 44 +189C>T patients, one was identified with a milder phenotype due to somatic mosaicism. This provides us the rationale for a base editing approach for correcting the intron 11 mutation, as correction of the mutation in just a proportion of cells, comparable to somatic mosaicism, would likely be disease modifying.

Base editing uses modified CRISPR-Cas enzymes with nickase activity fused to a deaminase in order to make precise, single base pair edits anywhere in the genome that matches a provided guide RNA. To correct the .930+189C>T variant, several possible base editor guide sequences based on predictive machine learning algorithms were identified and cloned into plasmids. These guides were paired with matching base editors and expressed in HEK293 cells and two patient-derived fibroblast cell lines. The results of these experiments were used to refine guide sequences, cell models, and expression vectors. The combined editor and guide can now be expressed in an easily translatable single adeno-associated virus vector targeting muscle fibroblasts, with the potential to permanently ameliorate the severe Ullrich muscular dystrophy symptoms to a milder phenotype.

ABSTRACTS

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- **Boyek G**, Orbach R, Gottlieb K, Duff J, Lenk G, Bonnemann CG. FIG4 loss of function: Unraveling the phenotypic spectrum for clinical trial readiness. World Muscle Society Annual Congress, Prague, 2024.

PROFESSIONAL MEETINGS

- American Heart Association Scientific Sessions, Philadelphia, PA; Nov. 11-13, 2023.
- American Society for Cell and Gene Therapy Annual Meeting, Baltimore, MD; May 8-11, 2024.

EMAD A. CHISHTI

University of Kentucky College of Medicine

MENTOR

Sameer S. Kadri, M.D., Head

Critical Care Medicine Department, Clinical Epidemiology Section, NIH Clinical Center (CC)

Association Between Hospital Type and Resilience During Caseload Stress: A Natural Quality-of-Care Experiment from the COVID-19 Pandemic, 620 U.S. Hospitals, July-November 2021

Imbalances between hospital caseload and care resources that strained U.S. hospitals during the COVID-19 pandemic have persisted post-pandemic. Understanding which hospital types were more resilient to pandemic overcrowding-related excess deaths can help prioritize patient safety during future crises. The objective of this study was to determine whether hospital type stratified by capabilities and resources (i.e. extracorporeal membrane oxygenation (ECMO) capability, multiplicity of ICU types, and native bed-capacity) influenced COVID-19 volume-outcome relationships during the Delta wave surge.

This study was a retrospective cohort study using the PINC-AI database, an administrative database covering ~20% of overall US hospitalizations. We stratified hospital-months by surge index (severity-weighted COVID-19 inpatient caseload relative to pre-pandemic bed-capacity) percentiles. We used hierarchical models to evaluate the impact of log-transformed surge index on the adjusted odds ratio (aOR) of in-hospital mortality or discharge-to-hospice, adjusting for case-mix, hospital characteristics, local staffed-bed occupancy, social vulnerability, and state COVID-19 vaccination ranking. We assessed for effect modification by four mutually exclusive hospital types.

Among 620 hospitals reporting 223,380 Delta wave COVID-19 inpatients, there were 208 ECMO-capable, 216 multi-ICU, 36 large (≥200-bed), and 160 small (<200-bed) single-ICU hospitals. 50,752 (23%) patients required ICU admission, 34,274 (15.3%) died. The aOR for mortality was 1.28 (95% confidence interval [CI], 1.22-1.34) per unit increase in log surge index (strain attributable mortality=7375 [95% CI 5936-8813]; one in five COVID-19 deaths). Test for interaction revealed no difference (p=0.77) in log surge index-mortality relationship across hospital types. Results were consistent after excluding transferred patients, restricting to acute respiratory failure and mechanically ventilated patients on admission, and using alternative strain metrics.

Comparably detrimental relationships between COVID-19 caseload and survival were observed across all hospital types including highly advanced centers, well beyond the pandemic's learning curve. This finding emphasizes the importance of minimizing caseload-staff imbalance for patient safety during public health crises.

PUBLICATIONS

- Neupane M, Warner S, Mancera A, Sun J, Yek C, Sarzynski SH, Amirahmadi R, Richert M, **Chishti E**, Walker M, Swihart B, Mitchell SH, Hick J, Rochwerg B, Fan E, Demirkale CY, Kadri SS. Association between hospital type and resilience during caseload stress: A natural quality-of-care experiment from the COVID-19 pandemic, 620 U.S. hospitals, July-November 2021. *Ann Intern Med*. [Under review]

ABSTRACTS

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- Neupane M, Warner S, Mancera A, Sun J, Yek C, Sarzynski SH, Amirahmadi R, Richert M, **Chishti E**, Walker M, Swihart B, Demirkale CY, Kadri SS. Did hospital critical care infrastructure impact COVID-19 survivability during caseload surges? A natural experiment of resilience to inform future care delivery, 620 U.S. hospitals, July-November 2021. American Thoracic Society Annual Meeting, San Diego, CA; May 17-22, 2024. [Podium]

PROFESSIONAL MEETINGS

- Infectious Diseases Society of America Annual Meeting, Boston, MA; Oct. 11-15, 2023.
- American College of Cardiology Annual Meeting, Atlanta, GA; Apr. 6-8, 2024.

AWARDS

- NHLBI Director's Award: COVID-19 Response Award, 2024. [Received as member of Clinical Epidemiology Lab]

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MENTORS

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Exploring the Skin Microbiome in Central Centrifugal Cicatricial Alopecia: A Pilot Study

Central Centrifugal Cicatricial Alopecia (CCCA) is a form of scarring alopecia predominantly affecting young to middle aged women of African descent. It presents as scarring hair loss on the top of the scalp which spreads centrifugally over time, profoundly impacting quality of life. While its pathogenesis is unclear, it is believed to involve irreversible damage to the epithelial stem cells in the bulge of the hair follicle due to lymphocytic inflammation. There is likely a genetic predisposition, and emerging research points to scalp dysbiosis as a potential contributing factor. To analyze the skin microbiome, 19 women of African descent were recruited: CCCA subjects (n=12; age range 30s-50s, median 38.5 years) and healthy controls (n=7; age range late 20s-late 40s, median 34 years). CCCA diagnosis was confirmed with biopsy, and degree of hair loss was assessed using a validated physician-graded scale. Hair care practices did not differ significantly between cohorts (chemicals: p=.68; heat: p >.99; tension: p=.43).

Analyses of shotgun metagenomic data were conducted on skin swabs from four anatomical sites, including the vertex and occipital scalp. The vertex scalp microbiome of women with CCCA clustered distinctly from controls (p=.02). Corynebacterium was significantly more abundant in the CCCA cohort (median relative abundance (RA) 9.8%, IQR 0.89%–21.9%) compared to controls (median RA 0.14%, IQR 0.08%–0.75%; p=.01). Conversely, Lawsonella was significantly less abundant in the CCCA cohort (median RA 0.27%, IQR 0.02%–1.8%) compared to controls (median RA 19.7%, IQR 12.7%–23.3%; p=.04). Species-level analysis revealed that the vertex scalp of those with CCCA hosted a variety of different Corynebacterium species, while the control group exhibited minimal Corynebacterium species prevalence and abundance. This study contributes to a limited but growing body of scalp microbiome data, underscoring the need for further research to decipher its role in CCCA's complex etiology.

PUBLICATIONS

- **Firek A**, Hou P, Han J, Holmes C, Suh G, Frey C, Kong HH, Castelo-Soccio L. Exploring the microbiome in central centrifugal cicatricial alopecia: a pilot study. [In preparation]

ABSTRACTS

- **Firek A**, Holmes C, Kong HH, Paller A, Silverman R, Castelo-Soccio L. Challenges of JAK-inhibitor use in immunodeficient patients with Netherton Syndrome. Pediatric Dermatology Research Alliance Annual Conference, Atlanta, GA; Nov. 2-4, 2023. [Poster]
- Strong J, **Firek A**, Hickstein D, Pavletic S, Childs R, Dimitrova D, Kanakry J, Kanakry C, Cowen E, Castelo-Soccio L, Brownell I. Demodicosis and ivermectin-associated Mazzotti-like reactions in hematopoietic cell transplant recipients: a case series. American Academy of Dermatology Annual Meeting, San Diego, CA; Mar. 1-5, 2024. [Poster]
- **Firek A**, Hou P, Han J, Castelo-Soccio L, Kong HH. Exploring the microbiome in central centrifugal cicatricial alopecia: a pilot study. Society for Investigative Dermatology Annual Meeting, Dallas, TX; May 15-18, 2024. [Poster]

PROFESSIONAL MEETINGS

- Pediatric Dermatology Research Alliance Annual Conference, Atlanta, GA; Nov. 9-11, 2023.
- Society for Investigative Dermatology Annual Meeting, Dallas, TX; May 15-18, 2024.

JONATHAN E. FREEMAN

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MENTOR

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Fibrous Dysplasia Progression in Patients with Craniofacial Involvement of the Frontal and Zygomatic Bones

Fibrous dysplasia (FD) is characterized by expansile fibro-osseous lesions that may occur in association with endocrinopathies as part of McCune-Albright syndrome (MAS). The purpose of this study was to evaluate expansion rates in craniofacial lesions associated with significant morbidity, including the frontal bone and zygomas.

Patients with craniofacial FD and serial CT imaging from a natural history study at the NIH were evaluated. Volumetric analyses of CT scans were performed using MIM Encore. Generalized mixed model analysis was used to account for intra-subject correlation, with FD lesion volume as the dependent variable. In addition to age, effects of MAS-associated endocrinopathies, sex, skeletal disease burden, and history of bisphosphonate treatment were evaluated.

64 total lesions (frontal, n =28; zygomatic, n=36) in 33 patients were evaluated longitudinally in serial CT scans. Frontal and zygomatic lesion volume increased with age ($p<0.001$), and expansion rate decreased over time ($p<0.001$). There were no associations between expansion rates and MAS-associated endocrinopathies, sex, skeletal disease burden, or bisphosphonate treatment. Compared to recently reported expansion rates in gnathic bones in this cohort (Pan et al., J Bone Miner Res 2023, mandibular=42, maxillary=65), frontal FD lesions expanded at a greater rate than all other lesions (5.19 cm3/year, 95% CI 4.33–6.05, $p<0.001$), followed by mandibular FD lesions (0.99 cm3/year, 95% CI 0.15–1.85 $p<0.022$). There was no difference in expansion rates between maxillary and zygomatic lesions. Craniofacial lesion expansion rates were most rapid in younger children and declined as patients approached adulthood.

FD lesions involving the frontal bone and mandible expand at greater rates than other facial bones. These differences in growth rates indicate that location-specific analyses are required to assess FD progression. The availability of quantitative natural history data will guide clinicians in identifying candidates for medical and surgical interventions and clinical trials for preventative therapies.

ABSTRACTS

- **Freeman JE**, Pan KS, Elbashir II, Boyce AM. Fibrous dysplasia progression in patients with craniofacial involvement of the frontal and zygomatic bones. J Bone Miner Res Plus. International Conference on Children's Bone Health, Salzburg, Austria; June 22-25, 2024. [Podium]

PROFESSIONAL MEETINGS

- International Conference on Children's Bone Health, Salzburg, Austria; June 22-25, 2024

AVERY T. FUNKHOUSER
University of South Carolina School of Medicine, Greenville

MENTOR

Jack Shern, M.D., Lasker Clinical Research Scholar
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Mechanisms of MYOD1 Rhabdomyosarcoma Aggressiveness

Rhabdomyosarcoma (RMS) is the most common pediatric soft tissue tumor. The MYOD1L122R variant is associated with poor therapeutic responses and outcomes. Despite clinical recognition, the molecular underpinnings of MYOD1-mutant RMS (MM-RMS) remain underexplored. Preliminary studies suggest a MYC-like gene expression alteration. This study aimed to delineate the molecular mechanisms of MM-RMS aggressiveness.

We employed WTC11 induced pluripotent stem cells (iPSCs) modified via CRISPR to generate the MYOD1L122R mutation. Directed differentiation assays assessed the mutation's impact on muscle differentiation and oncogenic potential. Additionally, the RMS cell line RD was modified to express MYOD1WT, MYOD1L122R, and MYC. Binding partner analysis via co-immunoprecipitation mass spectrometry (Co-IP/MS). growth rates, and gene expression profiling compared MYOD1L122R versus c-MYC.

Preliminary results with the modified RD cell lines showed MYOD1L122R cells do not proliferate faster than controls. Cell morphology differed between the four lines. Treatment with cyclophosphamide showed no significant difference in cytotoxicity.

This work aimed to provide insights into MM-RMS aggressiveness to develop risk-adapted therapies. Early findings show MYOD1L122R is an enigmatic molecular aberration. The MYOD1L122R RD line does not recapitulate the spindling formation seen in the spindling RMS TCCC-ST78, which harbors an endogenous MYOD1 mutation. Further experiments with different chemotherapeutics are planned. Ongoing work seeks to describe changes in differentiation potential, gene expression, and binding partners. RMS typically expresses MYOD1 and myogenin but fails to differentiate. The MYOD1L122R isogenic stem cell line should provide insight into the mutation's role in preventing differentiation.

ABSTRACTS

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PROFESSIONAL MEETINGS

- American Society for Investigative Pathology Annual Meeting, Baltimore, MD; Apr. 20-23, 2024.
- 8th Annual Children’s Cancer Foundation Research Symposium, Greenbelt, MD; June 5, 2024.

MANASA GADIRAJU
University of Missouri – Kansas City School of Medicine

MENTORS

Michael A. Solomon, M.D., MBA, Head
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Jason Elinoff, M.D., Head
Pulmonary Vascular Biology Section, Critical Care Medicine and Pulmonary Branch, National Heart, Lung, & Blood Institute (NHLBI)

Leniolisib PI3Kδ Inhibition in a Rodent Model of Pulmonary Arterial Hypertension

Class I phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling has been implicated in endothelial cell dysfunction in in vitro models of pulmonary arterial hypertension (PAH). We investigated the role of PI3K inhibitors in an in vivo murine model of PAH with ex vivo analysis of PI3Kδ inhibition in splenocytes to confirm biologic activity. Study cycles were eight weeks and consisted of subcutaneous injection of a VEGFR-2 inhibitor (Sugen) with three subsequent weeks of hypoxia for all rats to induce a PAH-like phenotype. Rats were then kept at normoxia and randomized to PI3Kδ inhibitor (leniolisib) or vehicle negative control, administered twice daily via oral gavage for four weeks.

After eight weeks, rats underwent right and left heart catheterization and were sacrificed for necropsy. Ex vivo analysis was performed on collected splenocytes via flow cytometry to assess PI3K/AKT pathway activity in PAH leniolisib-treated and untreated rats. Two study cycles were performed to compare drug response in placebo-treated, sildenafil-treated, and 15 mg/kg, 30 mg/kg, and 60 mg/kg leniolisib-treated rats (n=8 per leniolisib group and n=4 for placebo and sildenafil). In the subsequent two cycles, sildenafil and 15 mg/kg leniolisib were omitted for simplicity, with n=8 per group. In cycles 1 and 2, significant phenotypic variability was noted in the placebo groups. In cycles 3 and 4, placebo phenotypic variation was reduced, but leniolisib did not reduce right ventricular systolic pressure or right ventricular hypertrophy as measured by Fulton Index, with no significant difference between groups or compared to placebo. On ex vivo analysis, there was no significant difference between p70S6 ribosomal protein, used as a marker of PI3K/AKT pathway activity, between leniolisib-treated and placebo-treated PAH rat splenocytes. Leniolisib did not have therapeutic benefit in our PAH rodent model, which initially demonstrated high degree of phenotypic variability. Future studies will investigate different PI3K subunit inhibitors and upstream AKT inhibitors in our PAH rodent model.

ABSTRACTS

- **Gadiraju M**, Hersi K, Elinoff J. Use of pulmonary vasodilators in hepatopulmonary syndrome: a case report. Metropolitan DC American Thoracic Society. Apr 2024. [Poster]

PROFESSIONAL MEETINGS

- Metropolitan DC American Thoracic Society. Apr 2024.

AWARDS

- Metropolitan DC American Thoracic Society 2024 Annual Meeting - Best Clinical Case Report

DAVID G. GELIKMAN
University of Central Florida College of Medicine

MENTOR

Baris Turkbey, M.D., Head
Artificial Intelligence Resource and Magnetic Resonance Imaging Section, Molecular Imaging Branch, Center for Cancer Research, National Cancer Institute (NCI)

Evaluating Artificial Intelligence-Assisted Prostate Biparametric MRI Interpretation: An International, Multi-Reader Study

Interpretation of biparametric magnetic resonance imaging (bpMRI) for prostate cancer is subject to significant inter-reader variability. Artificial intelligence (AI) has the potential to enhance diagnostic accuracy and consistency among radiologists. This study aims to evaluate a deep learning-based prostate cancer detection AI model in assisting radiologists for interpretation of prostate bpMRI.

Six radiologists (3 prostate-focused and 3 general body readers) from different institutions each evaluated 120 prostate bpMRIs using PI-RADS v2.1. Of these, 80 were cases with pathologically confirmed prostate cancer and 40 were biopsy-proven, cancer-negative controls. In phase 1 of the study, readers had AI assistance for half of these patients. After a one-month washout period, in phase 2, readers had AI assistance for the other half of the patients. AI-assisted and non-assisted reads were randomized between phases. A patient-level analysis compared sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for lesion detection at bpMRI with and without AI. Inter-reader agreement on lesion measurements and PI-RADS scores was evaluated with quadratic weighted Cohen's kappa (κ).

The patient cohort had a median age of 63 years (IQR, 57-68) and prostate-specific antigen of 7.1 ng/mL (IQR, 5.1-10.8). Patient-level accuracy improved by 5% and 2% for two prostate-focused readers and by 3% for one general radiologist. Improvements and decreases in sensitivity and specificity were variable across readers. AI assistance resulted in a significant reduction in lesion size measurement discrepancy between readers (1.53 mm vs 0.85 mm, $p < .0001$). There was an improvement in average PI-RADS v2.1 score agreement for lesions read by the same readers with AI ($\kappa = 0.689$) vs without AI ($\kappa = 0.535$).

AI assistance can improve accuracy of bpMRI interpretation for some readers. Despite improvements in measurement agreement and PI-RADS scores, the varied impact of AI on different readers calls for further investigation into how AI tools can best complement radiologists in an effective and consistent manner.

PUBLICATIONS

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- Esengur OT, **Gelikman DG**, Turkbey B. Role of Prostate MRI for Post-Focal Treatment Assessment and Surveillance. In *Imaging and Focal Therapy of Early Prostate Cancer*, Ed. Polascik T. Springer, Cham. [In press]
- Yilmaz EC, Esengur OT, **Gelikman DG**, Turkbey B. Interpreting prostate multiparametric MRI: beyond adenocarcinoma – anatomical variations, mimickers, and interventional changes. *Semin Ultrasound CT MR*. [In press]
- Hsueh JY, Nethala D, Singh S, Hyman JA, **Gelikman DG**, Linehan WM, Ball MW. Exploring the feasibility of GPT-4 as a data extraction tool for renal surgery operative notes. *Urol Pract*. [In press]
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- Rathi N, Blake Z, Hyman J, Nemirovsky DR, **Gelikman DG**, Enders JJ, Hesswani C, Koller C, Nethala D, Mendhiratta N, Kenigsberg AP, Pillai A, Noun J, Dahut W, Karzai FY, Linehan WM, Pinto PA, Turkbey B, Gurram S. MRI-based measurements of androgen-sensitive muscles: a novel, objective marker for hypogonadism. *J Urol*. [Under review]
- Yilmaz EC, Harmon SA, Law YM, Huang EP, Belue MJ, Lin Y, **Gelikman DG**, Ozyoruk KB, Yang D, Xu Z, Tetreault J, Xu D, Hazen LA, Garcia C, Lay NS, Eclarinal P, Toubaji A, Merino MJ, Wood BJ, Gurram S, Choyke PL, Pinto PA, Turkbey B. Evaluating a deep learning-based prostate lesion detection algorithm on paired external and in-house biparametric MRIs. *Radiol Imaging Cancer*. [Under review]
- Song M, Huth H, Borde T, Saccenti L, Anibal J, **Gelikman D**, Hazen L, Kassin M, Levy E, Ukeh I, Varble N, Turkbey B, Chen A, Wood B. Radiomics-guided biopsy to predict biopsy quality. *J Vasc Interv Radiol*. [Under review]

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- **Gelikman DG**, Kenigsberg AP, Yilmaz EC, Harmon SA, Parikh S, Hyman J, Huth H, Koller CR, Nethala D, Hesswani C, Gurram S, Choyke PL, Wood BJ, Pinto PA, Turkbey B. Evaluating diagnostic accuracy of the Prostate Imaging after Focal Ablation (PI-FAB) scoring system in detecting clinically significant prostate cancer after primary focal therapy. American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA; Jan. 25-27, 2024. [Poster]
- **Gelikman DG**, Mena E, Lindenberg L, Yilmaz EC, Harmon SA, Azar WS, Schuppe K, Rathi N, Wood BJ, Gurram Sandeep, Choyke PL, Pinto PA, Turkbey B. Effect of urinary stagnation in the prostatic urethra on generating false-positive midline lesions on 18F-DCFPyL PSMA PET/CT. American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA; Jan. 25-27, 2024. [Poster]

- Yilmaz EC, Harmon SA, Belue MJ, Lin Y, Huang EP, **Gelikman DG**, Merriman KM, Ozyoruk KB, Lay NS, Eclarinal P, Toubaji A, Merino MJ, Wood BJ, Gurram S, Law YM, Choyke PL, Pinto PA, Turkbey B. Performance evaluation of a bpMRI-based AI algorithm on paired external and in-house prostate MRIs for lesion detection. Society of Abdominal Radiology Annual Meeting, Hollywood, FL; Apr. 14-19, 2024. [Podium]
- **Gelikman DG**, Yilmaz EC, Harmon SA, An JY, Azamat S, Law YM, Margolis DJA, Marko J, Panebianco V, Gaur S, Bicchetti M, Huang EP, Gurram S, Shih JH, Choyke PL, Wood BJ, Pinto PA, Turkbey B. Evaluating AI assistance in prostate bpMRI interpretation: A multi-reader study. American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 3-6, 2024. [Podium]
- Hesswani C, Yilmaz EC, Harmon SA, **Gelikman DG**, Koller CR, Parikh SH, Schuppe KC, Azar WS, Kenigsberg AP, Azari S, Gurram S, Turkbey B, Pinto PA. Evaluation of an MRI AI algorithm for the detection of prostate cancer using spatial annotations on wholemount prostate pathology. AUA Annual Meeting, San Antonio, TX. May 3-6, 2024. [Poster]
- Hsueh J, Nethala D, Singh S, Hyman J, **Gelikman DG**, Linehan WM, Ball MW. Exploring the feasibility of GPT-4 as a data extraction tool for nephrectomy operative notes. Urologic Oncology Research Symposium at the AUA Annual Meeting, San Antonio, TX; May 3, 2024. [Poster]
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PROFESSIONAL MEETINGS

- Focal Therapy Society Annual Meeting, Washington, D.C.; Sep. 7-9, 2023.
- Soc. of Urologic Oncology Annual Meeting, Wash, D.C.; Nov. 28-Dec. 1, 2023.
- American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA; Jan. 25-27, 2024.
- American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024.
- American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 3-6, 2024.

ALEXA E. GOLBUS
Medical University of South Carolina

MENTOR

Marcus Y. Chen, MD, Senior Research Physician, Director
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Deep Learning Artificial Intelligence Image Reconstruction for Cardiac and Pulmonary Imaging

Coronary artery calcium score (CACS) determined by ECG-gated cardiac CT is widely validated to predict risk of cardiovascular events and mortality. Dedicated cardiac CT for CACS exposes to patients to a radiation dose of approximately 1 millisievert (mSv). A new CT scout method utilizing ultra-low dose helical CT (3D Landmark) offers tomographic cross-sectional imaging to identify anatomic structures, in conjunction with artificial intelligence assisted anatomic landmark detection for automated scan planning. These 3D Landmark helical scout images provide axial images, from which coronary artery calcium (CAC) can be identified and estimated. The purpose of our study was to analyze the association and agreement between estimated CAC burden on 3D Landmark scout imaging vs ECG-gated Agatston CAC score.

Consecutive patients undergoing clinically indicated non-contrast ECG-gated cardiac CT planned with 3D Landmark scout imaging, from July 2023-April 2024 were included. Extent of coronary artery calcium on 3D Landmark scout imaging was scored from 0-3 (absent, mild, moderate, severe). Standard Agatston CACS on ECG-gated cardiac CT was converted to an ordinal score from 0-3, corresponding to absent (0), mild (1-100), moderate (100-400), or severe (>400). Fischer's exact test, kappa coefficient, and paired t-tests were used for analysis.

150 patients were included with 51.3% female, mean age 49.0 ± 16.8 years, and mean BMI 28.6 ± 12.3 kg/m2. Sensitivity of 3D Landmark in identifying calcium was 98.7%, with specificity of 100%. There was strong interrater agreement between 3D Landmark calcium score and Agatston CACS, with quadratic weighted kappa coefficient 0.97 ± 0.01(CI 0.95-0.99). Radiation dose-length-product was significantly lower for 3D Landmark imaging vs. cardiac CT (9.7 ± 3.6 vs 43.8 ± 26.4 mGy·cm, $p<0.001$). Similarly, effective dose was 78% lower for 3D Landmark vs cardiac CT (0.14 ± 0.05 vs. 0.61 ± 0.37mSv, respectively, $p<0.001$)

CAC burden on 3D Landmark scout imaging correlates strongly with Agatston CACS, demonstrating utility in assessing cardiovascular risk without introducing additional radiation exposure or costs.

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- **Golbus AE**, Schuzer JL, Rollison SF, Bronson KC, Chen MY. 3D Landmark scout imaging accurately assesses presence and extent of coronary calcification with lower radiation exposure, Society of Cardiovascular Computed Tomography

PROFESSIONAL MEETINGS

- Asian Oceanian Congress of Radiology, Taipei, Taiwan; Mar. 22-25, 2024.
- American College of Cardiology 2024, Atlanta, GA; Apr. 6-8, 2024.
- American Thoracic Society, San Diego, CA; May 17-22, 2024.

ASHLEY L. GOLBUS
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MENTOR

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Modifiers of Arterial Stenosis in Williams Syndrome: Using Genomics to Discover Drivers of Vessel-Specific Outcomes

Williams syndrome (WS) results from a hemizygous deletion of 1.5-1.8 Mb of chromosome 7q11.23, with deletion of the elastin gene (ELN) resulting in associated vascular phenotypes including supravalvar aortic stenosis (SVAS), supravalvar pulmonic stenosis (SVPS), and branch pulmonary artery (PA) stenosis. While genetic modifiers of SVAS severity have been described, it is unclear whether pulmonary vascular outcomes are modified by the same gene variants and pathways. We sought to deeply phenotype pulmonary artery disease in a large cohort of people with WS; to identify gene variants associated with surgical SVAS, surgical PA stenosis, and bilateral surgical stenosis; and to identify whether similar or unique pathways modify stenosis severity in each location.

As part of a collaborative phenotyping study, we collected records on 473 individuals with WS. From those, 334 participants met inclusion criteria. SVAS and PA stenosis (main PA and/or branch PA) were categorized as surgical, mild/moderate, or none, based on review of medical records and imaging reports. Extreme phenotype modifier analysis was also performed utilizing a previously described small cohort size pipeline that included non-synonymous variant prioritization, gene set enrichment, and pathway-level association tests.

An association was identified between severity of SVAS and PA stenosis (P=8.2e-15). Pathways modifying stenosis were identified with bilateral surgical stenosis, surgical SVAS, and surgical PA stenosis sharing extracellular matrix pathways; surgical SVAS modified by lipid metabolism and PI3K ATP pathways; surgical PA stenosis modified by GTPase and glycosylation pathways; and bilateral surgical stenosis modified by focal adhesion and protein modification pathways.

Genetically-derived determinants of these phenotypes can be identified using bioinformatic tools and include variants in extracellular matrix pathways for individuals with any surgical stenosis type, while other pathways such as lipid metabolism and focal adhesion may be tissue-specific. Knowledge of these pathways can aid investigators in prioritizing therapeutic targets for generalized vs site-specific stenosis.

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PROFESSIONAL MEETINGS

- American College of Medical Genetics and Genomics, Toronto, Ontario, Canada; Mar. 12-16, 2024.

BRADY D. GREENE
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

MENTOR

Carlos A. Zarate Jr., M.D., Chief
Experimental Therapeutics & Pathophysiology Branch, Section on the Neurobiology and Treatment of Mood Disorders, National Institute of Mental Health (NIMH)

Out of Sight but Not Out of Mind: Correlates of Interoception in Treatment-Resistant Depression

Individuals with major depressive disorder exhibit differences in interoception, the process through which the nervous system senses and processes internal stimuli from the body. Less is known about its role in treatment-resistant depression (TRD). Interoceptive sensibility - the subjective perception of one's internal state, and a way to assess components of interoception - can be measured using subscales of the Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). This study hypothesized that worse interoceptive sensibility would correlate with greater symptomatology and treatment refractoriness in TRD.

Sixty-six adult TRD patients (59% female, 86% unipolar depression, 14% bipolar depression) completed the MAIA-2, the Montgomery-Åsberg Depression Rating Scale (MADRS) (depression severity), the Hamilton Anxiety Rating Scale (HAM-A) (anxiety severity), and the Maudsley Staging Method (MSM) score (treatment resistance). Suicidal ideation was measured using a weighted sum of the MADRS and Hamilton Depression Rating Scale suicide items. We used correlations to assess relationships between interoceptive sensibility, depressive episode severity, anxiety severity, and treatment resistance.

There were significant negative relationships between MADRS ($r = -0.32$, $p = 0.008$), suicidal ideation ($r = -0.29$, $p = 0.02$), HAM-A ($r = -0.35$, $p = 0.01$), and the Self-Regulation subscale (distress regulation via attention to body sensations). We also detected significant negative relationships between MADRS ($r = -0.38$, $p = 0.002$), suicidal ideation ($r = -0.29$, $p = 0.02$), HAM-A ($r = -0.30$, $p = 0.02$), and the Trusting subscale (experiencing one's body as safe and trustworthy). Controlling for anxiety severity, these findings were no longer statistically significant.

Components of interoceptive sensibility negatively correlated with clinical presentation and comorbid symptoms of anxiety in TRD, suggesting transdiagnostic associations with both depression and anxiety. Additional research is underway to assess relationships between neurophysiology and interoceptive sensibility by magnetoencephalography. Further research on interoception as a potential treatment target is recommended.

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PROFESSIONAL MEETINGS

- 2nd Annual NIH Investigator Meeting for Interoception Research, Bethesda, MD; Nov. 11, 2023.
- American Psychiatric Association Annual Meeting, New York, NY; May 4 -8, 2024.
- Society of Biological Psychiatry Annual Meeting, Austin, TX; May 9-11, 2024.

JESSICA Y. HSUEH
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MENTOR

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Characterization of Metabolic and Imaging Profiles in the Diagnosis of Hereditary Pheochromocytomas and Paragangliomas

Hereditary pheochromocytomas and paragangliomas are associated with mutations in the mitochondrial enzyme succinate dehydrogenase. Because they have heterogenous clinical presentations, there are no clear universal screening guidelines. We sought to examine the utility of metabolic testing and imaging in diagnosing hereditary pheochromocytomas and paragangliomas.

Our retrospective study included patients with confirmed familial succinate dehydrogenase mutations and histologically proven pheochromocytomas/paragangliomas or with suggestive metabolic and imaging features. We extracted information on age, race, sex, tumor size, tumor location, urine and plasma metabolic testing, and diagnostic imaging. Patients with incomplete diagnostic information were excluded.

Our cohort consisted of nine patients with 13 tumor occurrences from 2003 to 2023. The average age at diagnosis was 31.7 years with a 2.9 cm average tumor size. Five tumors (38.5%) were biochemically silent, with all tumors detected on imaging. Most of the remaining tumors had a noradrenergic profile, with positive norepinephrine and normetanephrine in plasma and urine. MIBG was the least sensitive (50%) imaging modality, and DOTATATE PET/CT was the most sensitive (100%). 10 (76.9%) tumors were treated with surgical resection; all metabolic results were subsequently negative, except in patients with metastatic disease.

Our investigation adds to the current literature on diagnosing hereditary pheochromocytomas and paragangliomas. We highlight the importance of multimodal screening that consists of both imaging and metabolic screening, especially given the prevalence of biochemically silent tumors.

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PROFESSIONAL MEETINGS

- Society for Urologic Oncology Annual Meeting, Washington, DC; Nov. 28 - Dec. 1, 2023.
- American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 3 - May 6, 2024.

HANNAH B. HUTH
University of Tennessee Health Science Center

MENTOR

Bradford J. Wood, M.D., Senior Investigator

Director
Center for Interventional Oncology, NIH Clinical Center (CC)

Chief
Interventional Radiology Section, Radiology and Imaging Sciences Department, CC

Wearable Spirometry: Feasibility of Measuring Volume of Inspiration via Non-invasive Motion Sensors

Postoperative pulmonary complications (PPCs) encompass a broad and heterogenous spectrum of conditions leading to suboptimal surgical outcomes. Incentive spirometry has served as a cornerstone in the prophylaxis and management of PPCs; however, its use is limited by poor patient compliance, nursing burden, and lack of longitudinal tracking. Continued advancements in artificial intelligence present a compelling opportunity to address these gaps.

In this pilot study, a motion sensor was adhered to the right thorax of healthy volunteers as they took measured breaths (250-2500 mL) via incentive spirometry while seated. Motion waveforms were parsed out by corresponding volume of inspiration and grouped into low, medium, and high volumes. A machine learning model was trained on these sequences, learning to recognize patterns in chest wall motion associated with each lung volume category. A leave-one-out validation strategy was used to assess the model performance.

All subjects (n=6: 3 males, 3 females) were healthy volunteers. Movement along the y-axis was perpendicular to the chest wall, while the z-axis signal indicated upward and outward motion. There were visible differences in waveform amplitude in the y and z axes as participants took higher-volume breaths. When the model was tested against traditional spirometry volumes of inspiration, the average AUC across all participants was 0.80 (range 0.68-0.92). The model performed best at identifying low-volume breaths (average AUC 0.85) and high-volume breaths (average AUC 0.80).

These results, while limited, suggest that wearable technology and corresponding custom models can determine volume of inspiration from chest wall motion alone. As such, this technology could be used to improve compliance and potentially even clinical outcomes by offering more standardized and consistent monitoring, documentation, and data analysis. Further research involving a broader and more diverse patient population is underway to fully pilot and examine these hypotheses in real-world clinical settings.

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- Saccenti L, Borde T, Varble N, Li M, **Huth H**, Hazen L, Xu S, et al. Evaluation of a 3D-printed needle guide for simplification of smartphone augmented reality application for percutaneous interventions. Society of Interventional Radiology Annual Meeting, Mar. 26, 2024. [Podium]
- **Huth H**, Zakieh A, Hari. Patients’ paths to chimeric antigen receptor t-cell therapy in B-ALL: No two journeys are alike. American Society of Pediatric Hematology/Oncology Conference, Apr. 5, 2024. [Poster]
- Anibal J, **Huth H**, Wood B. Voice HER: Multimodal audio data for health. Bridge2AI Conference, Bethesda, MD; Apr. 18, 2024. [Poster]

PROFESSIONAL MEETINGS

- Society of Interventional Radiology Annual Scientific Meeting, Salt Lake City, UT; Mar. 23-28, 2024.
- American Society for Pediatric Hematology Oncology, Seattle, WA; Apr. 2-6, 2024.
- Bridge2AI All Hands Conference, Bethesda, MD; Apr. 17-19, 2024.
- Children's Cancer Foundation Research Symposium, Bethesda, MD; June 5, 2024.

KRISTEN R. IBANEZ
University of Central Florida College of Medicine

MENTOR

Jung-Min Lee, M.D., Head
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Dual Inhibition of ATR and PI3K Pathways Promotes Cell Death in Platinum-Resistant Endometrial Cancer Cells by Increasing DNA Damage

The copy number high (CNH) subtype (15-25%) of endometrial cancer (EC) is associated with impaired G1/S checkpoint regulation (~85% CNH EC), making cells rely on ATR-mediated G2/M cell cycle checkpoints for DNA replication and repair. Additionally, >80% of ECs exhibit PI3K pathway activation (e.g., PIK3CA mutations), linked to enhanced DNA repair and drug resistance. Therefore, we hypothesized that dual ATR and PI3Kα inhibition would enhance DNA damage, increasing cell death in EC.

CNH EC cell lines included platinum-resistant (KLE, MFE280, HEC1A, ARK2) and platinum-sensitive (ARK1) lines, and were used to evaluate the activity of ATR inhibitor (ATRi) camonsertib and PI3Kα inhibitor (PI3Kαi) inavolisib. Cell growth was assessed by 3-day XTT and 9-12-day colony-forming assays. The degree of combination synergy, additivity, or antagonism was calculated using SynergyFinder with a reference highest single agent (HSA) model. DNA damage endpoints were measured by alkaline comet assay.

All tested EC cell lines showed sensitivity to clinically attainable doses of ATRi monotherapy (IC50 0.03 – 0.98 μM), but varying sensitivity to PI3Kαi monotherapy (IC50 0.03 – 67.01 μM) unrelated to their PIK3CA mutation status. Combination treatment using clinically attainable concentrations yielded additivity in all cell lines independent of platinum sensitivity (HSA synergy scores -2.7–11.0). Notably, increased cytotoxic effects were observed in both PIK3CA wild-type (KLE and ARK2) and PIK3CA-mutant (MFE280 and HEC1A) platinum-resistant lines by colony-forming assays (2.1- to 46.4-fold decrease in colony-forming ability relative to ATRi; 1.4- to 17.9-fold decrease relative to PI3Kαi). ATRi and PI3Kαi combination induced greater DNA damage, evidenced by elevated mean comet tail moment relative to ATRi (increased 1.7- to 2.5-fold; $p < 0.01$) or PI3Kαi (increased 2.8- to 3.1-fold; $p < 0.01$) regardless of PIK3CA mutation status.

Our results suggest that dual inhibition of ATR and PI3K pathways induces greater cell death by increasing DNA damage in platinum-resistant EC cells independent of PIK3CA mutation status.

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- **Ibanez KR**, Donohue D, Malys T, Lee J-M. Gynecologic Cancer Intergroup CA125 response has a high negative predictive value for CHK1 inhibitor RECIST response in recurrent ovarian cancer. *Sci Rep*. [In press]

ABSTRACTS

- **Ibanez KR**, Huang TT, Sotiriou S, Lin YG, Lee J-M. Dual inhibition of ATR and PI3K pathways promotes cell death in platinum-resistant endometrial cancer cells by increasing DNA damage. American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024. *Cancer Research*. 2024;84(6S):3369-3369. [Poster]
- **Ibanez KR**, Donuhue D, Malys T, Lee J-M. Use of Gynecologic Cancer Intergroup CA125 criteria to evaluate cell cycle checkpoint kinase 1 inhibitor (CHK1i) prexasertib response and disease progression in recurrent high-grade serous ovarian cancer. American Society of Clinical Oncology Annual Meeting, Chicago, IL; May 31–June 4, 2024. *J Clin Oncol*. 2024 May 23.

PROFESSIONAL MEETINGS

- American College of Obstetricians and Gynecologists District IV Annual Meeting, Washington, DC; Oct. 20-22, 2023.
- American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024.

AWARDS

- H.O.W. - Hearing the Ovarian Cancer Whisper - Dr. Robert C. Knapp Medical Student Award

MEGAN G. JIAO
McGovern Medical School, University of Texas Health Science Center at Houston

MENTORS

Philip Shaw, M.B. M.Ch., Ph.D., Head
Neurobehavioral Clinical Research Section, Social and Behavioral Research Branch, National Human Genome Research Institute (NHGRI)

Susan Persky, Ph.D., Director,
Immersive Simulation Program, Social and Behavioral Research Branch, National Human Genome Research Institute (NHGRI)

Piloting a Virtual Reality-Based, Gamified Intervention with Multidomain Cognitive Training for Children and Adolescents with ADHD

Attention-deficit hyperactivity disorder (ADHD), a childhood-onset neurodevelopmental disorder, is associated with impairment in multiple cognitive domains, which affects daily function and quality of life. Computerized cognitive training may improve ADHD symptoms and cognitive function, but prior studies primarily targeted only one domain at a time, and little is known about the mechanisms driving improvement. Additionally, cognitive training requires repetition and prolonged concentration, which can cause disengagement in individuals with ADHD. However, immersive virtual reality (VR) and video games have proven highly engaging for youth, particularly those with attentional challenges. Thus, we are conducting an open-label, proof-of-concept study evaluating a novel intervention using multidomain-targeting, VR-based, gamified cognitive training.

This is an ongoing, phase I pilot study assessing the intervention's safety, usability, feasibility, and preliminary efficacy. Participants will include 30 total children aged 10-16 and diagnosed with ADHD but not receiving treatment for the study duration. They receive the intervention at home using Meta Quest 2 headsets for 20 total sessions of 20 minutes each across four weeks. The intervention targets four domains associated with impairment in individuals with ADHD: inhibitory control, visuospatial working memory, temporal information processing, and processing speed. Training intensity is tailored to an individual's skill in each domain, personalizing sessions to their strengths and weaknesses. We are evaluating symptomatic and cognitive changes pre- and post-intervention, as well as functional neuroimaging through fMRI. This will parse how symptomatic change may reconfigure brain networks, making this the first neuroimaging investigation of the neural mechanisms underlying cognitive changes with training for children with ADHD.

Preliminary results in participants (n=3) demonstrate that the intervention is well-tolerated with no related adverse events reported. Behavioral symptoms did not worsen and may have improved, with quantified results pending. Following this pilot, there will be a phase II double-blinded, randomized, controlled trial primarily evaluating efficacy.

PUBLICATIONS

- Persky S, **Jiao MG**. A quantitative content analysis of systematic and scoping reviews assessing extended reality for pain management. *J Med Extended Reality*. [Under review]

ABSTRACTS

- **Jiao MG**, Chen J, Persky S. Facilitating user-avatar affiliation through embodiment in VR-based health education. Annual Virtual Reality and Healthcare Global Symposium, Sarasota, FL & Tampa, FL; Feb. 29-Mar. 3, 2024. [Podium]
- **Jiao MG**, Persky S. From virtual beaches to sports games: exploring the landscape of content inclusion in reviews assessing extended reality for pain management. Virtual Medicine Conference, Los Angeles, CA; Mar. 28-29, 2024. [Poster]

- Jiao MG, Parra JS, Norman LJ, Persky S, Shaw P. A gamified, virtual reality-based intervention for multidomain cognitive training in children and adolescents with ADHD. Medical Extended Reality Summit, College Park, MD; Apr. 16-17, 2024. [Poster]
- Jiao MG, Aneni K. Playing with cognition: considerations for developing and utilizing serious video games for diagnosis and treatment in youth mental health. International Neuroethics Society Annual Meeting, Baltimore, MD; Apr. 17-19, 2024. [Poster]

PROFESSIONAL MEETINGS

- Annual Virtual Reality and Healthcare Global Symposium, Sarasota, FL & Tampa, FL; Feb. 29-Mar. 3, 2024.
- Virtual Medicine Conference, Los Angeles, CA; Mar. 28-29, 2024.
- Medical Extended Reality Summit, College Park, MD; Apr. 16-17, 2024.
- International Neuroethics Society Annual Meeting, Baltimore, MD; Apr. 17-19, 2024.

SHELBY V. JOHNSON, MPH
Dell Medical School at the University of Texas at Austin

MENTOR

Andrew M. Blakely, M.D., Assistant Research Physician
Surgical Oncology Program, Center for Cancer Research, National Cancer Institute (NCI)

A Multi-Omics Interrogation of SDH-Deficient Primary and Metastatic Gastrointestinal Stromal Tumors

Succinate dehydrogenase-deficient (SDH-def) gastrointestinal stromal tumors (GIST) are a rare subset of GISTs that lack the typical KIT/PDGFRA mutations that drive most GISTs. SDH-def GISTs are more likely to metastasize and tend to be resistant to conventional tyrosine kinase inhibitor therapy. Systemic therapy options are lacking, and their tumor biology and metastatic progression remain to be more fully elucidated. Therefore, we sought to characterize tumor microenvironment (TME) differences among primary versus metastatic lesions to enhance the cellular and molecular understanding of SDH-def GIST progression.

Patients with histologically-confirmed SDH-def GISTs were enrolled prospectively in clinical trial NCT04557969. Patient tissue was collected during resection, depending on disease pathology. Tissue for research use was collected, some of which was formalin-fixed and paraffin-embedded. Two patients were selected for this study based on SDH deficiency. Histopathologic analysis, next-generation sequencing, multiplex fluorescent immunohistochemistry, and spatiotemporal analysis at the single-cell level were conducted on gastric lesions, lymph node metastases, and liver metastases.

Next-generation sequencing revealed different pathogenic mutations between the two patients. Patient A displayed mutations in SDHA and TP53, whereas Patient B displayed pathogenic mutation only in PTEN; hence, the etiology of the latter SDH-def GIST was epigenetic silencing of SDHC via promoter hypermethylation. Histopathologic analyses showed morphology consistent with spindle cell neoplasms and the presence of immune cells. Further analysis with multiplex fluorescent immunohistochemistry confirmed the presence of immune cells, with the liver metastases being significantly immune-rich. Additionally, we found a diffuse T-cell predominance across all tumor sites.

Future directions include analyzing spatial transcriptomic data to reveal cell classifications, cell quantifications, and cell lineage. This will allow us to further classify T-cell population and determine if these are resident or infiltrative immune cells. This will enhance understanding of tumor biology and hopefully assist in identifying potential immune-based treatment strategies.

ABSTRACTS

- Sarvestani AL, Rainey A, Perati SR, **Johnson SV**, Holewiniski R, Andresson T, Hernandez J, Blakely AM, Gregory S. In vivo analysis of protein level effects of hyperthermic intraperitoneal chemotherapy. Society of Surgical Oncology Annual Meeting, Atlanta, GA; Mar. 20-23, 2024. [Poster]

ANNETTE Y. KAMINAKA
Albany Medical College

MENTORS

Johnny Tam, Ph.D., Senior Investigator
Clinical and Translational Imaging Section, Ophthalmic Genetics and Visual Function Branch, National Eye Institute (NEI)

Laryssa A. Huryn, M.D., Medical Officer
Ophthalmic Clinical Genetics Section, Ophthalmic Genetics and Visual Function Branch, National Eye Institute (NEI)

Adaptive Optics Retinal Imaging Reveals Cone Photoreceptor Enlargement and Loss of Regularity in RHO-associated Retinitis Pigmentosa

Secondary cone degeneration following progressive rod loss has been reported in RHO-associated retinitis pigmentosa (RHO-RP). In this study, we use adaptive optics (AO) retinal imaging to investigate changes in cone photoreceptor size and regularity in RHO-RP.

Multimodal imaging from a custom-built AO instrument was acquired in 7 patients with molecularly confirmed RHO-RP. Cones were identified and segmented at regions of interest (ROIs) selected across retinal eccentricities between 1.0 to 5.5 mm by expert graders assisted by deep learning software (PMID33507868) and compared to normative data measured from 24 healthy subjects. Longitudinal AO imaging was performed in 3 patients (3 visits; time between visits 1.8 ± 1.1 years, mean ± SD), for which two longitudinally registered ROIs were selected for each visit (located at 1 mm and at an eccentric location near the boundary of preserved cones).

Cone photoreceptor diameter was enlarged across all measured eccentricities in the RHO-RP cohort by an average of 22.1 ± 5.6% (n=19,408 cones from 7 patients, $p<0.01$). In general, cone diameter was more variable in RHO-RP compared to healthy individuals, resulting in an increased ratio of maximum to minimum cone diameter within each ROI (3.3 ± 0.8 vs 2.1 ± 0.3; n=182 ROIs, $p<0.01$). Longitudinal AO imaging revealed overall stability in cone diameter enlargement over three visits ($p=0.52$). Despite the relatively constant and stable enlargement in cone diameter, there was a decrease in the percentage of cones with six-sided Voronoi neighbors when comparing eccentric locations to the 1 mm location (48.2 ± 9.4% vs 59.6 ± 6.8%, $p<0.01$). This disruption to hexagonal packing was stable across 3 visits ($p=0.51$).

Our results are suggestive of increased disorganization of the cone mosaic near the boundary of preserved cones. Investigation of cone photoreceptor size and regularity may lead to new insights about the impact of rod degeneration on the cone photoreceptors.

ABSTRACTS

- **Kaminaka A**, Liu T, Aguilera N, Giannini J, Zein WM, Huryn LA, Tam J. Adaptive optics retinal imaging reveals cone photoreceptor enlargement and loss of regularity in RHO-associated retinitis pigmentosa. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 4-9, 2024. [Poster]
- Huryn LA, **Kaminaka A**, Benson M, Agather A, Orencia S, Swaroop A, Stasheff SF. A novel neural retina leucine zipper-associated retinopathy phenotype provokes genetic and developmental consideration. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 4-9, 2024. [Poster]

PROFESSIONAL MEETINGS

- Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 4-9, 2024.

ELIZABETH N. KARANJA
University of Missouri School of Medicine

MENTOR

Steven M. Holland, M.D.

Director
Division of Intramural Research

Chief
Immunopathogenesis Section, National Institute of Allergy and Infectious Disease (NIAID)

Autoantibodies to Interferon Lambda in Chronic Granulomatous Disease

There is a growing interest in autoantibodies targeting cytokines in both immunodeficiency and immune dysregulatory disorders due to their potential as biomarkers and therapeutic guides. Anti-cytokine autoantibodies have been identified in various conditions, including anti-IFN-γ in disseminated nontuberculous mycobacterial disease, anti-GM-CSF in pulmonary alveolar proteinosis, cryptococcal meningitis, and disseminated nocardiosis, and anti-type I interferons in severe coronavirus disease 2019 (COVID-19). However, the prevalence of autoantibodies in patients diagnosed with chronic granulomatous disease (CGD) has not yet been explored. This study aimed to address this gap by investigating the anti-cytokine autoantibody profile in a cohort of CGD patients.

Plasma samples collected from CGD patients (n=154) and healthy individuals (n=57) were assessed for various anti-cytokine autoantibodies using a particle-based screening assay. The neutralizing capacity of the autoantibodies in the patients' plasma was evaluated by flow cytometry on A549 cells using STAT1 phosphorylation as a readout.

We found that 17 out of 154 (11%) CGD patients had elevated levels of autoantibodies against type III interferons, 9 of which (6%) demonstrated neutralizing activity against at least one interferon lambda. In contrast, 2 of 57 healthy control samples showed high level binding, but none showed neutralizing activity ($p<0.0001$).

Here, we report the novel observation of anti-interferon lambda autoantibodies in CGD patients. Our data show that these CGD patients have a higher incidence of autoantibodies against type III interferons compared to healthy controls. Previous literature has highlighted the critical role of IFNλ cytokines in viral immunity, particularly at epithelial surfaces, and in neutrophil responses to fungal infections, specifically Aspergillus fumigatus. Given these considerations, we plan to further investigate the presence and role of neutralizing autoantibodies in this and other rare disease groups.

ABSTRACTS

- **Karanja E**, Rosen LB, Zerbe CS, Holland SM. Neutralizing interferon lambda 1 autoantibodies in a pediatric patient with chronic granulomatous disease and colitis. Clinical Immunology Society Annual Meeting, Minneapolis, MN; May 1-4, 2024. [Poster]

PROFESSIONAL MEETINGS

- Clinical Immunology Society Annual Meeting, Minneapolis, MN; May 1-4, 2024.
- Digestive Disease Week Annual Meeting, Washington, D.C; May 19-24, 2024.

ALEXANDER K. KARIUS
Johns Hopkins University School of Medicine

MENTOR

Paul M. Hwang, M.D., Ph.D., Senior Investigator
Cardiovascular Branch, National Heart, Lung & Blood Institute (NHLBI)

Deficiency of Mitochondrial Disulfide Relay Carrier CHCHD4 Leads to Cardiac Hypertrophy

Innate immune activation is critical for cardiac hypertrophy; however, its upstream regulation is less well understood. Coiled-coil-helix-coiled-coil-helix domain 4 (CHCHD4) is an essential carrier for the import of various mitochondrial proteins including TP53-regulated inhibitor of apoptosis 1 (TRIAP1). CHCHD4 was recently identified as a candidate gene in patients with dilated cardiomyopathy and was separately found to mediate innate immune signaling in skeletal muscle. Therefore, we hypothesized that CHCHD4 may play a role in the development of cardiac hypertrophy by regulating innate immunity.

Genetically modified C57BL/6 mice overexpressing CHCHD4 (CHCHD4 Tg) or haploinsufficient in CHCHD4 (CHCHD4+/-) were utilized. Mice were injected either with low dose (2 mg/kg) or high dose (30 mg/kg) isoproterenol (ISO) daily for up to 3 wks to induce hypertrophy.

CHCHD4+/- mice spontaneously developed cardiac hypertrophy by 28 weeks ($p<0.001$) and had reduced ejection fraction (EF) by 1 year ($p<0.001$) when compared with wild-type or CHCHD4 Tg mice. In a low dose ISO experiment, CHCHD4+/- mice had reduced EF at 2 weeks compared to wild-type or CHCHD4 Tg mice ($p<0.001$). In a high dose ISO treatment, wild-type mice developed cardiac hypertrophy by 1 week and impaired EF by 3 weeks, while CHCHD4 Tg mice remained normal. ISO treatment caused reduction of CHCHD4 levels in both the 24-hour and 1-week states. This reduction was associated with decreased TRIAP1 and activation of the cGAS-STING-NFkB pathway in wild-type, but not CHCHD4 Tg mice. Further, plasma mitochondrial DNA (mtDNA) was 2.3 times higher ($p=0.011$) in wild-type mice treated with high dose ISO for 1 week compared to wild-type control while that of CHCHD4 Tg mice was not significantly changed by ISO.

Our findings suggest that CHCHD4 may be a key upstream regulator of innate immune activation mediating cardiac hypertrophy and that cell-free mtDNA could be a potential biomarker of pathogenesis.

PUBLICATIONS

- Ma J, Wang P, Zhuang J, Son AY, **Karius AK**, Syed AM, Nishi M, Wu Z, Mori MP, Kim Y, Hwang PM. CHCHD4-TRIAP1 regulation of innate immune signaling mediates skeletal muscle adaptation to exercise. *Cell Rep*. 2024 Jan;43(1):113626. PMID: 38157298.
- **Karius AK**, Son AY, Syed AM, Ma J, Mori MP, Nishi M, Springer DA, Wang P, Hwang PM. Mitochondrial disulfide relay carrier CHCHD4 signaling mediates cardiac hypertrophy and heart failure. *J Biol Chem* [Under review]

ABSTRACTS

- **Karius AK**, Ma J, Son AY, Syed AM, Wang P, Hwang PM. Deficiency of mitochondrial disulfide relay carrier CHCHD4 leads to cardiac hypertrophy. American Heart Association Basic Cardiovascular Sciences. Chicago, Il; July 22-25, 2024. [Poster]

AMIR M. KASKAS
Louisiana State University Health Shreveport School of Medicine

MENTOR

Clint T. Allen, M.D., Chief
Head and Neck Section, Surgical Oncology Program, Center for Cancer Research, National Cancer Institute (NCI)

Complete Tumor Resection Reverses Neutrophilia-associated Suppression of Systemic Anti-Tumor Immunity

Neoadjuvant immune checkpoint blockade for head and neck squamous cell carcinoma (HNSCC) is yielding promising results. Neutrophilic cells that infiltrate HNSCC are immunosuppressive, and their increased frequency associates with a lack of pathologic response to neoadjuvant immunotherapy. Although increased peripheral neutrophilia also associates with lack of response to immune checkpoint blockade therapy in the relapsed setting, the contribution of peripheral neutrophils to systemic anti-tumor immunity is poorly understood. Here, we investigated whether the peripheral neutrophilia that occurs with tumor progression in immunocompetent mice contributes to systemic immunosuppression, and if complete primary tumor surgical resection could reverse neutrophil-induced systemic anti-tumor immune suppression.

A syngeneic murine oral cancer model was used to study the role of neutrophils in systemic anti-tumor immunity in tumor-bearing and tumor-resected mice. Proteomic and functional immune assays studying plasma cytokine concentration, peripheral immune frequencies, and systemic anti-tumor immunity with and without complete primary tumor resection were used. We observed that Ly6G+ neutrophils accumulated in the periphery of mice as primary tumors progressed, and that this accumulation associated with plasma G-CSF concentration – a cytokine critical for mediating myelopoiesis. These circulating neutrophils were functionally immunosuppressive in ex vivo T cell suppression assays. Complete resection of the primary tumor reversed peripheral G-CSF elevation and neutrophilia and resulted in enhanced systemic anti-tumor immunity. The observed enhancements of systemic anti-tumor immunity seen after tumor resection were reproduced by selectively depleting neutrophils in the periphery of tumor-bearing mice, validating the ability of peripheral neutrophils to mediate suppression of systemic anti-tumor immunity.

These data indicate that surgical resection itself may allow a more immune permissive periphery and directly improve a HNSCC patient's anti-tumor immunity following neoadjuvant immunotherapy. Our study provides critical context for the role of immunosuppressive neutrophils in the periphery and provides additional support for the continued study of neoadjuvant immunotherapy, specifically for patients with newly diagnosed HNSCC unrelated to HPV.

PUBLICATIONS

- **Kaskas A**, Clavijo P, Friedman J, Craveiro M, Allen CT. Complete tumor resection reverses neutrophilia-associated suppression of systemic anti-tumor immunity. *Oral Oncol*. 2024 Mar;150:apers. PMID: 38280289**.**

ABSTRACTS

- **Kaskas A**, Clavijo P, Friedman J, Craveiro M, Allen CT. Complete tumor resection reverses neutrophilia-associated suppression of systemic anti-tumor immunity. American Head & Neck Society at Combined Otolaryngology Spring Meetings, Chicago, IL; May 15-18, 2024. [Poster]

- Luff M, Craveiro M, Dar MS, McKinnon K, **Kaskas A**, Allen CT, Saloura V. Epigenetic landscape of CD8+ T cell exhaustion and tissue residency in HPV-negative head and neck squamous cell carcinoma. American Association of Cancer Research Annual Meeting, San Diego, CA; Apr 5-10, 2024. [Poster]

PROFESSIONAL MEETINGS

- Combined Otolaryngology Spring Meetings, Chicago, IL; May 15-18, 2024.

AWARDS

- Best Poster, Cancer Biology Section of American Head & Neck Society at Combined Otolaryngology Spring Meetings. May 16, 2024.

KATHY P. LI
Medical College of Georgia at Augusta University

MENTOR

Rosandra N. Kaplan, M.D., Head
Tumor Microenvironment Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Combinatorial Cellular Therapy in Pediatric Solid Tumors with Natural Killer Cells and Genetically Engineered Myeloid Cells

Early studies with natural killer (NK) cells have demonstrated their ability to infiltrate tumors and be tumoricidal in the setting of low/no tumor MHC expression. However, these effects are limited by the immunosuppressive tumor microenvironment (TME), where TGF-β and downstream SMAD3 signaling in NK cells leads to decreased cytokine production, downregulation of activating cell surface receptors, and attenuated cytotoxic function. Exposure to TGF-β during ex vivo expansion generates NK cells with increased TGF-β resistance, dubbed TGF-β imprinted NK cells. These cells exhibit enhanced in vitro cytokine production and cytotoxicity in the presence of TGF-β. However, their in vivo trafficking, modulation of the TME, and therapeutic efficacy remain understudied.

Our lab previously showed that when given to tumor-bearing mice, myeloid cells modified to produce IL-12 (IL-12 Genetically Engineered Myeloid cells, IL-12 GEMys) are effective at homing to tumor, pre-metastatic, and metastatic sites where they increase NK cell presence and activation and may enhance NK cell effectiveness.

To study this combination, we utilized the xCELLigence real-time cell analysis system. The human rhabdomyosarcoma cell line RH-30 was evaluated for cell death after 48 hours of co-culture with healthy donor (WT NK) or TGF-β imprinted NK cells alone and in combination with IL-12 GEMys. TGF-β imprinted NK cells were significantly more effective at tumor cell killing compared to WT NK cells alone ($p < 0.0001$), but IL-12 GEMy treatment was able to significantly enhance tumor killing by WT NK cells vs control ($p < 0.01$). Both WT and TGF-β imprinted NK cells co-cultured with IL-12 GEMys also had > 5-fold increase in IFNγ production ($p < 0.001$).

These initial experiments provide insight into the promising effectiveness of NK-myeloid cell combination therapies in the treatment of pediatric sarcomas. Our preliminary results provide a rationale to continue studying the in vivo efficacy and mechanism of combination therapy with TGF-β imprinted NK cells and IL-12 GEMys in the treatment of tumor-bearing NSG mice.

PUBLICATIONS

- Aber ER, Contreras CF, Sikder MOF, **Li KP**, Forbes GE, Jackett K, Ju W, Browne A, Olgun G, Del Rivero J, Hernandez J, Hoang CD, Nilubol N, Flowers C, Glod JW, Widemann BC, Wedekind MF, Roper N, Reilly KM, Ahmed S, Bernstein D, Thomas BJ, Kaczanowska S, Gopalan V, Hannenhalli S, Kaplan RN. Transcriptional profiling of human metastasis-free tissues reveals a cancer-conditioned microenvironment program underlying metastasis. *Cell*. [Under review]
- Segal J, Cronk J, **Li KP**, Jackett K, Ball B, Osorno AM, Montalvan ESA, Forbes G, Browne A, Kaplan RN. Tumor microenvironment establishment based on developmental pathways. In *Developmental Oncology: Principles and Therapy of Cancers of Children and Young Adults*. Eds. Kentsis A, Gutierrez A. Chapter 14 [Under review]

ABSTRACTS

- Aber ER, Contreras CF, Sikder MO, **Li KP**, Forbes GE, Gopalan V, Hannenhalli S, Kaplan RN. Transcriptional profiling uncovers a unified program underlying the human metastatic and adjacent microenvironments. American Association for Clinical Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024. [Poster]
- Contreras CF, Kaczanowska S, **Li KP**, Hartley F, Van Ess A, Buffa F, Kaplan RN. Identification of drivers of monocyte-mediated trogocytosis of tumor cells. American Association of Immunologists Annual Meeting, Chicago, IL; May 3-7, 2024. [Poster]
- Contreras CF, Aber ER, Sikder M, **Li KP**, Jackett K, Forbes G, Browne A, Kaczanowska S, Gopalan V, Hannenhalli S, Kaplan RN. Going the distance: Uncovering a global myeloid reprogramming in human metastatic and adjacent microenvironments. Myeloid Targeting Strategies for Cancer Treatment, Keystone Symposia, Killarney, IE; May 6-9, 2024. [Podium]
- **Li KP**, Cronk J, Kaczanowska S, Kaplan R. Combinatorial cellular therapy in pediatric solid tumors with Natural Killer (NK) and genetically engineered myeloid cells. American Society of Clinical Oncology Annual Meeting, Chicago, IL; May 31-June 4, 2024. [Poster] Also presented at 8th Annual Children's Cancer Foundation Research Symposium, Greenbelt, MD; June 5, 2024. [Poster]

PROFESSIONAL MEETINGS

- American Association for Cancer Research 2024 Annual Meeting, San Diego, CA; April 5-10, 2024.
- American Society of Clinical Oncology 2024 Annual Meeting, Chicago, IL; May 31–June 4, 2024.
- 8th Annual Children's Cancer Foundation Research Symposium, Greenbelt, MD; June 5, 2024.

AWARDS

- Certificate of Meritorious Scientific Poster, Children's Cancer Foundation Research Symposium, 2024

MARIE K. LUFF
David Geffen School of Medicine at UCLA

MENTORS

Vassiliki Saloura, M.D., Ph.D., Stadtman Investigator
Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute (NCI)

Clint Allen, M.D., Chief
Head and Neck Section, Surgical Oncology Program, Center for Cancer Research, National Cancer Institute (NCI)

Epigenetic Landscape of CD8+ T Cell Exhaustion and Tissue Residency in HPV-negative Head and Neck Squamous Cell Carcinoma

Human Papilloma Virus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) overall survival rates remain low (25-40% at 5 years) despite advances in treatments. CD8+ T cell differentiation into activated/cytotoxic, exhausted (TEX) and tissue-resident memory (TRM) phenotypes is a major determinant of successful cancer immunotherapy, which relies on the ability of CD8+ T cells to detect and eliminate cancer cells. Understanding the epigenetic profile of each of these states can help determine the major epigenetic regulators that lead to exhaustion and tissue residency, paving the way for improved T cell-based immunotherapies.

An in vitro human CD8+ T cell stimulation assay using healthy donor cells was utilized to generate different T-cell phenotypes. Naïve T cells underwent CD3/CD28, TCR-independent stimulation for 9 days to promote an activated/cytotoxic (3 days) and a TEX phenotype (9 days). TGF-β exposure (days 0-9) occurred to induce a TRM phenotype. Flow cytometry with 15 cell-surface markers aimed to validate the induction of T cell states. Genome-wide mapping for activating (H3K4me1, H3K4me3, H3K27Ac) and repressive (H3K9me3, H3K27me3, H4K20me3) histone marks utilizing CUT&Tag was conducted, together with RNA-seq. CUT&Tag and RNA-seq will be utilized to characterize the epigenetic profiles of CD8+ T cells from HPV-negative HNSCC tumors (n=5). Findings will be correlated with results from our in vitro CD8+ T cell states.

Flow cytometry supported the successful induction of activated, TEX and TRM phenotypes in three healthy human donors. Feasibility of conducting genome-wide mapping for activating and repressive histone marks using CUT&Tag on unstimulated CD8+ T cells was also confirmed. CUT&Tag-generated DNA libraries from T cells derived from three healthy human donors and stimulated via our in vitro protocol are being sequenced and analyzed, along with correlations with RNA-seq data.

PUBLICATIONS

- Tsai DE, Lovanov A, Abdelmaksoud A, Akhtar J, Dar MS, **Luff MK**, McKinnon K, Kim S, Robbins Y, Huynh A, Bernard B, Sinkoe A, Murali M, Luo X, Allen CT, Saloura V. Smyd3-mediated immuno-modulation in HPV-negative head and neck squamous cell carcinoma mouse models. *Cell Reports*. [Under review]
- Saeed A*, Murali M*, Kim S, Cheng H, Moshiri A, Akhtar J, Tsai DE, **Luff MK**, Burkitt K, Baktiar K, Saloura V. SMYD3 drives cell cycle and epithelial-mesenchymal transition pathways in HPV-negative head and neck squamous cell carcinoma. M*olecular Cancer Research*. [Under review] *Equal contribution

ABSTRACTS

- **Luff MK**, Craveiro M, Dar MS, McKinnon K, Kim, S, Kaskas A, Allen CT, Saloura V. Epigenetic landscape of CD8+ T cell exhaustion and tissue residency in HPV-negative head and neck squamous cell carcinoma. American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024. [Poster]

PROFESSIONAL MEETINGS

- American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024.

SAHIT N. MENON
University of California, San Diego School of Medicine

MENTOR

Sarah H. Lisanby, M.D., Director
Noninvasive Neuromodulation Unit, Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health (NIMH)

Discovering Domain-Specific Transcranial Magnetic Stimulation Targets for Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in two primary domains, social communication and restricted, repetitive patterns of behavior, as outlined in the DSM-5. The pathological findings in autism may relate to dysfunctional brain networks, which may provide putative targets for novel interventions such as repetitive transcranial magnetic stimulation (rTMS). rTMS is a form of non-invasive brain stimulation that has been shown to induce long-term changes in distributed networks, resulting in therapeutic effects across neuropsychiatric disorders, including depression. However, few studies have evaluated the efficacy of rTMS in ASD.

Using the publicly available imaging datasets (e.g., ABIDE II), we will investigate the relationship between ASD behavioral domains (defined by Social Responsiveness Scale-II (SRS-II) subscale scores) and network connectivity with an aim to identify rTMS targets. Data will be included from participants with an ASD diagnosis who are age 5-40 and have standardized full-scale IQ and SRS-II scores. We will utilize imaging data, including resting-state fMRI (rs-fMRI) and diffusion weighted imaging (DWI).

Using rs-fMRI, a connectivity matrix will be created for each individual. Ridge regression analysis will be conducted to map ASD domains to the networks. We will utilize network controllability to identify the nodes within the identified networks that may be responsive to modulation. We will then evaluate the identified nodes for TMS accessibility. Once putative networks have been identified, we will validate the identified targets in a holdout subset of the data. The overarching goal in applying rTMS as a therapeutic intervention is to modulate the functional state of specific brain networks associated with domain-specific clinical symptoms in ASD.

PUBLICATIONS

- **Menon SN**, Torrico T, Luber BM, Gindoff B, Cullins L, Regenold W, Lisanby SH. Educating the next generation of psychiatrists in the use of clinical neuromodulation therapies: what should all psychiatry residents know? *Front Psych* 2024. May 15;15:1397102. PMID: 38812486.

ABSTRACTS

- **Menon SN**, Francis SM, Beynel L, Robins PL, Deng ZD, Thurm A, White T, Pereira F, Taylor P, Oberman LM, Lisanby SH. Discovering domain-specific TMS targets for ASD. National Institute of Mental Health (NIMH) Julius Axelrod Symposium. Apr. 5, 2024. [Podium]

PROFESSIONAL MEETINGS

- American Academy of Child and Adolescent Psychiatry Annual Meeting, New York, NY; Oct. 25-27, 2023.

AWARDS

- Lightning Talk, 2024 NIMH Julius Axelrod Symposium

MONICA S. NAIR
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

MENTOR

Nirali Shah, M.D., Lasker Clinical Research Scholar; Head
Hematologic Malignancies Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Predicting Hematotoxicty After CAR T-Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)

Predicting CAR T-cell therapy associated toxicities is critical to applying risk mitigation strategies and improving outcomes. The CAR-HEMATOTOX (HT) model has been validated to predict hematotoxicity in adults with large B-cell lymphoma. Its utility in patients with relapsed/refractory B-ALL is unknown.
HT scores were retrospectively determined for patients with B-ALL treated on a phase I CAR T-cell trial targeting CD19 and/or CD22. Scores were calculated based on the original HT methods using platelet, absolute neutrophil count (ANC), hemoglobin, C-reactive protein, and ferritin values before lymphodepletion. The primary outcome was assessment of severe prolonged neutropenia (ANC <500/µL for >14 days within day +30 post-infusion) stratified by HT score. The secondary objective was to modify HT to improve its performance in B-ALL.

Across 156 B-ALL patients, median age was 16 years (range 4-39) and 87% (n=94) were high risk (HR) by HT score; substantially higher than the 48.9% in the published lymphoma cohort. Due to the high number of HT-HR patients limiting the utility of HT in B-ALL, we created an ALL-Hematotox (ALL-HT) model which incorporates the same variables as HT, except replaces ferritin with baseline bone marrow (BM) disease. With the ALL-HT model, 46% (n=72) of patients were assigned to the HR group, representing a more balanced risk-stratification. In an ROC curve, ALL-HT scores had a significant association with severe prolonged neutropenia (AUC=0.84, p<0.0001). Notably, there was a shorter 2-year overall survival (OS) and shorter 2-year event free survival (EFS) in the ALL-HT HR group compared to the low risk (LR) group (log-rank p=0.0003, p=0.002; respectively). These findings were confirmed in two external validation cohorts.

The ALL-HT model shows promise in predicting severe prolonged neutropenia in B-ALL, as well as having associations with OS and EFS. Future efforts will be directed towards understanding ALL-HT score and associations with infection risk and length of hospitalization.

PUBLICATIONS

- **Nair MS**, Silbert SK, Rejeski K, Lamble A, Valtis Y, Yates B, Wilson K, Morales Arana A, Annesley C, Gardner RA, Park JH, Subklewe M, Shah NN. Predicting hematotoxicty after CAR T-cell therapy in B-cell acute lymphoblastic leukemia: development of ALL-Hematotox (ALL-HT). [In preparation]

ABSTRACTS

- **Nair M**, Gertz M, Yates B, Ruppin E, Shah NN, Silbert S. Utilization of machine learning to develop a pediatric B-cell acute lymphoblastic leukemia (B-ALL) CAR T-cell comorbidity index (CAR-CI). Pediatric Transplant and Cellular Therapy Consortium's Annual Education Meeting Seattle, WA; Apr. 2, 2024. [Poster]
- **Nair M**, Silbert S, Arana AM, Yates B, Shah NN. Evaluating the prognostic utility of CAR-Hematotox score in predicting CAR T-cell toxicities in children and young adults with R/R B-cell acute lymphoblastic leukemia (B-ALL). Tandem Transplantation and Cellular Therapy Annual Meeting, San Antonio, TX; Feb. 21-24, 2024. [Poster]

PROFESSIONAL MEETINGS

- Tandem Transplantation and Cellular Therapy Annual Meeting, San Antonio, TX; Feb. 21-24, 2024.
- Pediatric Transplant and Cellular Therapy Consortium's Annual Education Meeting, Seattle, WA; Apr. 2, 2024.
- American Society of Pediatric Hematology/Oncology Conference, Seattle, WA; Apr. 3-6, 2024.
- Children's Cancer Foundation Inc. 8th Annual Research Symposium, Greenbelt, MD; Jun. 5, 2024.

AWARDS

- Young Investigator Award, Pediatric Transplant and Cellular Therapy Consortium, 2024
- Outstanding Poster Award, Pediatric Transplant and Cellular Therapy Consortium, 2024

SAMANTHA M. NISHIMURA
Drexel University College of Medicine

MENTOR

Ellen Sidransky, M.D., Chief
Molecular Neurogenetics Section, National Human Genome Research Institute (NHGRI)

Fifteen-year Evaluation of Non-motor Symptoms in a Cohort with Homozygous and Heterozygous GBA1 Variants

GBA1 variants are the most common genetic risk factor for Parkinson disease (PD), yet most patients with a GBA1 variant never develop PD, highlighting the importance of discovering clinical parameters that might help identify individuals on a PD trajectory. GBA1-PD is associated with earlier age at onset, more cognitive dysfunction, and increased frequency and progression of non-motor symptoms. Therefore, this study analyzed neuropsychological data from 155 patients over 15 years, including patients with Gaucher disease (GD), patients carrying a heterozygous GBA1 variant (GC), patients with both GD and PD (GD/PD), and carriers with PD (GC/PD). Our efforts focused on results of the Non-Motor Symptoms Questionnaire (NMSQ); Beck Depression Inventory (BDI); Fatigue Severity Scale (FSS); Epworth Sleepiness Scale (ESS); State-Trait Anxiety Index (STAI); and full-scale IQ (FSIQ), performance IQ (PIQ), and verbal IQ (VIQ) tests.

At baseline, patients with GD/PD demonstrated significantly higher total non-motor symptoms on the NMSQ than GC/PD, GD, and GC groups. This pattern was recapitulated in the BDI and ESS, while on the FSS and STAI, the GD/PD group showed significantly higher symptoms only compared to GC and GD. The VIQ, PIQ, and FSIQ demonstrated no significant difference among the groups at baseline. A longitudinal subanalysis of 45 genetically at-risk GD patients and carriers with a family history of PD showed no progression of prodromal PD symptoms, with no significant differences on the NMSQ, BDI, FSS, and STAI between first and last visit.

This is the largest and longest evaluation of prodromal features in a GBA1 variant-carrying cohort. While patients with GD/PD reported significantly greater total non-motor symptoms at baseline on the NMSQ, some scales may not be sensitive enough to assess differences among the groups, emphasizing the need for more in-depth neurophenotyping incorporating tools such as sleep studies, cardiac PET scans, and protein aggregation studies.

PUBLICATIONS

- Ryan E*, **Nishimura S***, Lopez G, Tayebi N, Sidransky E. Phenotypic consequences of GBA1 pathological variant R463C (p.R502C). Am J Med Genet A. 2024 Apr:e63630. PMID: 38647370 *Equal contribution

ABSTRACTS

- **Nishimura S**, Torres AM, Lichtenberg J, Tayebi N, Ryan E, Sidransky E, Lopez G. 15-year evaluation of non-motor symptoms in a cohort with homozygous and heterozygous GBA1 mutations. WORLD Symposium Annual Meeting, San Diego, CA; Feb. 4-9, 2024. [Poster]
- Sidransky E, Ryan E, **Nishimura S**, Tayebi N, Lichtenberg J, Lopez G. 15-year evaluation for prodromal Parkinson features in an at-risk cohort with Gaucher disease. First International GBA1 Meeting 2024.

PROFESSIONAL MEETINGS

- WORLD Symposium Annual Meeting, San Diego, CA; Feb. 4-9, 2024.

SADÉ B. OREJOBI
Duke University School of Medicine

MENTORS

Andrew J. Mannes, M.D., Chief
Department of Perioperative Medicine, NIH Clinical Center (CC)

Miroslav Bačkonja, M.D., Clinical Director
Pain Research Center, National Center for Complementary and Integrative Medicine (NCCIH)

Gait Analysis for the Quantification of Neuropathic Foot Pain: A Step in the Right Direction

Evaluation of pain often relies on subjective patient reported outcomes (PROs) such as the Brief Pain Inventory. Supplementing such measures with objective endpoints can provide a deeper assessment of acute and chronic pain. In the present study, we evaluated quantitative gait analysis using a podiatric walkway that records pressure measurements and spatiotemporal parameters during a full gait cycle. We hypothesized that patients with neuropathic foot pain due to Morton neuroma (MN) would have abnormal gait and altered pressure loading from the affected foot detectable using these methods.

We recruited healthy volunteers (HV) and patients with symptomatic MN pain (MN) from the local community to form a normative dataset and an investigational pain cohort, respectively. Gait measurements from 39 HV and 6 MN revealed stability of gait parameters among HV and potential differences in MN gait patterns. The variance of metatarsal peak pressure (MPP) across all steps stabilized at 11 steps (CV=13.54%) for HV and 15 steps (CV=12.76%) for MN, indicating reliability of the measurement. We observed an overall trend of lower MPP in MN (524.61 +45.32 vs. 582.16 +15.62 kPa), although more patients are needed.

While we did not detect significant group-level differences between HV and MN, HV data demonstrate stable phenotyping of normative gait. Further, several metrics such as contact area (CA) and MPP showed promising trends. One patient entering the study with a pain rating of 5 (out of 10) showed up to 76% reduction in CA of the affected foot relative to her healthy foot. This behavior was not mirrored in other MN patients, indicating individual differences in pain compensation that may diverge from larger cohort patterns as the study continues. These observations support application of gait analysis as a surrogate measure of pain, which may enhance objective endpoints in future clinical evaluations of functional outcomes in pain management.

ABSTRACTS

- **Orejobi S**, Sapio M, Iadarola MJ, Backonja M, Mannes MJ. Gait analysis for the quantification of neuropathic foot pain. Association of University Anesthesiologists Annual Meeting, St. Louis, MO; Mar. 22-24, 2024. [Poster presentation]. Also presented at US Association for the Study of Pain Annual Scientific Meeting, Seattle, WA; Apr. 14-17, 2024. [Poster]

PROFESSIONAL MEETINGS

- Society for Neuroscience Annual Meeting, Washington, D.C.; Nov. 11-15, 2023.
- Association of University Anesthesiologists Annual Meeting, St. Louis, MO; Mar. 22-24, 2024.
- Student National Medical Association, Annual Medical Education Conference, New Orleans, LA; Mar. 27-31, 2024.
- US Association for the Study of Pain Annual Scientific Meeting, Seattle, WA; Apr. 14-17, 2024.

SARAH A. PHILLIPS
Eastern Virginia Medical School

MENTOR

Nicolas Wentzensen, M.D., Ph.D.

Deputy Director
Clinical Genetics Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute (NCI)

Head
Clinical Epidemiology Unit, NCI

Association of a Polygenic Risk Score with Risk of Abnormal Ultrasound Findings and Ovarian Cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Polygenic risk scores (PRS) combining certain ovarian cancer susceptibility loci have shown limited performance at predicting ovarian cancer risk. However, the utilization of PRS with ovarian cancer screening tests, such as transvaginal ultrasound (TVU), warrants further evaluation. This study investigated the association between a polygenic risk score and ovarian cancer risk and abnormal TVU screening in a large-scale randomized controlled ovarian cancer screening trial.

A PRS was constructed using weighted sums of risk alleles of ovarian cancer single nucleotide polymorphisms (SNPs) identified in previous genome-wide association studies. The association of the PRS with abnormal TVU screening results and ovarian cancer outcomes was evaluated in female participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Complete genotyping information, TVU results, and ovarian cancer outcomes were available for 15,722 females (mean age 62.2 + 5.3 years) with European ancestry. Polygenic risk scores were categorized as quartiles and odds ratios (OR) were calculated to assess risk of ovarian cancer or abnormal TVU result using the lowest PRS quartile as a reference category.

TVU screening results were abnormal for 732 (732/15,722, 4.66%) participants and normal for 14,990 (14,990/15,722, 95.3%) participants at trial baseline. PRS within the fourth quartile demonstrated increased risk of ovarian cancer with reference to the lowest quartile (OR 2.29, 95% CI: 1.31-3.99). Similarly, women in the highest quartile of the PRS had increased odds of an abnormal TVU screening result (OR 1.33, 95% CI: 1.08-1.64) compared to women in the lowest PRS quartile.

A polygenic risk score including SNPs previously shown to be associated with ovarian cancer risk showed an association with increased ovarian cancer risk in the PLCO trial. Furthermore, the PRS was also associated with abnormal ultrasound results. Our findings support further evaluation of polygenic risk scores and transvaginal ultrasound for ovarian cancer risk stratification and screening approaches.

ABSTRACTS

- **Phillips SA**, Landy R, Bordelon C, Machiela M, Wentzensen N. Association of genome-wide significant ovarian cancer susceptibility loci with abnormal ultrasound findings in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Society for Epidemiologic Research Mid-Year Meeting. Virtual; Mar. 4-8, 2024. [Podium]
- **Phillips SA**, Arbyn M, Clarke MA, Wentzensen N. Accuracy of HPV self-collection compared to HPV provider collection and cytology: a meta-analysis. American Society for Colposcopy and Cervical Pathology Annual Meeting, New Orleans, LA; May 2-4, 2024. [Podium]

- **Phillips SA**, Landy R, Bordelon C, Machiela M, Wentzensen N. Association of a polygenic risk score with risk of abnormal ultrasound findings and ovarian cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. American Society of Clinical Oncology Annual Meeting, Chicago, IL; May 31-June 4, 2024. [Poster]

PROFESSIONAL MEETINGS

- Society for Epidemiologic Research Mid-Year Meeting, Virtual; Mar. 4-8, 2024.
- American Society for Colposcopy and Cervical Pathology Annual Meeting, New Orleans, LA; May 2-4, 2024.
- American Society of Clinical Oncology Annual Meeting, Chicago, IL; May 31-June 4, 2024.

AWARDS

- Finalist, Elevator Pitch Competition, NIH Graduate Student Research Symposium, 2024

MINALI PRASAD
Boston University Chobanian & Avedisian School of Medicine

MENTORS

Emily Y. Chew, M.D.

Director
Division of Epidemiology and Clinical Applications, National Eye Institute (NEI)

Chief
Clinical Trials Branch, NEI

Catherine Cukras, M.D., Ph.D., Lasker Clinical Research Scholar
Unit on Clinical Investigation of Retinal Disease, National Eye Institute (NEI)

Longitudinal Study of Ocular Manifestations of von Hippel-Lindau Disease: A 30-Year Follow-Up

Von Hippel-Lindau (VHL) disease is a rare genetic multi-system tumor syndrome presenting with peripheral or optic nerve retinal hemangioblastomas (RH) and other tumors. We characterized the progression of ocular VHL disease.

This was a longitudinal cohort study of 508 eyes (288 participants) with VHL disease and at least 2 years of ophthalmic follow up. We graded baseline and follow-up color fundus photographs for development of ocular VHL, defined as the presence of new RHs or treatment scars among participants with no pre-existing disease. Progression in eyes with existing ocular VHL was defined as RHs or treatment scars in a new location, increase in extent of retinal involvement, or end-stage disease including enucleation or phthisis. Generalized linear model analysis of variance was used to compare change in visual acuity score between study groups.

Mean follow-up period was 12.2 ± 6.8 years (2.1-30.9 years). Among eyes with no pre-existing disease (n=271), those with new optic nerve RH (n=5, -18.60 ± 22.91 letters) had a significantly greater decrease in VA ($p<0.001$) compared to eyes that remained stable (n=191, -2.88 ± 8.56). This was not seen among eyes with new peripheral RH (n=71, -5.03 ± 14.18, $p=0.14$) or new peripheral and optic nerve RH (n=4, -1.25 ± 7.00, $p=0.71$). Among eyes with pre-existing disease (n=237), eyes developing end-stage disease (n=9, -34.00 ± 28.81, $p<0.001$) or progressing from peripheral to both optic nerve and peripheral RH (n=16, -28.63 ± 27.81, $p<0.001$) had a significantly greater decrease in VA compared to stable eyes (n=216, -6.56 ± 19.17). Eyes increasing in extent of retinal involvement (n=32, -18.19 ± 21.03) had a significantly greater decrease in VA ($p=0.004$) compared to stable eyes (n=205, -6.83 ± 20.21).

Progression of ocular VHL disease is associated with adverse visual outcomes over a 30-year follow up period. Given that we cannot predict the development or progression of ocular VHL disease, all patients with systemic VHL disease should undergo routine eye exams for early disease detection and management.

ABSTRACTS

- **Prasad M**, Duic C, Cukras CA, Chew EY. Association of patient-reported functional deficits with choriocapillaris flow deficits in age-related macular degeneration. Vit-Buckle Society Annual Meeting, Miami, FL; April 4-6, 2024. [Poster]
- **Prasad M**, Duic C, Cukras CA, Chew EY. Association of patient-reported functional deficits with choriocapillaris flow deficits in age-related macular degeneration. Vit-Buckle Society Annual Meeting, Miami, FL; April 4-6, 2024. [Poster]

- Arunachalam T, Jeffrey B, Abraham M, Orndahl C, Menezes S, Mukherjee S, Duic C, **Prasad M**, Siddig F, Bellur S, Thavikulwat A, Cukras C, Wong W, Chew EY, Keenan TDL. Effect of oral minocycline on geographic atrophy progression: longitudinal microperimetry results of a phase II trial. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 5-9, 2024. [Poster]
- Vitale S, Le J, Agron E, Arunachalam T, **Prasad M**, Chew EY. Changes in health-related quality of life before and after development of geographic atrophy in AREDS participants. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 5-9, 2024. [Poster]
- Siddig F, Vitale S, Agron E, **Prasad M**, Arunachalam T, Duic C, Keenan TDL, Chew EY. Progression of diabetic retinopathy and dietary fat intake in the ACCORD study. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 5-9, 2024. [Poster]
- **Prasad M**, Agron E, Siddig F, Arunachalam T, Duic C, Dimopoulos, I, Lu A, Chew EY. Diabetic retinopathy progression and health-related quality of life in the ACCORD trial. Association for Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 5-9, 2024. [Poster]

PROFESSIONAL MEETINGS

- American Academy of Ophthalmology Annual Meeting, San Francisco, CA; Nov. 3-6, 2023.
- Vit-Buckle Society Annual Meeting, Miami, FL; April 4-6, 2024.
- Association in Research in Vision and Ophthalmology Annual Meeting, Seattle, WA; May 5-9, 2024.

AWARDS

- Academic Grant, Vit-Buckle Society, 2024
- Retina Research Foundation/Joseph M. and Eula C. Lawrence Travel Grant, Association for Research in Vision and Ophthalmology, 2024

SHIVANI RAMOLIA
Rutgers Robert Wood Johnson Medical School

MENTOR

Nyall R. London, M.D., Ph.D., Investigator
Surgical Oncology Program, Center for Cancer Research, National Cancer Institute (NCI)

Characterization of Cancer Stem Cells in Olfactory Neuroblastoma Identifies Increased PD-L1 Expression

Olfactory neuroblastoma (ONB) is a rare malignant neoplasm arising from the olfactory neuroepithelium. Patients with recurrent or metastatic disease have a poor prognosis and limited treatment options. Cancer stem cells (CSCs) are self-renewing oncogenic cells that drive tumor progression, proliferation, and recurrence. The objective of this study was to characterize CSC density and PDL1 expression in ONB using multispectral immunofluorescence.

A tissue microarray (TMA) including 47 ONB samples was obtained from our tertiary care hospital. A cancer stem cell panel, including fluorescently-labeled antibodies to CD15, CD24, ALDH1A1, PDL1, synaptophysin and DAPI, was validated in ONB tissue. Characterization of the TMA slides was manually performed using HALO image analysis to objectively identify CSCs (CD15+ CD24+ ALDH1A1+ cells).

Twenty-seven samples were included in the final analysis. Seven out of 27 patients had high Hyams grade tumors (III/IV) and 22 out of 27 patients had high Kadish stage tumors (C/D). The median CSC density was 1.13 cells per mm2 of tumor parenchyma. There was no difference in quantities of CSCs between low and high Hyams grade tumors ($p=0.08$) or low and high Kadish stage tumors ($p=0.86$). However, there was a significant difference in the median number of PDL1+ CSCs versus PDL1- CSCs in all tumors (0.97 vs 0.39 cells/mm3, respectively, $p<0.001$).

This study evaluated the presence of CSCs in ONB and demonstrated that while CSCs are present in ONB, they are rare. A significant fraction of the CSCs are PDL1+, revealing a potential immunotherapy strategy for ONB by targeting this particular cell population through PD-1/PD-L1 immune checkpoint blockade.

PUBLICATIONS

- **Ramolia S**, Larkin R, Robbins Y, Lopez DC, Lassoued W, Gulley JL, Gallia GL MD, Allen C, London NR Jr. Characterization of cancer stem cells in olfactory neuroblastoma identifies increased PD-L1 expression. *Int Forum Allergy Rhinol*. [Under review]

ABSTRACTS

- **Ramolia S**, Larkin R, Robbins Y, Lopez DC, Lassoued W, Gulley JL, Gallia GL MD, Allen C, London NR Jr. Characterization of cancer stem cells in olfactory neuroblastoma identifies increased PD-L1 expression. North American Skull Base Society Annual Meeting, Atlanta, GA; Feb. 16-18, 2024. [Podium]

PROFESSIONAL MEETINGS

- North American Skull Base Society Annual Meeting, Atlanta, GA; Feb. 16-18, 2024.

IHIKA RAMPALLI
Baylor College of Medicine

MENTOR

Prashant Chittiboina, M.D., Investigator
Neurosurgery Unit for Pituitary and Inheritable Diseases, Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke (NINDS)

Multiomic Analysis of Spinal Ependymomas Reveals Mechanisms of Tumor Aggressiveness with MYCN Amplification

Grade-3 spinal ependymomas, particularly those harboring MYCN amplification, have dismal prognoses despite optimal treatment regimens. MYCN functions as a transcription factor (TF) to drive the expression of key tumor driver genes. Our aim is to identify mechanisms underlying tumor aggressiveness and treatment resistance in MYCN-amplified ependymomas.

MYCN amplification in spinal ependymomas was identified with custom next generation sequencing panels and bulk methylation analysis. We then conducted paired single-nucleus RNA (snRNA-seq) and chromatin accessibility (snATAC-seq) sequencing of grade-2 (n=2, 1 patient) and grade-3 spinal ependymomas (n=6, 6 patients, 4 MYCN-amplified). Comparator snRNA-seq datasets (grade-2/grade-3; 8/2) were included from a publicly available dataset (GSE163686; all non-MYCN-amplified).Canonical cell classes were identified with a combination of cluster- and cell-based strategies. Downstream analysis was conducted using R 4.3 (Seurat, Signac, clusterProfiler, CellChat), and Python 3.11 (scanpy) packages.

We identified ependymoma tumor cells distinct from canonical immune cell classes with gene expression analysis and confirmed a distinct copy-number-variation pattern in these cells with chromosome 1 and 2p gain, and chromosome 6p and 22q loss. MYCN-amplified tumor cells (compared to non-MYCN-amplified grade2/3 tumor cells) showed increased differential accessibility at genes including VEGFA. Increased MYCN TF activity was confirmed with gene overexpression of downstream targets including NOTCH3, CREB5, PLK1, and VEGFA.Other genes that were highly accessible and overexpressed in MYCN-amplified tumor cells were related to oxidative stress, differentiation, and anti-apoptotic pathways. MYCN-amplified tumor cells modified the tumor microenvironment with increased VISTA signaling between MYCN-amplified tumor cells and tumor-associated macrophages, creating an immunosuppressive environment. We confirmed these effects by observing a higher proportion of M2-like macrophages in MYCN-amplified tumors (29.6% vs 18.2%).

In conclusion, MYCN-amplification in spinal ependymomas upregulates tumor cell proliferation, angiogenesis, and M2-like macrophage recruitment/programming.

ABSTRACTS

- Johns JD, Zalewski C, Allemang N, Laws M, **Rampalli I**, Chittiboina P, Kim HJ, Longitudinal characterization of the impact of cochleovestibular schwannoma on audiovestibular dysfunction in neurofibromatosis-II. American Neurotology Society
- Laws MT, Asuzu DT, Stroica S., **Rampalli I**, Mullaney D., Laraba L., Mandal D., Arhin M, Celano E, Bhatt S., Zhang X, Elkahloun A, Sisay B, Maric D., Johnson K, Abdullaev Z, Ray-Chaudhury A, Aldape K, Shern J, Parkinson D, Chittiboina P. A VEGF+ subpopulation of Schwann cells drives vestibular schwannoma tumorigenesis.American Association of Neurological Surgeons Annual Meeting

- Laws MT, **Rampalli I**, Asuzu DT, Hogan E, Alvarez R, Hayes C, Cortes M, McGlotten R, Tatsi C, Nieman L, Chittiboina P. Optimized strategy for management of Cushing's Disease with cavernous sinus invasion. North American Skull Base Society Annual Meeting
- Allemang LN, Kim HJ, **Rampalli I**, Laws MT, Johns JD, Chisholm J, Christensen J, Bilokon A, Brewer C, Poling GL, Chittiboina P, Zalewski C. Longitudinal hearing phenotype in patients with neurofibromatosis type 2. American Audiology Society
- Bilokon A, Kim HJ, Chittiboina P, Laws M, **Rampalli I**, Johns JD, Chisholm J, Poling GL, Brewer C, Allemang LN, Zalewski C. Investigation of postural stability and cochleovestibular growth rates in patients with neurofibromatosis type 2. American Audiology Society

NITYAM RATHI
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

MENTOR

W. Marston Linehan, M.D., Chief
Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Next Generation Analyses to Inform Precision Management of Renal Tumors in von Hippel-Lindau Syndrome

Von Hippel-Lindau (VHL) is an autosomal dominant hereditary renal cancer syndrome characterized by tumorigenesis in several organs. Studies of sporadic renal cell carcinoma (RCC) suggest that tumor evolution proceeds via clonal genetic alterations that define distinct evolutionary subtypes. However, the weightage of personalized factors, such as germline variation, environmental exposures, and cell and tissue contexts remains unclear. This uncertainty arises, as sporadic RCC has a singular clonal origin, whereas hereditary RCC has the advantage of having defined germline genetic VHL alterations.

VHL-associated renal tumors from 132 patients with VHL who were followed at the NIH underwent comprehensive genomic analysis to elucidate tumor evolution. Targeted panel sequencing evaluated somatic variants in RCC driver genes, somatic copy number alterations, and overall ploidy. These analyses show distinct mutational profiles of known RCC driver genes by lesion type. Hierarchical clustering revealed grouping of lesions in a tissue-specific manner. Thus, despite a constant founder mutation (VHL loss), the tissue of cancer origin is a powerful constraint on subsequent, stochastic evolution. Comprehensive genomic analyses further led to the characterization of genomically clonal renal tumors that recur over time and space. These tumors are enriched in loss of chromosome 9p and 14q, have a significantly faster growth rate, and a greater propensity to metastasize. Together, these data support the utility of genomic and radiographic analyses to inform personalized management of RCC in VHL.

PUBLICATIONS

- Gelikman DG, Mena E, Lindenberg L, Azar WS, **Rathi N**, Yilmaz EC, Harmon SA, Schuppe KC, Hsueh JY, Huth H, Wood BJ, Gurram S, Choyke PL, Pinto PA, Turkbey B. Reducing false-positives due to urinary stagnation in the prostatic urethra on 18F-DCFPyL PSMA PET/CT with MRI. *Clin Nucl Med*. 2024 Jul 1;49(7):630-636. PMID: 38651785.
- **Rathi N**, Blake Z, Hyman J, Nemirovsky DR, Gelikman DG, Hesswani C, Koller C, Nethala D, Mendhiratta N, Kenigsberg AP, Noun J, Dahut W, Karzai FY, Linehan WM, Turkbey B, Gurram, S. MRI-based measurements of androgen-sensitive muscles: a novel, objective marker for hypogonadism. *J Urol*. [Under review]
- **Rathi N**, Gautam R, Hyman J, Nethala D, Linehan WM, Ball MW, Gurram S. Growth kinetics of renal tumors during pregnancy in patients with hereditary renal cancer syndromes. *Eur Urol Oncol*. [Under review]
- Gurram S, **Rathi N.** Device-assisted therapy in non-muscle-invasive bladder cancer. *Bladder Cancer*. [Under review]
- Nethala D, Hyman J, **Rathi N**, Hsueh J, Koller C, Hesswani C, Kenigsberg AP, Mendhiratta N, Lawson K, Miller M, Parikh S, Azar W, Schuppe K, Merino MJ, Vocke CD, Ricketts CJ, Srinivasan R, Gurram S, Linehan WM, Ball MW. Renal surgery following HIF-2α antagonist therapy: surgical Indications, outcomes and growth kinetics. *Eur Urol*. [Under review]
- Nethala D, Hsueh JY, **Rathi N**, Linehan WM, Ball MW. Diagnosis and management of hereditary renal cell carcinoma. *Nat Rev Urol*. [Under review]

ABSTRACTS

- Nethala D, Hyman J, **Rathi N**, Hsueh J, Koller C, Hesswani C, Kenigsberg AP, Mendhiratta N, Lawson K, Miller M, Parikh S, Azar W, Schuppe K, Merino MJ, Vocke CD, Ricketts CJ, Srinivasan R, Gurram S, Linehan WM, Ball MW. Renal surgery following HIF2a antagonist therapy: growth kinetics and surgical outcomes. American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 3-6, 2024. [Podium]
- **Rathi N**, Nethala D, Hyman J, Hsueh J, Hesswani C, Koller C, Kenigsberg AP, Mendhiratta N, Lawson K, Parikh S, Azar W, Schuppe K, Vocke C, Ball MW, Montenegro GB, Gurram S, Linehan WM, Srinivasan R. Natural history of metastatic renal cell carcinoma (RCC) associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC). AUA Annual Meeting, San Antonio, TX; May 3-6, 2024. [Podium]
- **Rathi N,** Attawettayanon W, Kazama A, Yasuda Y, Munoz-Lopez C, Lewis K, Maina E, Wood A, Palacios DA, Li J, Abdallah N, Weight CJ, Eltemamy M, Krishnamurthi V, Abouassaly R, Campbell SC. Accurate and simple prediction of new baseline renal function after partial nephrectomy. New England Student Urology Symposium, Providence, RI; Mar. 9-10, 2024 and AUA Annual Meeting, San Antonio, TX; May 3-6, 2024. [Podium]

PROFESSIONAL MEETINGS

- Focal Therapy Society, Washington, D.C.; Sep. 7-9, 2023.
- Society of Urologic Oncology Annual Meeting, Washington, D.C.; Nov. 28 -Dec. 1, 2023.
- American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 3-6, 2024.
- New England Student Urology Symposium, Providence, RI; Mar. 9-10, 2024.

AWARDS

- New England Student Urology Symposium, Best Abstract & Oral Presentation Award, 2024

FRANCISCO J. RODRIGUEZ-MATOS
San Juan Bautista School of Medicine, Puerto Rico

MENTOR

Tim F. Greten, M.D.

Deputy Chief
Thoracic and GI Malignancies Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI)

Deputy Director
CCR/NCI

Co-Director
Liver Cancer Program, CCR/NCI

Epigenetic Landscape of CD8+ T Cell Exhaustion and Tissue Residency in HPV-negative Head and Neck Squamous Cell Carcinoma

Liver cancer pathophysiology is driven by complex genetic and inflammatory processes that are not yet completely understood. To study liver cancer, multiple mouse models have been established, where some liver cancers may require specific mouse strains, whereas others can be employed across strains. Previous studies have found that the distribution of major immune cell populations differ across mouse strains in peripheral blood and hematopoietic tissues at baseline. Additionally, variations in immune responses have been described and/or characterized among mice strains, but these studies have not been performed in the context of liver pathology including metabolic-associated fatty liver disease (MAFLD) and hepatocellular carcinoma (HCC).

We performed comprehensive spectral flow cytometry analysis on the livers and spleens of three mouse strains (BALB/c, C57BL/6, and FVBN). The subsets of cells identified in our analysis include CD4+ T cells, CD8+ T cells, innate-like T cells, B cells, innate lymphoid cells, as well as myeloid cells. MAFLD was induced with a methionine-choline deficient (MCD) diet. To promote HCC, a tumorigenic phenotype (MYC-sgp53) was induced by administration of vectors via hydrodynamic tail-vein injection. Our results confirm throughout this study that the hepatic immune microenvironment, although presenting with a dominance of CD4+ T, CD8+T and invariant natural killer T cells, is characterized by significant variation in the composition and proportions of these cells among mouse strains. Moreover, this study shows that shifts of immune cell populations also differ across mouse strains, when induced with MAFLD or HCC.

In conclusion, we highlight that commonly used mouse strains present with distinct immune profiles in the presence of liver pathology, suggesting that mouse strains should be considered as an important variable in the study of immune oncology of HCC.

PUBLICATIONS

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- Benmebarek MR, Oguz C, Seifert M, Ruf B, Myojin Y, Bauer KC, Huang P, Ma C, Villamor-Payà M, **Rodriguez-Matos F**, Soliman M, Trehan R, Monge C, Xie C, Kleiner DE, Wood BJ, Levy EB, Budhu A, Hung MH, Mayer CT, Wang XW, Lack J, Telford W, Korangy F, Greten TF. Anti-VEGF treatment potentiates immune checkpoint blockade responses through a BAFF and IL-12-dependent reprogramming of the tumor microenvironment. *Immunity*. [Under review]

ABSTRACTS

- Rodriguez-Matos FJ, Huang H, Trehan R, Ruf B, Ma C, Greten TF. Immune cell population variations in the livers of commonly used mouse strains. American Association of Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024. [Poster]

PROFESSIONAL MEETINGS

- American Association for Cancer Research Annual Meeting, San Diego, CA; Apr. 5-10, 2024.

SASWAT SAHOO
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

MENTOR

Dimitrios Kapogiannis, M.D., Deputy Laboratory Chief
Laboratory of Clinical Investigation, Human Neuroscience Section, National Institute on Aging (NIA)

Neuronal Extracellular Vesicle Biomarkers of Alzheimer's Disease and Brain Insulin Signaling in Diabetic Cognitive Impairment

Multiple epidemiological studies have established prediabetes (PreD) and type 2 diabetes mellitus (T2DM) as risk factors for cognitive impairment and Alzheimer's Disease (AD). Preclinical models have demonstrated that peripheral insulin resistance, the hallmark of PreD/T2DM, may lead to cognitive impairment by promoting neurodegenerative changes, including AD-characteristic neuropathology (β-amyloid plaques and tau neurofibrillary tangles). However, human autopsy studies evaluating the association between AD neuropathology and PreD/T2DM show conflicting findings. Additionally, it has not been established whether dysregulated brain insulin signaling is an extension of peripheral insulin resistance in PreD/T2DM.

This study will address these gaps in knowledge by utilizing extracellular vesicles of neuronal origin (NEVs) to characterize biomarkers of AD neuropathology (Aβ-40, Aβ-42, total Tau, and pTau-217) and insulin signaling (pIR, pIRS1, pAkt, pGSK3β, pmTOR, pS6K) and their respective associations with cognitive impairment (normal, mild cognitive impairment, dementia) and metabolic markers of peripheral insulin resistance (HbA1c, HOMA-IR) in persons with PreD/T2DM. Using a two-step procedure of size-exclusion chromatography followed by indirect immunoprecipitation with neuronal markers L1CAM, GAP43, and NLGN, NEVs will be isolated from plasma samples from a cross-sectional cohort of 467 participants with either PreD or T2DM. NEV biomarkers will be measured in a manner blinded to participants' clinical characteristics.

NEV biomarkers will be compared across cognitive categories using ANOVA, and significantly different biomarkers will be included as predictors of cognitive status in multinomial/ordinal logistic regression models. Principal component analysis and hierarchical clustering will be used to identify subgroups with different AD and insulin signaling biomarker profiles. Lastly, multivariable linear regression will be used to assess relationships between HbA1c/HOMA-IR and NEV biomarkers.

Characterization of AD neuropathology and brain insulin signaling through NEVs will help establish a framework for more precise prevention, diagnosis, and treatment of cognitive impairment in the growing population of individuals with PreD/T2DM.

PROFESSIONAL MEETINGS

- American Epilepsy Society Annual Meeting, Orlando, FL; Dec. 1-5, 2023.
- American Academy of Neurology Annual Meeting, Denver, CO; Apr. 13-18, 2024.

KYLE C. SCHUPPE
Washington State University Elson S. Floyd College of Medicine

MENTOR

Leonard M. Neckers, Ph.D., Senior Investigator
Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

Inhibition of Oxidative Phosphorylation in Castration-Resistant Prostate Cancer Through Direct and Indirect Therapies Results in a Hormone-Sensitive Phenotype

Prostate cancer (PCa) is a major cause of cancer-related deaths among American men, often due to resistance to androgen receptor (AR) targeting therapies, crucial in metastatic disease management. Resistance to these therapies typically marks a progression to terminal disease. Recent studies at our institution demonstrated that the complex I inhibitor IACS-010759 resensitizes androgen deprivation therapy (ADT)-resistant PCa cell lines, such as 22RV1, to androgen signaling inhibitors (ASIs) such as enzalutamide and abiraterone. However, phase I clinical trials revealed toxicity, necessitating safer alternatives.

We evaluated metformin alongside IACS-010759 to suppress oxidative phosphorylation (OXPHOS) and resensitize castration-resistant prostate cancer (CRPC) cells to ASIs. In vitro assays were conducted using 22RV1 (castrate-resistant), LnCap (castrate-sensitive), and RWPE-1 (normal prostate epithelial) cell lines. Cells were seeded in 96-well plates, treated with drug solutions, and analyzed using the Seahorse XF Analyzer to measure mitochondrial respiration and the IncuCyte live-cell analysis system to monitor growth and confluence over 7-10 days. Both IACS-010759 and metformin were tested in isolation and in combination with ASIs, and their effects were compared head-to-head.

Seahorse XF mitochondrial stress tests showed that both IACS-010759 and metformin effectively suppressed OXPHOS in 22RV1 cells, significantly reducing oxygen consumption rates (OCR). Growth inhibition assays indicated significant antiproliferative effects of both drugs on 22RV1 cells, especially when combined with enzalutamide or abiraterone, suggesting potential resensitization to ASIs. Both inhibitors showed similar efficacy in reducing OCR and inhibiting cell growth in 22RV1. LnCap cells exhibited consistent dose-response inhibition to metformin, while RWPE-1 cells demonstrated no significant growth response.

Both IACS-010759 and metformin effectively inhibit OXPHOS in CRPC cells and may resensitize them to ASIs. Metformin presents a safer, more accessible alternative to IACS-010759, highlighting a significant metabolic vulnerability in CRPC. Further studies are needed to optimize dosing and evaluate clinical potential alongside focal therapies, surgery, and radiation.

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ABSTRACTS

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- Siva J, Mendhiratta N, Azar W, Parikh S, **Schuppe K**, Kenigsberg AP, Koller C, Hesswani C, Merino M, Wood BJ, Turkbey B, Gurram S, Pinto PA, Pillai A. Clinical outcomes of patients on active surveillance for low-risk prostate cancer with small index lesions on MRI. Society of Urological Oncology Annual Meeting, Washington, DC; Nov. 28-Dec. 1, 2023. [Poster]
- **Schuppe KC**, Kenigsberg AP, Azar WS, Hesswani C, Parikh SH, Koller C, Mendhiratta N, Azari S, Gelikman DG, Nethala D, Gurram S, Turkbey B, Pinto PA. The impact of magnetic resonance imaging-detected zonal location on prostate cancer recurrence: implications for preoperative risk stratification. American Urological Association (AUA) Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster]
- **Schuppe KC**, Koller C, Parikh S, Hesswani C, Azar WS, Azari S, Kenigsberg AP, Rathi N, Hyman J, Gelikman D, Mendhiratta N, Nethala D, Gurram S, Merino M, Choyke P, Turkbey B, Pinto PA. Does pre-prostatectomy magnetic resonance imaging reduce racial disparities in oncologic outcomes for African American patients: a propensity score-matched analysis. AUA Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster].
- **Schuppe KC**, Hesswani C, Parikh SH, Koller CR, Azar WS, Kenigsberg AP, Mendhiratta N, Azari S, Nethala D, Gelikman DG, Gurram S, Merino MJ, Choyke P, Turkbey B, Pinto PA. Beyond the bulge: the correlation between extracapsular extension on multi-parametric magnetic resonance imaging with pathological findings and long-term oncologic outcomes following robot-assisted radical prostatectomy. Urological Society for American Veterans, AUA Annual Meeting, San Antonio, TX; May 5, 2024. [Poster]
- **Schuppe KC**, Echtenkamp F, Ito T, Neckers L. Inhibition of complex I resensitizes castration-resistant prostate cancer cells to androgen signaling inhibitors providing significant opportunity for investigation into primary and adjuvant treatments. Independent Practice Research Symposium, AUA Annual Meeting, San Antonio, TX; May 4, 2024. [Poster]
- Parikh S, Hesswani C, **Schuppe KC**, Koller C, Azar W, Kenigsberg A, Gelikman DG, Mendhiratta N, Azari S, Nethala D, Gold S, Gurram S, Madan RA, Karzai F, Turkbey B, Pinto PA. The impact of novel neoadjuvant androgen signaling inhibitors on robotic radical prostatectomy: a propensity score-matched comparison of intraoperative and short-term outcomes. Urological Society for American Veterans, AUA Annual Meeting, San Antonio, TX; May 5, 2024. [Poster]
- Azar WS, Hesswani C, **Schuppe KC**, Koller CR, Parikh SH, Azari S, Kenigsberg AP, Mendhiratta N, Nethala D, Noun J, Merino MJ, Turkbey B, Pinto PA, Gurram S. Does location of positive margins after radical prostatectomy affect risk of biochemical recurrence? Urological Society for American Veterans, AUA Annual Meeting, San Antonio, TX; May 5,h 2024. [Poster]
- Parikh SH, Hesswani C, **Schuppe KC**, Koller CR, Azar WS, Gelikman DG, Kenigsberg AP, Mendhiratta N, Nethala D, Azari S, Hyman JA, Wood BJ, Gurram S, Madan RA, Karzai F, Pinto PA. Effect of novel neoadjuvant androgen signaling inhibitors prior to robotic radical prostatectomy on pathological or short-term survival outcomes Urological Society for American Veterans, AUA Annual Meeting, San Antonio, TX; May 5th 2024. [Podium]
- Azar WS, Hesswani C, **Schuppe KC**, Koller CR, Parikh SH, Azari S, Kenigsberg AP, Mendhiratta N, Nethala D, Merino MJ, Turkbey B, Pinto PA, Gurram S. Is it time we include high-risk MRI features in nomograms to calculate the risk of lymph node invasion prior to radical prostatectomy? Urological Society for American Veterans, AUA Annual Meeting, San Antonio, TX; May 5th 2024. [Podium]

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- Azar WS, Koller CR, Parikh SH, Hesswani C, **Schuppe KC**, Azari SS, Kenigsberg AP, Mendhiratta N, Hyman J, Noun J, Siva J, Nethala D, Gelikman DG, Merino MJ, Parnes HS, Wood BJ, Turkbey IB, Gurram S, Xu S, Pinto PA. Is it time to abandon the transrectal probe in prostate biopsy? AUA Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster]
- Parikh SH, Hesswani C, Azar WS, Koller CR, **Schuppe KC**, Kenigsberg AP, Mendhiratta N, Azari S, Nethala D, Wu Y, Wiskin J, Boctor E, Klock J, Wood B, Gurram S, Turkbey B, Pinto PA. A new look: the promising use of 3-dimensional quantitative transmission ultrasound tomography for the detection of prostate cancer an ex vivo study. AUA Annual Meeting, San Antonio, TX; May 2-6, 2024. [Poster]
- Azari S, Mason JB, Kenigsberg AP, Koller C, Parikh S, Azar W, **Schuppe KC**, Siva J, Hesswani C, Mendhiratta N, Nethala D, Merino M, Wood BJ, Choyke PL, Parnes HL, Gurram S, Turkbey B, Pinto PA, Blake Z, Nemirovsky DR, Mezhiritsky V. Impact of PI-RADS 5 lesions on active surveillance for grade group 1. Society of Urological Oncology Annual Meeting, Washington, DC; Nov. 28-Dec. 1, 2023. [Poster]

PROFESSIONAL MEETINGS

- Focal Therapy Society Annual Meeting, Washington, DC; Sep. 7-9, 2023.
- Society of Urological Oncology Annual Meeting, Washington, DC; Nov. 28-Dec. 1, 2023.
- American Urological Association (AUA) Annual Meeting, including the Independent Practice Research Symposium and the Urological Society for American Veterans Annual Meeting, San Antonio, TX; May 2-6, 2024.
- New Frontiers in Liquid Biopsies: Data, Technology and Translational Potential, Bethesda, MD; May 13-14, 2024.

AWARDS

- Best Poster, American Urological Association (AUA) Annual Meeting, 2024
- Best Poster, AUA Independent Practice Research Symposium, 2024

GUSTAVO SERRANO-BERRIOS
Ponce Health Sciences University School of Medicine

MENTORS

Miroslav Bačkonja, M.D., Clinical Director
Division of Intramural Research, National Center for Complementary and Integrative Health (NCCIH)

Andrew J. Mannes, M.D., Chief
Department of Perioperative Medicine, NIH Clinical Center (CC)

Thermosensory Loss is Correlated with Primary Afferent Nociceptive Fibers Deletion in Postmortem Dorsal Root Ganglion and Spinal Cord in a Cancer Patient Treated with Resiniferatoxin (RTX)

Pain from advanced cancer is often intractable leading to significant impairment of quality of life. The standard of care for relieving cancer pain relies on opioids, which can be incompletely efficacious, and cause adverse effects such as addiction and respiratory suppression. A major priority of the pain field is the development of novel non-opioid analgesic strategies to improve patient care.

In this study we correlate the clinical presentation of a single well-characterized patient treated with lumbar intrathecal resiniferatoxin (IT-RTX) with a molecular phenotype from postmortem dorsal root ganglia (DRG) and spinal cord (SC) tissue collected at autopsy, approximately 4-5 months after IT-RTX. RTX binds to the ion channel TRPV1 expressed in nociceptive afferent neurons.Intrathecal injection bathes and ablates only centrally-projecting axons of TRPV1-expressng neurons, leaving DRG cell bodies intact.

The patient had metastatic appendiceal carcinoma with unmanageable perineal and pelvic pain, and was enrolled in a Phase 1 Study of IT-RTX for treatment of pain in advanced cancer (NCT00804154). Following IT-RTX, the patient experienced a modest decrease in pain, but also developed loss of thermal sensation in hands, feet and trunk. Postmortem, we stained the DRG and SC with markers of nociceptive sensory afferents such as calcitonin gene-related peptide (CGRP) and Substance P (SP) to map the denervation and potential cell loss at different spinal levels. In the SC, a marked decrease in primary afferent-derived SP and CGRP was observed at all rostro-caudal levels, consistent with the clinical presentation showing decreased sensation to heat to all extremities and torso. In the DRG, quantitative cell counts for mRNA expression and nociceptive protein markers showed minimal loss of neuronal cell bodies, consistent with our previous work.

This clinical observation formed the basis for an ongoing reverse translational effort to assess the effects of dose, rate, and volume on RTX spread in the intrathecal space of rats and pigs.

ABSTRACTS

- **Serrano-Berrios G**, Sapio MR, Nara P, Manalo A, Ghetti A, Iadarola MJ, Mannes AJ. Thermosensory loss is correlated with primary afferent nociceptive fibers deletion in postmortem dorsal root ganglion and spinal cord in a cancer patient treated with resiniferatoxin (RTX). United States Association for the Study of Pain, Seattle, WA; Apr. 14-17, 2024. [Poster]

PROFESSIONAL MEETINGS

- Neuroscience 2023 Annual Meeting, Society for Neuroscience, Washington, DC; Nov. 11-15, 2023.
- United States Association for the Study of Pain (USASP) Annual Scientific Meeting, Seattle, WA; Apr. 14-17, 2024.
- Internal Medicine Meeting 2024, American College of Physicians (ACP), Boston, MA; Apr. 18-20, 2024.

SONAL SHARDA
UMass Chan Medical School

MENTOR

Tiffany M. Powell-Wiley, M.D., MPH, Stadtman Investigator
Social Determinants of Obesity and Cardiovascular Risk Laboratory, National Heart, Lung, and Blood Institute (NHLBI)

A Multi-Omics Interrogation of SDH-Deficient Primary and Metastatic Gastrointestinal Stromal Tumors

Social Determinants of Health (SDOH) encompass the economic, psychosocial, and environmental factors that influence one's health, especially those in historically underserved populations. Further connecting adverse SDOH to cardiovascular disease (CVD) pathogenesis and CVD-related complications of cancer therapeutics, are underlying biological pathways. One mechanism is clonal hematopoiesis (CH), partially driven by epigenetic regulatory genes, including TET2. The TET2 gene has been implicated in CVD and malignancies, in part by promoting inflammation and immune cell dysfunction. Little is known on how epigenetic modulation of TET2 itself may relate to the immune system and subsequent disease development along with the potential role of adverse SDOH, such as socioeconomic status (SES), in these pathways.

60 African American adults (93% female, 61 ± 11 years) at risk for CVD, living in the Washington DC area, participated in a cross-sectional, community-focused study. Participants self-reported their SES as household incomes. 18FDG-PET/CT assessed immune system activity via splenic activity (SpleenA), ELISA measured serum cytokine levels, and DNA methylation analysis of buffy coat samples evaluated the epigenetic modulations of TET2. Multivariable regression analysis adjusted for ASCVD 10-year risk score and BMI was used to examine associations.

Out of 33 TET2 methylation sites, 3 sites significantly related to SES. Notably, only Tet2cg09666717 (SES β=0.310, p=0.038) also associated with SpleenA (β=-0.453, p=0.036) and 2 cytokines: IL-1β (β=-0.382, p=0.003) and TNFa (β=-0.456, p=0.000) along with trending to significance with IFN-γ (β=-0.258, p=0.062).

Thus, we found that lower SES associated with hypomethylation of Tet2cg09666717 which further related to SpleenA and inflammatory markers. Our findings are hypothesis-generating and suggest that lower SES may relate to immune system dysregulation via epigenetic modulation of TET2. Future work should examine how these findings relate to CVD or cardio-oncology outcomes and the potential importance of one specific methylation site in cardiovascular and cardioncological risk, prognosis, as well as outcomes.

PUBLICATIONS

- Baah FO*, **Sharda S***, Davidow K, Jackson S, Kernizan D, Jacobs JA, Baumer Y, Schultz CL, Baker-Smith CM, Powell-Wiley TM. Social determinants of health in cardio-oncology: multi-level strategies to overcome disparities in care: JACC: CardioOncology State-of-the-Art review. *J Am Coll Cardiol CardioOnc*. 2024 May; *Equal contribution
- Powell-Wiley TM, Martinez MF, Heneghan J, Weatherwax C, Osei Baah F, Velmurugan K, Chin KL, Ayers C, Cintron MA, Ortiz-Whittingham LR, Sandler D, **Sharda S**, Whitley M, Bartsch SM, O'Shea KJ, Tsintsifas A, Dibbs A, Scannell SA, Lee BY. Health and economic value of eliminating socioeconomic disparities in US youth physical activity. JAMA Health Forum. 2024 Mar 1;5(3):e240088. PMID: 38488779.

ABSTRACTS

- **Sharda S**, Baumer Y, Pang APS, Saurabh A, Collins BS, Mitchell VM, Corley MJ, Powell-Wiley TM. Socioeconomic status as a potential driver of clonal hematopoiesis via epigenetic modulation of Tet2 gene. American Association of Cancer Research Annual Meeting, San Deigo, CA; Apr. 5–10, 2024. [Poster presentation]. Also presented at 19th Annual NHLBI DIR Research Retreat, Bethesda, MD; Mar 8, 2024. [Podium]
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- Sandler D, Baumer Y, **Sharda S**, Saurabh A, Tarfa H, Dave A, Pita M, Cintron M, Reynolds S, Hicks S, Ortiz-Whittingham L, Potharaju K, Baez A, Neally S, Vijayakumar N, Curlin K, Thompson K, Baah FO, Ayers C, Marah M, Wells A, Deguzman S, Redai A, Mitchell V, Collins B, Powell-Wiley TM. Discrimination as a moderator for the relationship between physical activity and monocyte subsets: data from the Step It Up physical activity intervention. American Psychosomatic Society
- Ortiz-Whittingham LR, Dave A, Peterson E, Regan S, Andrews M, **Sharda S,** Smith V, Marah M, Wells A, Collins B, Mitchell V, Baumer Y, Powell-Wiley TM. Associations between neighborhood socioeconomic deprivation and markers of chronic stress and hematopoietic activity from FDG-PET/CT scans among community-based women in Washington DC. American Psychosomatic Society
- **Sharda S**, Cintron MA, Baumer Y, Jacobs JA, Pang APS, Ortiz-Whittingham, LR, Kameswari PA, Baez AS, Saurabh A, Gutierrez-Huerta, CA, Chapparo EO, Collins BS, Mitchell VM, Corley MJ, Powell-Wiley TM. Epigenetic regulation of the Nf-kb pathway by the neural-hematopoietic-inflammatory axis as a potential link between psychosocial stress and cardiovascular risk: data from the Washington DC Cardiovascular Health and Needs Assessment. American Heart Association Epidemiology, Chicago, IL; Mar 18-21, 2024. [Poster]
- Cintron MA, Troendle JF, Pita MA, Tarfa HA, Baah FO, Potharaju K, Thompson K, Reynolds S, Hicks S, Sandler D, **Sharda S**, Gallagher JW, McCoy R, Heist M, Ortiz-Whittingham LR, Baez AS, Andrews M, Collins BS, Mitchell VM, Marah M, Wells A, Baumer Y, Dodge T, Powell-Wiley TM. Associations between digital health app engagement and changes in physical activity among African American women with cardiovascular-kidney-metabolic syndrome: data from the step it up digital health-enabled physical activity intervention. American Heart Association Epidemiology, Chicago, IL; Mar. 18-21, 2024. [Podium]
- Hicks S, Troendle JF, Pita MA, Tarfa HA, Baah FO, Potharaju K, Thompson K, Reynolds S, Sandler D, Dave A, **Sharda S**, Gallagher JW, McCoy R, Heist M, Ortiz Whittingham LR, Baez AS, Andrews M, Collins BS, Mitchells VM, Marah M, Wells A, Baumer, Dodge T, Powell-Wiley TM. Linking psychosocial and environmental factors to engagement in Step it UP digital health intervention. Society of Behavioral Medicine, Philadelphia, PA; Mar. 13-16, 2024. [Poster]

PROFESSIONAL MEETINGS

- 19th Annual National Heart, Blood, Lung Institute DIR Research Retreat, Bethesda, MD; Mar. 8, 2024.
- American Heart Association Epidemiology and Prevention - Lifestyle and Cardiometabolic Health Scientific Sessions, Chicago, IL; Mar. 18-21, 2024.
- American Association of Cancer Research, San Diego, CA; Apr. 5-10, 2024.

AWARDS

- Finalist, NHLBI Three Minute Talk competition (3rd place), 2024

JENNIFER A. STRONG
University of Maryland School of Medicine

MENTOR

Isaac Brownell, M.D., Ph.D., Chief
Cutaneous Development and Carcinogenesis Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Adaptive Optics Retinal Imaging Reveals Cone Photoreceptor Enlargement and Loss of Regularity in RHO-associated Retinitis Pigmentosa

Demodex mites are commensal organisms of the hair follicle that have been implicated in inflammatory folliculocentric eruptions of the face. Demodicosis is more likely to occur in immunosuppressed patients and cases associated with hematopoietic cell transplant (HCT) have been reported. In the post-transplant period, demodicosis must be differentiated from cutaneous manifestations of acute graft-versus-host disease (aGVHD). Herein we report a series of 17 patients with demodicosis diagnosed clinically within 100 days of HCT with supporting skin scrapings or skin biopsy.

Patients had a mean age of 39.2 years (range 13-75), and all 17 had received reduced-intensity pre-transplant conditioning. They presented, on average, 38.9 days after HCT (range 22-71) with erythematous folliculocentric papules or papulopustules on the sebaceous skin of the face, neck, and upper trunk. Nine patients (53%) experienced aGVHD before, during or after demodicosis. A total of 15 patients were treated with oral ivermectin. One patient was treated with topical permethrin 5% cream and the remaining patient was treated with systemic steroids. Although most patients had resolution of their demodicosis following treatment, four patients (24%) first experienced robust inflammatory responses with facial edema after ivermectin treatment.

We propose that ivermectin produced a Mazzotti-like reaction in which dead mites precipitated inflammation. Ivermectin has been associated with the Mazzotti reaction when treating onchocerciasis, and Mazzotti-like reactions have been reported with ivermectin when treating scabies mites. To our knowledge, this is the largest reported series of post-HCT demodicosis. When evaluating folliculocentric facial eruptions in patients after HCT, demodicosis should be considered. Further research is needed to determine if demodicosis in this context represents an infestation or a post-engraftment inflammatory response to commensal mites.

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- Ching, L, **Strong J**, Lee T, Kaufman H, Emerick K, Kim E, Patel V, Brownell I, Singh K, Neel V, Miller D, Gupta S. A closer look: evaluating Mohs surgery's role in the treatment of invasive melanoma of the head and neck. *J Cutan Oncol*. 2024; 2(1).
- **Strong J**, Miller DM, Lawrence DP, Brownell I. Tumor-infiltrating lymphocyte therapy receives FDA approval. *J Cutan Oncol*. 2024; 2(1).
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- Wang CJ, **Strong J**, Mohsin N, Lamanping E, Cowen EW, Koch H, Helwig C, Bajars M, Lee CR, Strauss J, Floudas CS, Gullet JL, Brownell I. Keratoacanthomas and other cutaneous adverse events in patients treated with bintrafusp alfa. *JAMA Netw Open*. [Under review]
- Wang CJ*, **Strong J***, Gatti-Mays ME, Abdul Sater H, Strauss J, Redman JM, Schlom J, Gulley JL, Brownell I. Case report: the immune architecture of immunotherapy-induced cutaneous sarcoidosis resembles peritumoral inflammation. *Front Immunol*. [Under review] *Equal contribution
- **Strong J**, Wojnarski M, Meltzer JC, Austin A, Sperling LC, Bloomquist L, Brownell I. Atypical fibrous histiocytoma mimicking a cutaneous metastasis on integrated F-18 fluoro-2-deoxyglucose PET-CT in a patient with stage IV melanoma. *JAAD Case Rep*. [Under review]

ABSTRACTS

- Newkirk R, **Strong J**, Mescher J, McTighe S, Keung ES, Brownell I. Nodal melanoma recurrence demonstrating emperipolesis 7 years after primary diagnosis in a patient with reactive lymphadenopathy from COVID-19 vaccine. American Academy of Dermatology Annual Meeting, San Diego, CA; Mar. 8-12, 2024.
- Wojnarski M, **Strong J**, Austin A, Sperling L, Bloomquist L, Brownell I. Atypical dermatofibroma mimicking a cutaneous metastasis on integrated F-18 fluorodeoxyglucose PET-CT in a patient with stage IV melanoma. American Academy of Dermatology Annual Meeting, San Diego, CA; Mar. 8-12, 2024.
- Winkie MJ, Whitecar SB, **Strong J**, Keung ES, Neelon DP, Gage MM, Schaffenburg WC, Simpson MM, Brownell, I. Molecular diagnosis of epidermotropic metastatic melanoma presenting as eruptive primary melanomas. American Academy of Dermatology Annual Meeting, San Diego, CA; Mar. 8-12, 2024.
- **Strong J**, Mohsin N, Coxon A, Brownell I. Why are patients with XMEN disease getting early onset Merkel cell carcinoma? Multicenter Merkel Interest Group Meeting, San Diego, CA; Mar. 8, 2024.
- **Strong J**, Wang CJ, Floudas CS, Brownell I. Keratoacanthomas in cancer patients treated with the TGF- β inhibitor bintrafusp alfa. Oncodermatology Society Annual Meeting, San Diego, CA; Mar. 8, 2024.

PROFESSIONAL MEETINGS

- Medical Dermatology Society Annual Meeting, San Diego, CA; Mar. 7, 2024.
- American Academy of Dermatology Annual Meeting, San Diego, CA; Mar. 8-12, 2024.
- Multicenter Merkel Interest Group Meeting, San Diego, CA; Mar. 8, 2024.
- Oncodermatology Society Annual Meeting, San Diego, CA; Mar. 8, 2024.

SI JIE (JESSICA) TANG
University of California Davis School of Medicine

MENTORS

Daniel Reich, M.D., Ph.D, Chief
Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke (NINDS)

Irene Cortese, M.D., Assistant Clinical Investigator
Experimental Immunotherapeutics Unit, National Institute of Neurological Disorders and Stroke (NINDS)

Autoantibodies to Interferon Lambda in Chronic Granulomatous Disease

In multiple sclerosis (MS), CD8+ T cells are present in active focal new lesions, chronic active lesions, and meningeal inflammatory aggregates. Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic infection caused by JC virus reactivation in immunocompromised patients. Excessive inflammatory activation during immune response (immune reconstitution inflammatory syndrome (PML-IRIS)) can lead to clinical worsening or death, but CD8+ T cells can control JCV dissemination. Currently, there is no method of tracking CD8+ T cells in vivo. 89Zr crefmirlimab berdoxam (minibody) was developed as a bivalent homodimer with a single-chain variable fragment attached to the human IgG1 CH3 domain with a high affinity for the CD8 glycoprotein.

5 MS and 5 PML patients will undergo positron emission tomography and computed tomography scans (PET-CT) 24 hours after minibody injection. PET-CT scans will be co-registered to baseline magnetic resonance imaging (MRI) to localize areas of high PET standard uptake values (SUV) for the tracer.
Two participants with MS (without evidence of focal active new lesions) have been recruited for the study so far. Scattered minibody hotspots were observed along the skull of both participants. The highest SUV was measured in the clivus and left and right occipital condyles of the skull base. Minibody hotspots were not observed in the brain parenchyma nor correlated with chronic active/inactive white matter lesions.

Minibody hotspots along the skull may indicate CD8 pockets in the skull marrow which have been shown to be directly associated with regulation of meningeal immunity. Ongoing trial recruitment will focus on MS participants with evidence of active focal inflammation with blood-brain barrier breakdown and subjects with PML. The ability to use a noninvasive imaging modality to detect CD8+ T cells may allow for the in-vivo differentiation of MS lesion types and detection of CSF inflammation as well early containment and survival in PML.

PROFESSIONAL MEETINGS

- Americas Committee for Treatment and Research in Multiple Sclerosis Annual Meeting, West Palm Beach, FL; Feb. 26-Mar. 2, 2024.
- American Academy of Neurology Annual Meeting, Denver CO; Apr. 13-15, 2024.

AWARDS

- American Academy of Neurology Futures in Neurological Research
- ACTRIMS Neurology Residents Summit in Multiple Sclerosis Travel Award
- NINDS Three Minute Talk Competition (3rd place)

JULIA M. TELISCHI
University of Miami Miller School of Medicine

MENTOR

Michael Hoa, M.D., Principal Investigator
Auditory Development and Restoration Program, Neurotology Branch, National Institute on Deafness and Other Communication Disorders (NIDCD)

Longitudinal Quantification of Inner Ear Fluid Spaces using MRI: Correlations to Audiovestibular Measurements in Patients with Hearing Instability

Hearing instability (HI) disorders, including Meniere's disease, autoimmune inner ear disease, and sudden sensorineural hearing loss, can be characterized histopathologically by endolymphatic hydrops (EH), an expansion of the endolymphatic space. Fluid sensitive magnetic resonance imaging (MRI) techniques combined with gadolinium-based contrast agents have been used to differentiate the two fluid spaces in the labyrinth, as such agents preferentially accumulate in the perilymph (PL) but not in the endolymph (EL). While several studies have quantified these fluid spaces and EH in the inner ear based on such MRI techniques, few studies to date have quantified them longitudinally.

A cohort of HI patients was evaluated with MRI imaging and audiovestibular testing at 3-month intervals. Contrast-enhanced delayed fluid attenuated inversion recovery (CED-FLAIR) and short tau inversion recovery (STIR) MRI sequences were taken at 3.0T 4-8 hours following intravenous gadoteridol (0.2 mmol/kg). STIR sequences detect total inner ear fluid (EL + PL) and CED-FLAIR detects only PL fluid, allowing a custom-developed semi-automated MRI processing and analysis pipeline to segment distinct fluid volumes and extract EL and PL volume of the cochlea and vestibule.

Fluid volume variance over time was higher in ears with fluctuating hearing, and MRI-designated EH and increasing endolymph to perilymph vestibule volume ratio correlated with worse hearing during hearing fluctuations ($r=0.75$, $p=5.67\times10-5$). Logistic regression modeling including demographic factors confirmed a significant positive relationship between vestibular EL/PL ratio and worse hearing level ($p=8.41e-6$) and between visit-to-visit change in EL/PL ratio and shift in hearing level ($p=0.0025$).

This analysis shows that longitudinal assessment of patients with HI utilizing contrast-enhanced delayed FLAIR MRI allows for detection of quantifiable changes in EH that correlate with changes in hearing. This methodology has the potential to monitor HI more efficiently over time and help better evaluate potential treatments for HI in which EH is present.

ABSTRACTS

- Adadey S, Benner A, Olszewski R, Gu S, Strepay D, **Telischi J**, Chisholm J, Butman J, Hoa M. Proteomics and immunophenotyping of patients with hearing instability disorders. Association for Research in Otolaryngology MidWinter Meeting, Anaheim, CA; Feb. 3-7 2024. [Poster]
- **Telischi J**, Chisholm J, Zalewski C, Christensen J, Allemang N, Bilokon A, Cheng H, Butman J, Brewer C, Hoa M. Longitudinal variability in vestibular evoked myogenic potentials and endolymphatic hydrops for patients with hearing instability. Association for Research in Otolaryngology MidWinter Meeting, Anaheim, CA; Feb. 3-7, 2024. [Podium]

- **Telischi J**, Strepay D, Li B, Gu S, Hsu LY, Butman J, Hoa M. Longitudinal quantification of inner ear fluid spaces and endolymphatic hydrops on contrast-enhanced delayed FLAIR MRI: reliability and correlation with changes in hearing. Association for Research in Otolaryngology MidWinter Meeting, Anaheim, CA; Feb. 3-7, 2024. [Symposium]
- **Telischi J**, Ellsperman S, Cheng H, Hoa M, Stucken E, SDoHVS Consortium. A multi-institutional review of the impact of social determinants of health on vestibular schwannoma management. Combined Otolaryngology Spring Meetings, Chicago, IL; May 15-19, 2024. [Poster]
- **Telischi J**, Chisholm J, NIDCD Audiology Unit, Cheng H, Hsu LY, Butman J, Hoa M. Phenotyping of hearing instability: correlating longitudinal changes in endolymph volume and electrocochleography. Combined Otolaryngology Spring Meetings, Chicago, IL; May 15-19, 2024. [Poster]

PROFESSIONAL MEETINGS

- Association for Research in Otolaryngology MidWinter Meeting, Anaheim, CA; Feb. 3-7, 2024.
- Combined Otolaryngology Spring Meetings, Chicago, IL; May 15-19, 2024.

AWARDS

- Second Place Poster Award, American Otological Society, Combined Otolaryngology Spring Meeting, 2024

JACOB T. TRIBBLE
University of Missouri – Kansas City School of Medicine

MENTORS

Eric A. Engels, M.D., MPH, Chief
Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI)

Michael R. Sargen, M.D., Assistant Clinical Investigator
Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI)

The Burden of Merkel Cell Carcinoma Attributable to Immunosuppression, Ultraviolet Radiation, and Merkel Cell Polyomavirus in the United States

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer. Quantifying the contribution of major potentially modifiable risk factors to the burden of MCC can inform prevention efforts. The objective of this study was to estimate the population attributable fraction (PAF) and number of MCC cases in the US attributable to immunosuppressing conditions (human immunodeficiency virus [HIV], solid organ transplantation, chronic lymphocytic leukemia [CLL]), ambient ultraviolet radiation (UVR) exposure, and Merkel cell polyomavirus (MCPyV) during 2001–2019.

MCC cases from 2001–2019 diagnosed in people with HIV (PWH), organ transplant recipients, and CLL patients were identified through population-based cancer registries and linkages with HIV and transplantation registries. UVR based on cloud-adjusted ambient UVR irradiance was merged with cancer registry data. We also meta-analyzed published studies reporting the prevalence of MCPyV in MCC specimens collected in the US.

During 2001–2019, 38,020 MCCs were diagnosed in the US. Compared to the general US population, MCC incidence was elevated among PWH (standardized incidence ratio 2.78), organ transplant recipients (13.1), and CLL patients (5.75). Due to the rarity of these conditions, 0.2% (CI: 0.1–0.3%) of MCC cases were attributable to HIV (n=86), 1.5% (CI: 1.4–1.7%) to solid organ transplantation (n=583), and 0.8% (CI: 0.5–1.3%) to CLL (n=312). Compared with individuals of other races/ethnicities, head and neck MCC incidence was elevated among non-Hispanic White individuals at lower and higher UVR exposure levels (incidence rate ratios 4.05 and 4.91, respectively). Overall, 65.1% (CI: 63.6–66.7%) of MCCs were attributable to UVR (n=24,751). Meta-analysis of 19 studies revealed that 63.8% (CI: 54.5–70.9%) of MCCs were attributable to MCPyV (n=24,257).

Most MCC cases in the US were attributable to UVR and MCPyV, with a small fraction due to immunosuppression. Efforts aimed at lowering MCC incidence should focus on limiting UVR exposure in non-Hispanic White individuals.

PUBLICATIONS

- **Tribble JT**, Pfeiffer RM, Brownell I, Cahoon EK, Sargen MR, Shiels MS, Luo Q, Cohen C, Drezner K, Hernandez B, Moreno A, Pawlish K, Saafir-Callaway B, Engels EA, Volesky-Avellaneda K. Merkel cell carcinoma attributable to immunosuppression, UVR, and Merkel cell polyomavirus in the US. *JAMA Dermatol* [Under review]

ABSTRACTS

- **Tribble JT**, Volesky-Avellaneda K, Luo Q, Sargen MR, Brownell I, Cahoon EK, Shiels MS, Pfeiffer RM, Moreno A, Hernandez B, Engels EA. Contribution of HIV to the burden of Merkel cell carcinoma in the US. Conference on Retroviruses and Opportunistic Infections, Denver, CO; March 3-6, 2024. [Poster]
- **Tribble JT**, Volesky-Avellaneda K, Luo Q, Sargen MR, Brownell I, Cahoon EK., Shiels MS, Pfeiffer RM, Moreno A, Hernandez B, Engels EA. The burden of Merkel cell carcinoma attributable to immunosuppression, ultraviolet radiation, and Merkel cell polyomavirus in the United States. American Association for Cancer Research Annual Meeting, San Diego, CA; April 5-10, 2024. [Poster]

- **Tribble JT**, Volesky-Avellaneda K, Sargen MR, Shiels MS, Engels EA. Measures of immunosuppression in the year prior to Merkel cell carcinoma diagnosis among people with HIV. Society for Investigative Dermatology Annual Meeting.

PROFESSIONAL MEETINGS

- Conference on Retroviruses and Opportunistic Infections, Denver, CO; March 3-6, 2024.
- American Association for Cancer Research Annual Meeting, San Diego, CA; April 5-10, 2024.

AWARDS

- Conference on Retroviruses and Opportunistic Infections New Investigator Scholarship, March 2024

ELIZABETH VARGHESE
Renaissance School of Medicine at Stony Brook University

MENTOR

Veronica Gomez-Lobo, M.D., Director
Pediatric and Adolescent Gynecology Program, National Institute of Child Health and Human Development (NICHD)

Possible Compensatory Mechanisms of Follicle Protection in the Retained Ovary after Unilateral Oophorectomy in Mouse Models

In women who undergo unilateral oophorectomy (UO), studies have shown that spontaneous pregnancy rates are similar to those who have both ovaries intact. Furthermore, women who underwent UO entered menopause approximately 1 year earlier than those who have both ovaries. Since these effects are less pronounced than what would be expected from the loss of half of the ovarian reserve, we investigated possible compensatory mechanisms of follicle protection in the retained ovary after UO in mouse models. 4–5 week-old B6 albino female mice underwent right UO (n = 10) or sham surgery (n = 10) and were sacrificed at 10 weeks of age. At time of sacrifice, the remaining left ovary was removed from the mice that underwent UO and right and left ovaries were removed from the mice that underwent sham surgery. Ovaries were collected for gross and histological analysis. Grossly, ovarian diameters and weights were measured and averaged.

Histologically, ovarian follicles were counted, classified, and averaged in evenly spaced sections throughout the ovary. Statistical significance was determined using unpaired t-tests. The remaining ovary in the mice that underwent UO weighed significantly more than bilateral ovaries in mice that underwent sham surgery ($p = 0.001$). Additionally, there was a significantly higher number of primordial follicles (PMFs) in the oophorectomy group compared to the sham surgery group ($p = 0.02$). While the number of growing follicles and the PMF:Growing ratio was greater in the oophorectomy group, the difference was not statistically significant.

These experiments demonstrate the existence of differences in size and histology in the remaining ovary in mice post-oophorectomy compared to the bilateral ovaries post-sham surgery. Further studies are necessary to discern the ovarian morphological differences leading to the size discrepancy and to determine the mechanisms leading to increased numbers of PMFs post-oophorectomy.

PUBLICATIONS

- **Varghese E**. Restructuring morbidity and mortality conferences to better prepare medical trainees to mitigate regret in surgical decision-making. *AMA Journal of Ethics*. [Under review]

ABSTRACTS

- **Varghese E**, Badger T, Kavarthapu R, Grinberg A, Balasubramanian R, Lou H, Sierra MDLL, Pfeifer K, Maher J, Gomez-Lobo V. Combinatory effects of unilateral oophorectomy plus cyclophosphamide treatment on ovarian reserve and fertility in a mouse model. North American Society of Pediatric and Adolescent Gynecology Annual Clinical and Research Meeting, Orlando, FL; Apr. 4-6, 2024. . J Pediatr Adolesc Gynecol. 2024;37(2):246 [Poster]. Also presented at Annual Conference of the Oncofertility Consortium, Pittsburgh, PA; Nov. 6-8, 2023 [Poster]
- **Varghese E**, Badger T, Kavarthapu R, Grinberg A, Balasubramanian R, Lou H, Sierra MDLL, Pfeifer K, Maher J, Gomez-Lobo V. Possible compensatory mechanisms of follicle protection in the retained ovary after unilateral oophorectomy in mouse models. North American Society of Pediatric and Adolescent Gynecology Annual Clinical and Research Meeting, Orlando, FL; Apr. 4-6, 2024. J Pediatr Adolesc Gynecol. 2024;37(2):227 [Podium]

PROFESSIONAL MEETINGS

- American College of Obstetrics and Gynecology District IV Annual Meeting, Washington D.C.; Oct. 20-22, 2023.
- Annual Conference of the Oncofertility Consortium, Pittsburgh, PA; Nov. 6-8, 2023.
- American College of Obstetrics and Gynecology Congressional Leadership Conference; Washington D.C.; Mar. 3-5, 2024.
- North American Society of Pediatric and Adolescent Gynecology Annual Clinical and Research Meeting; Orlando, FL; Apr. 4-6, 2024.

JACK H. VICTORY
West Virginia University School of Medicine

MENTOR

Jonathan M. Hernandez, M.D., Investigator
Surgical Oncology Program, Center for Cancer Research, National Cancer Institute (NCI)

Preclinical Evaluation of Carfilzomib for Novel Use in Hepatic Artery Infusion Pump Therapy

Advanced hepatobiliary malignancies portend poor outcomes. Hepatic arterial infusion (HAI) pump therapy has demonstrated survival benefit in select patients, resulting in renewed interest in this approach. Despite advancements in medical therapies, floxuridine has remained the standard pump agent since its introduction in the 1970s. The current study aimed to develop an evaluation algorithm for agents amenable to novel pump use. Carfilzomib, a proteasome inhibitor approved for use in multiple myeloma, was evaluated by this model.

An extensive in silico review identified all FDA-approved anti-neoplastic agents soluble in aqueous solution. Carfilzomib was selected for further study due to favorable pharmacokinetic (half-life <30 minutes), efficacy, and toxicity profiles. Solubility and stability testing were performed by reconstitution in dextrose 5% in water (D5W) and one-week incubation at 37℃ in a HAI pump with evaluation by mass spectrometry. Efficacy testing was performed on three independent patient-derived organoids of colorectal adenocarcinoma and cholangiocarcinoma origin, respectively. CellTiterGlo® was used to analyze cell viability. IC50 curves were generated following 1 hour and 96 hours of carfilzomib exposure to emulate systemic bolus and continuous HAI routes, respectively.

Carfilzomib demonstrated solubility at 2 mg/mL in D5W, a biorelevant concentration for pump use. 80% of parent drug remained following one week. Carfilzomib showed robust anti-tumor activity at 96 hours of continuous exposure (average IC50 of 10 nM) compared to 1 hour of exposure (average IC50 of 1 µM) in both organoid histologies.

Carfilzomib exhibits solubility and stability amenable for HAI pump use. A continuous drug exposure model, representative of a HAI approach, resulted in superior anti-tumor activity compared to a bolus exposure model at identical dosing. Future studies will investigate first-pass pharmacokinetic and safety profiles of carfilzomib using a novel ex vivo porcine hepatic perfusion model. A Phase I/II trial is being established to investigate carfilzomib use in HAI pump therapy.

PUBLICATIONS

- **Victory JH**, Smith EC, Ryan CE, Lambdin J, Sarvestani L, Friedman L, Eade A, Larrain C, Pu T, Luberice K, Ramamoorthy B, Rainey A, Hannah C, Smith K, Mabry D, Xie C, Davis JL, Blakely AM, Gulley JL, Schlom J, Monge C, Greten TF, Hernandez JM. Hepatic artery infusion pump therapy in combination with targeted delivery of IL-12 for patients with metastatic colorectal cancer or intrahepatic cholangiocarcinoma: a phase II protocol. *J Gastrointest Oncol*. [In press]

ABSTRACTS

- **Victory JH**, Smith EC, Ryan CE, Lambdin J, Sarvestani L, Friedman L, Eade A, Larrain C, Pu T, Luberice K, Ramamoorthy B, Rainey A, Hannah C, Smith K, Mabry D, Xie C, Davis JL, Blakely AM, Gulley JL, Schlom J, Monge C, Greten TF, Hernandez JM. Hepatic artery infusion pump (HAIP) therapy in combination with targeted delivery of IL-12 for patients with metastatic colorectal cancer or intrahepatic cholangiocarcinoma. American Society of Clinical Oncology Gastrointestinal Cancers Symposium, San Francisco, CA; Jan. 18-20, 2024. J Clin Oncol. 2024; 42 (3 suppl):TPS586. [Poster]
- **Victory JH**, Smith EC, Ryan CE, Lambdin J, Sarvestani L, Friedman L, Eade A, Larrain C, Pu T, Luberice K, Ramamoorthy B, Rainey A, Hannah C, Smith K, Mabry D, Xie C, Davis JL, Blakely AM, Gulley JL, Schlom J, Monge C, Greten TF, Hernandez JM. Hepatic artery infusion pump (HAIP) therapy in combination with targeted delivery of IL-12 for patients with metastatic colorectal cancer or intrahepatic cholangiocarcinoma. American Society of Clinical Oncology Gastrointestinal Cancers Symposium, San Francisco, CA; Jan. 18-20, 2024. J Clin Oncol. 2024; 42 (3 suppl):TPS586. [Poster]
- Pu T, Forsythe SD, Desai P, Joughin BA, Holewinski R, Anderson T, Larrain C, **Victory JH**, Sarvestani AL, Lin Y, Akmal SR, Kumar S, Nilubol N, Davis J, Blakely AM, Kleiner DE, Sadowski S, Del Rivero J, Yaffe MB, Hernandez JM. Phosphoproteomic mass spectrometry reveals a novel therapeutic target in well-differentiated gastroenteropancreatic neuroendocrine tumors. Society of Surgical Oncologists Annual Meeting, Atlanta, GA; Feb. 16-19, 2024. [Podium]
- Pu T, Forsythe SD, Desai P, Larrain C, **Victory JH**, Sarvestani AL, Lin Y, Akmal SR, Luberice K, Friedman L, Eade AV, Rainey A, Stepp H, Smith EC, Remmert K, Sinha S, Hannah C, Sadowski S, Del Rivero J, Hernandez JM. Patient-derived organoids reveal intrapatient drug response heterogeneity in pancreatic neuroendocrine liver metastases. Society of Surgical Oncologists Annual Meeting, Atlanta, GA; Feb. 16-19, 2024. [Poster]
- Larrain CM, Sarvestani L, Cabanas CM, Ryan C, Lambdin J, Rainey A, Lin Y, **Victory JH**, Pu T, Luberice K, Stepp H, Friedman L, Smith E, Peer CJ, Schmidt KT, Figg WD, Hernandez JM. A first step in the long road to bring new agents to hepatic artery infusion. Americas Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL; Apr. 4-7, 2024. [Poster]

PROFESSIONAL MEETINGS

- American Society of Clinical Oncology Gastrointestinal Cancers Symposium, San Francisco, CA; Jan. 18-20, 2024.
- Society of Surgical Oncologists Annual Meeting, Atlanta, GA; Feb. 16-19, 2024.

ERIN N. WALKER
University of South Carolina School of Medicine-Greenville

MENTOR

Desmond A. Brown, M.D., Ph.D., Head
Neurosurgical Oncology Unit, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke (NINDS)

Irreversible Targeting of the C-MYC/Topoisomerase I Axis in Glioblastoma: Dual Inhibition Using a Novel Indenoisoquinoline Inhibitor

Glioblastoma (GBM), the most common primary CNS malignancy, is notorious for its cellular and molecular complexity and uniform fatality. Overexpression of the c-MYC and Topoisomerase 1 (TOP1) oncogenes is implicated in more than 50% of human cancers. They are involved in the pathogenesis of glioblastomas with overexpression correlating with decreased overall median survival in glioblastoma patients. LMP744 is a non-camptothecin indenoisoquinoline small molecule inhibitor designed to target the C-MYC/TOP1 axis. The compound is inherently stable, has high brain penetrance, and irreversibly binds to its target, providing several advantages over the camptothecin class of drugs. We evaluated the anti-GBM efficacy of LMP744 in in vitro cell lines and in vivo murine tumor models.

Human glioblastoma cell lines GBMNS 12, GBMNS 28, GBMNS 43, dBT114, and dBT116, obtained from the Mayo Clinic, were treated with LMP744 and showed a dose-dependent decrease in viability with LD50 ranging between 50 and 100 nM compared to 100-200 µM following treatment with temozolomide in the same cell lines. Treatment resulted in a pro-apoptotic effect in exposed cells as well as S-phase arrest, as assessed by cell cycle analysis and apoptosis assays. Protein arrays and confirmatory western blots demonstrated increased CHK2 and decreased p53 and GSK-a/ß in treated cells. Orthotopic xenotransplantation via stereotactic injection of human glioblastoma cells (7×105 cells/4 µL) in nude mice showed exquisite sensitivity to LMP744 without adverse events. Administration of 20 mg/kg of LMP744 via tail vein injection resulted in total eradication of tumor signal on bioluminescent imaging.

These preliminary findings suggest that LMP744, and perhaps the class of non-camptothecin indenoisoquinolones, is a promising novel candidate for glioblastoma pharmacotherapy.

PUBLICATIONS

- **Walker EN**, Laws MT, Cozzi F, Quezado M, Brown DA, Burton EC. A case of disseminated spinal astroblastoma harboring a MAMLD1::BEND2 fusion. *Neuropathol*. 2023 Dec 21:10.1111/neup.12960. PMID: 38129983.
- Laws MT*, **Walker EN***, Cozzi FM, Ampie L, Jung MY, Burton EC, Brown DA. Glioblastoma may evade immune surveillance through primary cilia-dependent signaling in an IL-6 dependent manner. *Front Oncol*. 2023 Dec 18;13:1279923. PMID: 38188300. *Equal contribution
- **Walker EN**, Obeng M, Kaculini CM, Springer ML, Shamim Z, Brown DA. The rising interest of primary cilia in central nervous system malignancies: a bibliometric and altmetric analysis revealing the growth of a field. [Under review]
- **Walker EN**, Kaculini CM, Nusraty SA, Laws MT, Ampie LE, Breen K, Oishi M, Burton EC, Chaudhry H, Brown DA. Neurosurgical Oncology. In Neurosurgery Fundamentals, 2nd Edition, Chapter 13 [Under review]

PROFESSIONAL MEETINGS

- Congress of Neurological Surgeons Annual Meeting, Washington, D.C.; Sep. 9-13, 2023.
- Student National Medical Association, Annual Medical Education Conference, New Orleans, LA; Mar. 27-31, 2024.

SCOTT M. WILSON
Albert Einstein College of Medicine

MENTORS

Jason Elinoff, M.D., Head
Pulmonary Vascular Biology Section, Critical Care Medicine and Pulmonary Branch, National Heart, Lung, & Blood Institute (NHLBI)

Michael A. Solomon, M.D., MBA, Head
Cardiology Section, Critical Care Medicine Department, NIH Clinical Center (CC)

Targeting Inflammation in Pulmonary Artery Hypertension: A High-throughput Small Molecule Screen for Compounds Degrading Xeroderma Pigmentosum Group B Protein (XPB)

Pulmonary arterial hypertension (PAH) is a rare disease characterized by endothelial dysfunction, proliferative vascular remodeling, and a perivascular inflammation which is not directly targeted by available therapies. Spironolactone (SPL) improves survival in patients with left heart failure by improving endothelial function and reducing inflammation. SPL's anti-inflammatory effects are partly mediated by the proteasomal degradation of xeroderma pigmentosum group B protein (XPB), a subunit of the transcription factor IIH (TFIIH) core complex involved in inflammatory gene transcription. However, the concentrations of SPL necessary for XPB degradation in vitro are challenging to achieve clinically due to dose-dependent adverse effects. We sought to conduct a high-throughput small molecule screen to identify compounds capable of degrading XPB without the dose-limiting effects of SPL.

Endogenously expressed XPB protein was tagged with an 11-amino acid HiBiT luminescent reporter peptide using CRISPR-Cas9 gene editing. We screened three small molecule libraries, totaling over 19,000 compounds, with dose-response. Each compound was incubated for 4 and 24 hours to measure XPB-HiBiT reduction. Counter-screens were developed to detect cytotoxicity and assay interference.

HiBiT-tagged XPB remained susceptible to SPL-induced degradation and the peptide tag did not disrupt proper nuclear localization of XPB. High-throughput screening generated a list of "hits" that degrade XPB belonging to a variety of different drug classes, including inhibitors of PI3K, the L-type calcium channel, heat shock proteins, and several growth factors. One compound, epirubicin hydrochloride, a DNA topoisomerase inhibitor, was validated by Western blot and shown to reduce inflammatory signal transduction in two inflammatory reporter lines: Activator Protein-1 (AP-1) and Interferon-Stimulated Response Element (ISRE).

High-throughput small molecule screening unveiled a relatively exclusive group of compounds that may induce XPB degradation and potentially ameliorate inflammatory vascular remodeling in PAH. Lead compounds will be further evaluated in cellular models with a goal of future testing in pre-clinical models of PAH.

ABSTRACTS

- **Wilson SM**, Chen L, Lin Y, Henderson M, Marugan J, Cheng K, Elinoff JM. Targeting inflammation in pulmonary artery hypertension: A high-throughput small molecule screen for compounds degrading xeroderma pigmentosum group B protein. American Thoracic Society, San Diego, CA; May 18-22, 2024. Am J Respir Crit Care Med. 2024; 209:A6799. [Poster]

PROFESSIONAL MEETINGS

- MedStar Annual Heart Failure Summit, Washington DC; Oct. 21, 2023.
- Metropolitan DC Thoracic Society, Washington, DC; Apr. 16, 2024.
- American Thoracic Society, San Diego, CA; May 18-22, 2024.

AWARDS

- Best Basic Science Poster and Abstract, Metropolitan DC Thoracic Society, 2024

NATALIA S. YAKOBIAN
Saint Louis University School of Medicine

MENTOR

Rosa Nguyen, M.D., Ph.D., Lasker Clinical Research Scholar; Head
Pediatric Solid Tumor and Immunotherapy Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute (NCI)

IL-15 and IL-21 as Potent Enhancers of GD2 CAR T-Cell Therapy within the Tumor Microenvironment

Chimeric antigen receptor (CAR) T-cell therapy against solid tumors is limited by poor persistence and function within the immunosuppressive tumor microenvironment (TME). Prior studies suggest that interleukin (IL)-15 and IL-21 could enhance the efficacy of adoptive cell therapy. We developed an in vitro model to investigate the impact of IL-15 and IL-21 on T-cell biology and correlated these findings in a syngeneic mouse model.

GD2 is a disialoganglioside expressed on neuroblastoma (NB) and other tumors of neuroectodermal origin. GD2-CAR T-cells (GD2.CAR) were transgenically engineered to constitutively express IL-15 and IL-21 on the cell-surface. The murine MYCN-amplified GD2+ neuroblastoma (NB) cell line, 9464D.GD2, was grown in 3-dimensional (3D) spheroids and co-cultured with GD2-CAR T-cells (GD2.CAR) with or without membrane-tethered IL-15, IL-21, or both cytokines (GD2.CAR.15.21). Crude murine bone marrow (BM) cells were introduced to recreate the immunosuppressive cells typical of the NB TME. The 9464D.GD2 NB cells were also orthotopically implanted into C57BL/6 mice. Following effector cell treatment, tumor size was serially monitored by ultrasound. Dynamic cytokine profiles and effector polyfunctionality were assessed using the IMMUNOtron, a robotic platform that performs serial supernatant sampling. Additionally, the TME was characterized using multiome analysis and flow cytometry.

Tethered cytokines enhanced tumor lysis across all in vitro therapy groups. Although this effect was diminished in the presence of suppressive immune cells, serial cytokine analysis revealed that effectors armored with transgenic cytokines retained their polyfunctionality. Furthermore, GD2.15.21 cells maintained a stem cell memory phenotype, which correlated with highest efficacy in vivo.

T-cell-restricted delivery of IL-15 and IL-21 enhances GD2.CAR T-cell efficacy by promoting expansion and persistence of central memory CD8+ T-cells in vitro. This work highlights the potential of membrane tethered IL-15- and IL-21-augmented GD2-CAR T-cell therapy for patients with NB.

PUBLICATIONS

- Trautmann T, **Yakobian N**, Nguyen R. CAR T-cells for pediatric solid tumors: Where to go from here? *Cancer Metastasis Rev*. [Under review]

ABSTRACTS

- **Yakobian N**, Trautmann T, Rodriguez C, Okada R, Zhang L, Oh J, Nguyen R. Development of model systems to evaluate the immunological effects of cell-restricted delivery of IL-15. Annual Center for Cancer Research Fellows and Young Investigators Colloquium, NCI/CCR, Rockville, MD; April 18-19th, 2024. [Podium]
- **Yakobian N**, Trautmann T, Rodriguez C, Okada R, Zhang L, Gulley J, Oh J, Nguyen R. Cell restricted delivery of IL-15 & IL-21 for enhancement of CAR T-cell therapy within the tumor microenvironment. Children's Childhood Cancer Foundation Research Symposium, Greenbelt, MD; June 5, 2024. [Poster]

PROFESSIONAL MEETINGS

- Annual CCR Fellows and Young Investigators Colloquium, NCI/CCR, Rockville, MD; April 2024.

AWARDS

- Best Oral Presentation and Travel Grant Award, Annual CCR Fellows and Young Investigators Colloquium, 2024
- Best Poster Prize, Student Category, NCI POB Research Round-up, May 2024

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Electrical Stimulation of the Hippocampus Modulates High-Frequency Ripple Oscillations in Humans

High-frequency oscillation events, known as ripples, are involved in human memory encoding and retrieval. Numerous studies have demonstrated an increase in coupled ripples between the medial temporal lobe and association cortices during successful memory retrieval in awake humans. However, studies have yet to utilize brain stimulation to causally explore the role of ripples in human memory. While rodent studies have shown preliminary evidence that hippocampal stimulation holds the potential to disrupt or elongate ongoing ripples and even induce new ripples, we do not yet understand how stimulation modulates ripples in humans. We explored the feasibility of inducing ripples via hippocampal micro-stimulation in humans.

We collected human intracranial EEG recordings from neurosurgical epilepsy patients while delivering open-loop stimulation to the hippocampus at a range of microampere-level amplitudes. Nine distinct hippocampal locations in two patients were stimulated. On each qualifying electrode, we conducted a 5-minute stimulation sequence consisting of five cycles of a 30-second period without stimulation followed by a 30-second stimulation train with either 1 or 5 biphasic pulses (at 100 Hz) delivered once per second, with increasing amplitudes on each successive stimulation train.

We found significant elevations in ripple rate during stimulation trains compared to no-stimulation baselines, which increased with stimulation amplitude within and across patients. Alterations in cortical ripple rates coinciding with stimulation on select hippocampal electrodes were apparent. In such instances, the degree of ripple coupling between cortical sites and the stimulated hippocampal locations prior to stimulation correlated with the magnitude of cortical ripple rate increase in response to stimulation.

We provide direct evidence in humans that hippocampal stimulation locally amplifies high-frequency ripple oscillations. Further, we provide the first causal evidence probing the mechanisms of ripple-mediated dialogue between the hippocampus and association cortex. These results provide a basis for ripple-based modulation of memory in humans.

ABSTRACTS

- **Zarrin DA**, Mohan U, Fruchet O, Sundby K, Chapton JI, Xie W, Inati S, Zaghloul KA. The effect of real-time ripple oscillation interference on human memory retrieval. Context and Episodic Memory Symposium, Philadelphia, PA; May 30-31, 2024.

PROFESSIONAL MEETINGS

- American Association of Neurological Surgeons Annual Meeting, Chicago, IL; May. 3-6, 2024.
- Context and Episodic Memory Symposium Annual Meeting, Philadelphia, PA; May 30-31, 2024.