Medical Scientist Training Program

Retreat at Sunwood

October 2, 2022

Renaissance School of Medicine
Stony Brook University

Renaissance School *of* Medicine
Stony Brook University

Medical Scientist (M.D./Ph.D.) Training Program
41st Annual Retreat

Sunday, October 2nd, 2022

* student award presentations

9:45 AM – 10:15 AM Breakfast

10:15 AM – 10:25 AM Program Co-Director Introductory remarks

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10:30 AM – 11:10 AM Dean Peter Igarashi, General remarks and Q & A.

11:10 AM – 12:30 PM ***Session I (research talks [15' plus 4' Q&A])***

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Andrea Arreguin 5th Year Neuroscience Graduate Student
"Abnormal oligodendrogenesis in the corpus callosum of the mdx mouse"
Holly Colognato, Ph.D., Department of Pharmacological Sciences

Luke Torre-Healy 4th Year Biomedical Informatics Graduate Student
"Molecular subtyping in Pancreatic Ductal Adenocarcinoma"
Richard Moffitt, Ph.D., Department of Biomedical Informatics

John Yuen 4th Year Genetics Graduate Student
"Development of 5-FU-modified tumor suppressor microRNAs as a platform for novel microRNA-based cancer therapeutics"
Jingfang Ju, Ph.D., Department of Pathology

Josh Steinberg 5th Year Genetics Graduate Student
"3'-tRFs and H3K9me3: An intersection between small RNAs, transposons, and epigenetic modifications"
Rob Marteinssen, Ph.D., CSHL

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12:30 PM – 1:30 PM **Group Picture, Class Rep Elections, and Lunch**

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1:30 PM – 2:30 PM Preparing for and pursuing research-track / PSTP residencies panel

Ken Shroyer, M.D., PhD, Marvin Kuschner Professor and Chair of Pathology

Sandeep Mallipattu, M.D., FASN, Martin R. Liebowitz Professor of Medicine; Chief of Nephrology

Carine Mauer, M.D., Ph.D., Assistant Professor of Neurology; MSTP Associate Director
Director, Center for Tics and Tourette's Disorder

Georgios Georgakis, M.D., Ph.D., Assistant Professor of Surgery
Fellow, American College of Surgeons (FACS)

2:30 PM – 3:15 PM **Poster session**

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3:15 PM – 4:15 PM ***Session II (research talks)***

Alex Larkin 5th Year Molecular and Cellular Pharmacology Graduate Student
"*Understanding the Role of Cell Cycle State in Cancer Cell Extravasation***"**
Ben Martin, Ph.D. Department of Biochemistry and Cell Biology

Soma Kobayashi 4th Year Biomedical Informatics Graduate Student
"*A Computational Approach for the Histopathological Assessment of Colitis Mouse Models"*
Vince Yang, M.D., Ph.D, Department of Medicine &
Joel Saltz, M.D., Ph.D., Department of Biomedical Informatics

Allen Lee 5th Year Molecular and Cellular Pharmacology Graduate Student
"Investigating sphingolipid metabolism in the Golgi"
Yusuf Hannun, M.D, Department of Medicine

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E-Voting on posters and talks

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4:15 PM – 4:30 PM Presentation by Luke T-H on students' plans for representation and "offices"; discussion

Award Announcements and closing remarks

Alexander Cicala

Advisor: TBD

Status: 1st year MSTP student

Research Interests:
I am interested in studying the tumor stroma's role in tumor progression, immune infiltration - more specifically, conventional dendritic cells (cDC1 and cDC2) - and immunotherapeutic efficacy. I aim to understand why current immunotherapies are not effective against some tumors, as well as develop additional immunotherapeutic approaches.

Publications:

Deb G, **Cicala A**, Papadas A, Asimakopoulos F. Matrix Proteoglycans in Tumor Inflammation and Immunity. **Am J Physiol Cell Physiol**. 2022 Jul 25. doi: 10.1152/ajpcell.00023.2022. Epub ahead of print. PMID: 35876288.

Papadas A, **Cicala A**, Kraus S G., Arouz G, Deb G, Tong A, Deming D, Asimakopoulos F. (2022). Versican in Tumor Progression, Tumor–Host Interactions, and Cancer Immunotherapy. In: Kovalszky, I., Franchi, M., Alaniz, L.D. (eds) The Extracellular Matrix and the Tumor Microenvironment. **Biology of Extracellular Matrix, vol 11. Springer, Cham**. https://doi.org/10.1007/978-3-030-99708-3_5

Athanasios Papadas, Gauri Deb, **Alexander Cicala**, Adam Officer, Chelsea Hope, Adam Pagenkopf, Evan Flietner, Zachary T. Morrow, Philip Emmerich, Joshua Wiesner, Garrett Arauz, Varun Bansal, Karla Esbona, Christian M. Capitini, Kristina A. Matkowskyj, Dustin A. Deming, Katerina Politi, Scott I. Abrams, Olivier Harismendy, Fotis Asimakopoulos. Stromal remodeling regulates dendritic cell abundance and activity in the tumor microenvironment. **Cell Reports**. Volume 40, Issue 7, 2022, 111201, ISSN 2211-1247. https://doi.org/10.1016/j.celrep.2022.111201.

Wen Z, Rajagopalan A, Flietner ED, Yun G, Chesi M, Furumo Q, Burns RT, Papadas A, Ranheim EA, Pagenkopf AC, Morrow ZT, Finn R, Zhou Y, Li S, You X, Jensen J, Yu M, **Cicala A**, Menting J, Mitsiades CS, Callander NS, Bergsagel PL, Wang D, Asimakopoulos F, Zhang J. Expression of NrasQ61R and MYC transgene in germinal center B cells induces a highly malignant multiple myeloma in mice. **Blood**. 2021 Jan 7;137(1):61-74. doi: 10.1182/blood.2020007156. PMID: 32640012; PMCID: PMC7808014.

Papadas A, Arauz G, **Cicala A**, Wiesner J, Asimakopoulos F. Versican and Versican-matrikines in Cancer Progression, Inflammation, and Immunity. **J Histochem Cytochem**. 2020 Dec;68(12):871-885. doi: 10.1369/0022155420937098. Epub 2020 Jul 6. PMID: 32623942; PMCID: PMC7711242.

National Conference Posters/Presentations:

Papadas, A., Deb, G., Officer, A., Hope, C., Emmerich, P., Cicala, A., Wiesner J, Arauz G, Pagenkopf A, Matkowskyj K, Deming D, Politi K, Abrams S I., Harismendy O, and Asimakopoulos, F. (2021). 936 Stromal remodeling regulates dendritic cell abundance in the tumor microenvironment. *Journal for Immunotherapy of Cancer, 9*, A982. doi:https://doi.org/10.1136/jitc-2021-SITC2021.936

Papadas A, Flietner E, Morrow Z, Wiesner J, Cicala A, Pagenkopf A, Hope C, Rajagopalan A, Wen Z, Emmerich P, Deming DA, Miyamoto S, Hematti P, Callander N, Rakhmilevich AL, Otto M, Capitini CM, Zhang J and Asimakopoulos F; Abstract 5733: Versican proteolytic fragments (matrikines) synergize with STING agonists to elicit robust anti-tumor CD8+ T cell responses. *Cancer Res* 15 August 2020; 80 (16_Supplement): 5733. https://doi.org/10.1158/1538-7445.AM2020-5733

Papadas A, Flietner E, Morrow Z, Wiesner J, Cicala A, Pagenkopf A, Hope C L., Rajagopalan A, Wen Z, Emmerich P, Deming D, Miyamoto S, Hematti P, Callander N S., Rakhmilevich A, Otto M, Capitini C M., Zhang J and Asimakopoulos F. Versican Proteolytic Fragments (Matrikines) Regulate the Intratumoral Dendritic Cell Milieu In Vivo: Implications for in Situ Tumor Vaccination. Blood. Volume 134, Supplement 1, 2019. Page 1210. ISSN 0006-4971, https://doi.org/10.1182/blood-2019-131582

Papadas A, Flietner E, Morrow Z, Wiesner J, Cicala A, Pagenkopf A, Hope C L., Rajagopalan A, Wen Z, Emmerich P, Deming D, Miyamoto S, Hematti P, Callander N S., Rakhmilevich A, Otto M, Capitini C M., Zhang J and Asimakopoulos F. Reconstructing the Clonal and Mutational Architecture of Myeloma through Avian Leukosis Virus (ALV)-Mediated Genome Editing. Blood. Volume 132, Supplement 1, 2018. Page 4480. ISSN 0006-4971,https://doi.org/10.1182/blood-2018-99-115288

Dante Dullas

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract

Lack of resources to target bacterial infection is a pervasive and ever-compounding problem as new antibacterial agents are developed infrequently and as evolution renders current strategies ineffective. My previous research in the laboratory of Prof. Lynette Cegelski focused on elucidating the fundamental chemistry responsible for the assembly of bacterial biofilms, with emphasis on clinically relevant uropathogenic *E. coli* strains. Specifically, I worked on developing solid-state NMR methodology to investigate amyloid-polysaccharide interactions that define the structure of the *E. coli* insoluble extracellular matrix; additionally, I studied the biogenesis of bacterial amyloids and the mechanism of inhibition of novel small molecules. In my future research, I am interested in applying chemical and biophysical tools to interrogate intractable biological systems: I am fascinated by the physical properties and dynamism of cell membranes and membrane proteins, and I would like to pursue thesis work centered around these interests and their functions in cancer progression or immunological phenomena.

Rohini Guin

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract/Interests

I am primarily interested in applying immunomodulatory approaches to cancers, transplants, and infectious diseases. My most recent research experience at the NIH focused on evaluating the role of mTOR complexes in cancers and graft-versus-host disease (GVHD). My primary project focused on developing clonally-derived mTOR complex knockout lines in a human multiple myeloma model. I also worked to define a novel reciprocal regulatory pathway between the mTOR and Hippo signaling pathways in a lung cancer model. I supported ongoing efforts to determine the structure of mTOR Complex 3 using immmunoprecipitation assays and CryoEM. Further, I evaluated mTOR signaling in donor B-cells of allogeneic graft-recipient mice, and I studied mTOR Complex 3 activity in the development of oral GVHD. My undergraduate research at Emory University involved developing personalized therapeutic vaccines with metastatic tumor-specificity using a murine breast cancer (TNBC) model. I additionally supported senior colleagues on two additional projects. The first project aimed to evaluate the synergistic role of metformin and therapeutic vaccination, and the second project demonstrated the immunogenic potential of foreign peptides, such as fluorescent and luminescent markers, that are often used in research studies. I aim to synergize these experiences in my dissertation work, using preventive and treatment interventions to tune the immune system across disease contexts.

Publications:

Munoz L.E., Huang L., Bommireddy R., Sharma R., Monterroza L., **Guin R.N.**, Samaranayake S.G., Pack C.D., Ramachandiran S., Reddy S.J.C., Shanmugam M. and Selvaraj P. Metformin reduces PD-L1 on tumor cells and enhances the anti-tumor immune response generated by vaccine immunotherapy. Journal for ImmunoTherapy of Cancer. 2021. 9(11).

Huang L., Bommireddy R., Munoz L.E., **Guin R.N.**, Wei C., Ruggieri A., Menon A.P., Li X., Shanmugam M., Owonikoko T.K., Ramalingam S.S., Selvaraj P. Expression of tdTomato and luciferase in a murine lung cancer alters the growth and immune microenvironment of the tumor. PLOS ONE. 2021. 16(8).

Sabrina Hafeez

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract

Within the field of cancer biology, I am interested in multi-disciplinary and translational approaches to develop novel therapeutics for disease treatment. Throughout my undergraduate career, I investigated the impact of heme catabolism on triple negative breast cancer (TNBC) immune suppression by manipulating tumor-cell secreting enzymes and investigating the impact on macrophages. In the future, I hope to contribute to better understanding health disparities in breast cancer in order to effectively address them both in the clinic, and at the bench.

Publications:

Hafeez, SA and Williams, MM, Hammond, N, Christenson, JL, O'Neill, KO and Richer JK. Reversing an Oncogenic Epithelial-to-Mesenchymal Transition Program in Breast Cancer Reveals Actionable Immune-Suppressive Pathways. Pharmaceuticals (Basel). 2021 Nov 2;14(11):1122. doi: 10.3390/ph14111122.

Williams, MM, Christenson, JL, O'Neill, KI, **Hafeez, SA**, Ihle, CL, Spoelstra, NS, Slansky, JE, and Richer JK. MicroRNA-200c restoration reveals a cytokine profile to enhance M1 macrophage polarization in breast cancers. NPJ Breast Cancer. 2021 May 27;7(1):64. doi: 10.1038/s41523-021-00273-1.

Naheel Khatri

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract/Interests

I am currently interested in developing and applying computational tools to study the impact and importance of gene expression regulation has in neurodegenerative diseases at a multi-omics perspective. Previously, at Indiana University under Dr. Cary Lai, I worked in the nervous system to study the molecular mechanism in the activation of ErbB4, a protein whose malfunctioning has been implicated in Schizophrenia by Nrg3. Later, at the National Cancer Institute under Dr. Joana Vidigal, I took on a different field and studied the RNA-interference pathway, one of the many layers of tools that a mammalian cell uses to regulate its gene expression. I explored the catalytic activity of Ago3 and discovered that mice expressing catalytically inactive Ago3 tend to have phenotypes aligning with symptoms of Beckwith-Wiedemann Syndrome, and such phenotypes are exasperated further when both Ago2 and Ago3 are catalytically dead. Understanding how much we can learn about diseases by studying the epigenetic layers of gene expression regulation, I want to apply what I have learned in studying the RNAi pathway to investigate the changes in the gene expression profiles of cells in the context of neurodegenerative diseases while stepping my foot in the field of computational biology.

Isabelle Kwan

Advisor: TBD

Status: 1st Year MSTP, 1st Year Medical Student

Abstract

My current research interests are immunometabolism, microbiome, and T-mediated immunity. My undergraduate research evaluated neurological outcomes of different radiological treatments for vestibular schwannoma patients. I later continued my post-baccalaureate research at NCI, where I studied the role of the microbiome in homeostatic development and in cancer models treated with immune checkpoint blockade. Through my research, I explore new therapeutic and preventative strategies to deliver inclusive and precise care for patients.

Publications:

K. Mozaffari, D. Dejam, C. Duong, K. Ding, A. French, E. Ng, K. Preet, A. Franks, **I. Kwan**, H. W. Phillips, D. Kim, I. Yang. 2021. “Systematic review of Serum Biomarkers in Traumatic Brain Injury.” Cureus.

J. P. Shepperd, C. Lagman, T. Nguyen, H. Yokoi, S. H. Jeong, P. Luong, C. H. J. Chen, V. Ong, A. French, A. M. Franks, **I. Kwan**, M. Mekonnen, E. Ng, A. Evans, K. Preet, M. Udawatta, I. Yang. 2021. “Analysis of Academic Publishing Output among 1634 Successful Applicants in the 2011 – 2018 Neurosurgery Residency Match.” Journal of the Neurological Sciences.

K. Preet, V. Ong, J. P. Shepperd, M. Udawatta, C. Duong, P. Romiyo, T. Nguyen, **I. Kwan**, I. Yang. 2020. “Postoperative Hearing Preservation in Patients Undergoing Retrosigmoid Craniotomy for Resection of Vestibular Schwannomas: A Systematic Review of 2034 Patients.” Neurosurgery.

M. Udawatta, **I. Kwan**, K. Preet, T. Nguyen, V. Ong, J. P. Shepperd, C. Duong, P. Romiyo, P. Lee, S. Tenn, T. Kaprealian, Q. Gopen, I. Yang. 2019. “Hearing Preservation for Vestibular Schwannomas Treated with Stereotactic Radiosurgery or Fractionated Radiotherapy.” World Neurosurgery.

M. Udawatta, **I. Kwan**, T. Nguyen, V. Ong, J. P. Shepperd, P. Lee, S. Tenn, T. Kaprealian, Q. Gopen, I. Yang. 2019. “Post-radiation Hearing in Vestibular Schwannoma Patients.” UCLA Undergraduate Science Journal.

Preet, K., V. Ong, J. P. Shepperd, C. Duong, T. Nguyen, **I. Kwan**, I. Yang. 2018. “Postoperative Hearing Preservation in Patients Undergoing Retrosigmoid Craniotomy for Resection of Vestibular Schwannoma: A Meta-analysis of 2,088 Patients.” Neurosurgery.

Natalie Lo

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract

My undergraduate research in the field of DNA damage and repair focused on the fork protection complex protein, TIMELESS, and its role in protecting stalled replication forks to maintain genome stability. I am interested in further studying the mechanisms of other DNA repair pathways and their connection with cancer tumorigenesis to potentially develop cancer therapeutics that target these repair pathways.

Publications:

Weinheimer, A.S., Paung, Y., Rageul ,J., Khan, A., **Lo, N.,** Ho, B., Tong, M., Alphonse, S., Seeliger, M., Kim, H. (2022) Extended DNA binding interfaces beyond the canonical SAP domain contribute to the function of replication stress regulator SDE2 at DNA replication forks. *J. Biol. Chem.* 298 (8) 102268. https://doi.org/10.1016/j.jbc.2022.102268

Lo, N., Rageul, J., Kim, H. (2020) Roles of SDE2 and TIMELESS at active and stalled DNA replication forks. *Mol. Cell Oncol.* 8(1):1855053. doi: 10.1080/23723556.2020.1855053.

Rageul, J., Park, J.J., Zeng, P.P., Lee, E-A., Yang, J., Hwang, S., **Lo, N**., Weinheimer, A.S., Schärer, O.D., Yeo, J-E., Kim, H. (2020) SDE2 integrates into the TIMELESS-TIPIN complex to protect stalled replication forks. *Nature Communications.* 11:5495. doi.org/10.1038/s41467-020-19162-5

Julian Maceren

Advisor: TBA

Status: 1st Year MSTP Student

ABSTRACT

I am interested in using chemistry as a lens to examine biological systems and develop new therapeutics to treat and detect human diseases. As an undergraduate at the University of Rochester, I first developed this interest while working in a nanomedicine lab where I created polymeric drug delivery systems to administer antibiotics. During my post-graduate years at the Sloan Kettering Institute, I synthesized small-molecule antibiotics and pioneered a high-throughput screening assay to examine their ability to penetrate bacterial membranes. At Stony Brook, I hope to continue pursuing research at the interface of chemistry, biology, and medicine with a particular focus on understanding and treating neurodegenerative diseases.

Publications:

1. Sims, K. R.; **Maceren, J. P**.; Liu, Y.; Rocha, G. R.; Koo, H.; Benoit, D. S. W., Dual antibacterial drug-loaded nanoparticles synergistically improve treatment of Streptococcus mutans biofilms. *Acta Biomaterialia* 2020, 115, 418-431
2. Sims, K. R.; **Maceren, J. P**.; Strand, A. I.; He, B.; Overby, C.; Benoit, D. S. W., Rigor and reproducibility in polymer nanoparticle synthesis and characterization. *RSC Advances* 2020, 10 (5), 2513-2518
3. Fung, S. L.; Wu, X.; **Maceren, J. P**.; Mao, Y.; Kohn, J. "*In Vitro* Evaluation of Recombinant Bone Morphogenetic Protein-2 Activity for Regenerative Medicine," *Tissue Eng., Part C*, 2019

Margalit Mitzner

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract/Interests

I am interested identifying targets for improving treatment, management, and diagnosis of diseases with neurological and/or immunological pathologies, with the goal of integrating methods from multiple disciplines. Previously, I've studied limb regeneration in axolotl salamanders, pancreatic beta cell senescence in mice, and the organization and ultrastructure of the synaptic periactive zone at the *Drosophila* neuronal synapse. More recently, I've studied ocular diseases such as diabetic retinopathy and diabetic macular edema (DME), analyzing response to anti-VEGF injections in patient eyes with DME as well as working to develop methods to improve diagnosis and treatment of these conditions through identifying relevant biomarkers in the circulation and ocular fluids.

Publications:

Del Signore SJ, **Mitzner MG**, Silviera AM, Fai TG, Rodal AA. (2022). Quantitative Mapping of Synaptic Periactive Zone Architecture and Organization. BioRxiv. https://doi.org/10.1101/2022.06.16.496425

Fickweiler W, Park H, Park K, **Mitzner MG**, Chokshi T, Boumenna T, Gauthier J, Zaitsu Y, Wu I, Cavallerano J, Aiello LP, Sun JK, King GL. (2022). Elevated Retinol Binding Protein 3 Concentrations Are Associated with Decreased Vitreous Inflammatory Cytokines, VEGF, and Progression of Diabetic Retinopathy. Diabetes Care. https://doi.org/10.2337/dc22-0165.

Jacoba CMP, **Mitzner MG**, Cavallerano J, Silva PAS, Bhagat N, Zarbin MA, Aiello LP, Elmasry MA. (2022). Diabetic Macular Edema. American Academy of Ophthalmology, EyeWiki. https://eyewiki.org/Diabetic_Macular_Edema.

Fickweiler W, **Mitzner MG**, Jacoba CMP, Aiello LP, Sun JK. (2022). Circulatory Biomarkers and Diabetic Retinopathy: Focus on Racial and Ethnic Populations. Seminars in Ophthalmology. (in press)

Jacoba CMP, **Mitzner MG**, Robinson D, Silva PAS, Sun JK, Elmasry MA. (2022). Diabetic Macular Ischemia. American Academy of Ophthalmology, EyeWiki. https://eyewiki.org/Diabetic_Macular_Ischemia.

Madaleine Niznikiewicz

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract

I am interested in neurodegeneration and the role of the immune system in this process. My most recent research sought to elucidate, through application of genetic and biochemical techniques in *Saccharomyces cerevisiae,* the mechanisms by which prion formation is prevented, and controlled, by the eukaryotic cell. Specifically, I identified genetic relationships between a novel component of the yeast anti-prion system and other known and unknown actors found in previous research. In my earlier research I helped examine the role of inflammation in sleep.

Publications:
*(MSTP-supported publications indicated with an *)*

Wickner RB, Edskes HK, Son M, Wu S, **Niznikiewicz M**. Innate immunity to prions: anti-prion systems turn a tsunami of prions into a slow drip. Curr Genet. 2021 Jul 28. doi: 10.1007/s00294-021-01203-1. Epub ahead of print. PMID: 34319422.

Wickner RB, Edskes HK, Son M, Wu S, **Niznikiewicz M**. How Do Yeast Cells Contend with Prions? International Journal of Molecular Sciences. 2020; 21(13):4742. https://doi.org/10.3390/ijms21134742

Zielinski, M. R., Gerashchenko, D., Basheer, R., Strecker, R. E., **Niznikiewicz, M. M.**, & Johnston, A. M. (2018). 0033 Sleep Loss-induced Anxiety- And Depressive-like Behaviors Are Attenuated In Mice Lacking Nlrp3 Inflammasomes. Sleep, 41(suppl_1), A13–A14. https://doi.org/10.1093/sleep/zsy061.032

Gerashchenko, D., **Niznikiewicz, M. M**., Johnston, A. M., Basheer, R., Strecker, R. E., & Zielinski, M. R. (2018). 0032 Absence Of Nlrp3 Inflammasomes Reduces Cognitive Performance Impairments Induced By Sleep Loss. Sleep, 41(suppl_1), A13–A13. https://doi.org/10.1093/sleep/zsy061.031

Johnston, A. M., **Niznikiewicz, M. M**., Gerashchenko, D., Strecker, R. E., Basheer, R., & Zielinski, M. R. (2018). 0031 Nlrp3 Inflammasome Mediates Il-18 And Il-18 Receptor Responses To Sleep Loss. Sleep, 41(suppl_1), A13–A13. https://doi.org/10.1093/sleep/zsy061.030

Niznikiewicz, M. M., Gerashchenko, D., McKenna, J. T., Basheer, R., Strecker, R. E., McCarley, R. W., & Zielinski, M. R. (2017). 0021 SLEEP DEPRIVATION ACTIVATES NLRP3 INFLAMMASOMES IN NEURONS AND GLIA. Sleep, 40(suppl_1), A8–A8. https://doi.org/10.1093/sleepj/zsx050.020

William Sander

Advisor: TBA

Status: 1st year MSTP, 1st year medical student

Abstract:

In general, my research interests lie within the realm of understanding the biological and biochemical mechanisms of disease. Specifically, I would like to gear my graduate research towards investigating tumor microenvironments and studying patterns in cell growth and division. At UCLA I worked in the Courey Lab where I investigated the role of small ubiquitin-related modifiers (SUMO) in the Ras/MAPK pathway. We discovered preliminary evidence that SUMO contributes to Ras activation through a non-covalent interaction at a non covalent SUMO-interacting motif (SIM) and indirectly activating Raf through SUMOylation of the protein phosphatase, PP2A, which activates Raf by dephosphorylation of a serine residue. Ras and Raf activation are essential for downstream Ras/MAPK signaling and the recruitment of transcription factors involved in cell proliferation and apoptosis.

Shrey Thaker

Advisor: TBA

Status: 1st Year MSTP, 1st Year Medical Student

Abstract/Interests

My current research interests are related to the gastrointestinal tract and its autoimmune diseases. Specifically, I would like to explore pathologies that have been increasingly diagnosed, such as Inflammatory Bowel Disease, and further elucidate their multifactorial causes. My previous research has been under the umbrella of colon cancer, particularly through the lens of racial health disparity between Caucasian Americans and African Americans in Dr. Jennie Williams lab at Stony Brook University. My focus had been at the *in vitro* level, incorporating novel African American patient-derived colon cancer cell lines to assess the molecular basis for differential tumorigenesis and chemotherapeutic response. I assessed microRNA-34a and p53 tumor suppressing pathways, impact of dietary micronutrients (e.g. Folic Acid) on these pathways, and, most recently, comparing the standard of care fluoropyrimidine 5-fluorouracil with a novel compound called F10. I am fascinated with the impact of dietary molecules and potential synergy with pharmacological intervention. As such, I began to study a compound known as Lupeol which demonstrated promising preliminary synergy with the novel fluoropyrimidine F10 in treating both CA and AA colon cancer cells – a result that could develop into a methodology to overcome the clinically observed racial health disparity. By the same token, I would like to add to my experience with the increasingly common diagnosis of IBD and lifestyle/environmental factors that may help prevent or mitigate its severity.

Publications:

Williams, J., Paredes, J., & **Thaker, S**. (2022). Genetics of Colorectal Cancer Racial Disparities. In (Ed.), Gene Expression [Working Title]. IntechOpen. https://doi.org/10.5772/intechopen.1037

Eric Gerardi

Studying Age related diseases using the African Turquoise Killifish

Advisor: Chi-Kuo Hu, PhD, , Stony Brook University
Status: 2nd Year MSTP, 2nd Year Medical Student

Abstract

Aging is a major risk factor for almost all leading causes of death. Additionally, many diseases that decrease one's quality of life increase in incidence and prevalence with age. Recently, the African turquoise killifish (*Nothobranchius furzeri*) has emerged as an new model for studying aging. The advantages of N. Furzeri include its status as the shortest lived vertebrae, with a median lifespan of 6 months, and its ability to enter a dormant state known as diapause for up to two years. N. Furzeri can enter diapause during embryonic development, after developing a heartbeat and other organs. In order to robustly characterize this stage in this understudied emerging model, we are using RNAseq data on diapause vs. nondiapause fish to develop a fluorescent reporter line of fish that will fluoresce when exiting diapause. This is to allow for downstream cell sorting and further identification of genes involved in regulating dormancy using emerging techniques such as single-cell RNAseq. Additional future plans involve using the short-lived aspect of the killifish to study parkinson's disease, as N. Furzeri, unlike mice, exhibits endogenous alpha-synuclein accumulation and dopaminergic and cholinergic cell loss (Matsui et. al).

Publications:

Vargas KJ*, Colosi PL*, **Girardi E*** (*co-first authors),Chandra SS. a-Synuclein facilitates clathrin assembly in synaptic vesicle endocytosis. bioRxiv 2020.04.29.069344; doi:https://doi.org/10.1101/2020.04.29.069344

Crouse RB, Kim K, Batchelor HM, **Girardi E**, KamaletdinovaR, Chan J, Rajebhosale P,Pittenger ST, Role LW, Talmage DA, Jing M, Li Y, GaoX-B, Mineur YS, Picciotto MR.Acetylcholine is released in the basolateral amygdalain response to predictors ofreward and enhances the learning of cue-reward contingency.eLife 2020;9:e57335http://dx.doi.org/10.7554/eLife.57335

Snigdha Kanadibhotla

Advisor: Mehdi Damaghi, PhD, Department of Pathology

Status: 2nd Year Medical Student

Ovarian cancer is the fifth leading cause of death among people with uteruses in the United States, with 13,445 people dying of ovarian cancer in 2021 alone. Currently, first-line treatment of ovarian cancer includes cytoreductive surgery as well as treatment with platinum analogues and taxanes. However, treatment of this disease is hindered by the lack of effective early-detection screening options, as recurrence is a common issue among ovarian cancer patients diagnosed at a later stage. Targeted therapies such as Olaparib, which is a poly ADP-ribose polymerase inhibitor (PARPi), are recommended for recurrent cases of ovarian cancer and induce synthetic lethality in ovarian cancer cells. However, many patients develop resistance to PARPi. Several mechanisms of PARPi resistance have been elucidated in existing literature and this along with the vast amount of inter-tumor heterogeneity complicates a mechanistic approach to cancer resistance. Therefore, we propose approaching therapy resistance from an evolutionary standpoint with the aim of analyzing whether there are tradeoffs in the performance of certain traits in return for gaining a resistance phenotype. For example, our recent results show that there may be increased glutamine dependency among Olaparib-tolerant persister ovarian cancer cells. Relatedly, inhibiting glutaminase in the glutamine metabolic pathway increased ovarian cancer cell's sensitivity to PARPi. An understanding of the tradeoffs occurring in PARPi-resistant cells may help inform future treatments. In the present study, we analyze clonal dynamics and fitness of naïve ovarian cancer and ovarian cancer cells with the persister phenotype under glutamine-rich and -poor conditions at different concentrations of Olaparib.

Publications:

Grigsby, K.; Ledford, C.; Batish, T.; Kanadibhotla, S.; Smith, D.; Firsick, E.; Tran, A.; Townsley, K.; Reyes, K.-A.V.; LeBlanc, K.; Ozburn, A. Targeting the Maladaptive Effects of Binge Drinking on Circadian Gene Expression. *Int. J. Mol. Sci.* **2022**, *23*, 11084. https://doi.org/10.3390/ijms231911084

Abinash Kaur

Stress-induced APOBEC3 Expression Levels in Breast Cancer Cells

Advisor: Mehdi Damaghi, PhD
Department of Pathology, Stony Brook Cancer Center, Stony Brook Medicine, Stony Brook, NY, USA
Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, NY, USA

Status: 2nd Year Medical Student

Abstract

It has been shown that the hypoxic and acidic tumor microenvironment increases the genome instability and mutation rate in cancer cells. However, the mechanism of this mutation induction is not clear. APOBEC3B (A3B), a DNA cytosine deaminase, has been implicated as a somatic mutagenesis in a variety of solid cancer genomes and poor clinical outcomes. An upregulation of A3B in the HER2+ breast cancer subtype has been associated with an increased burden of mutations. Immunohistochemistry studies revealed that A3B, a predominantly nuclear protein, has increased expression in breast tumor tissue relative to normal breast tissue. Immunoblotting assays and quantitative PCR analyses were also performed for detection of A3B expression in cell lines adapted in acidic media, mimicking the high acid load in the tumor microenvironment. Hence, the dynamic A3B expression levels may be utilized as a predictive biomarker for breast cancer progression and treatment response.

Publications:

Muellers, S., Gonzalez, J., **Kaur, A**., Sapojnikov, V., Benzie, A., Brown, D., Parkin, D., Stockman, B. Ligand-Efficient Inhibitors of Trichomonas vaginalis Adenosine/Guanosine Preferring Nucleoside Ribohydrolase. ACS Infect. Dis., 2019, 5 (3), pp 345–352.

Stockman, B. J., **Kaur, A.**, Persaud, J. K., Mahmood, M., Thuilot, S. F., Emilcar, M. B., Canestrari, M., Gonzalez, J. A., Auletta, S., Sapojnikov, V., Caravan, W., Muellers, S. N. NMR-Based Activity Assays for Determining Compound Inhibition, IC50 Values, Artifactual Activity, and Whole-Cell Activity of Nucleoside Ribohydrolases. J Vis Exp. 2019 Jun 30; (148).

Erica Nebet

Advisor: N/A
1st Lab Rotation: Lonnie P. Wollmuth, PhD, Neurobiology and Behavior, Stony Brook University

Status: 2nd Year MSTP, 2nd Year Medical Student

Abstract

I have long been interested in the development of innovative treatments that target the underlying causes of neurological disorders, with a particular emphasis on epilepsy. My previous research has investigated the balance of excitatory and inhibitory activity in the hippocampus, a common seizure focus in the brain, to better understand seizure development and propagation. More specifically, I have studied the mechanism via which cannabidiol (CBD), the non-psychoactive component of Cannabis sativa, produces an anti-epileptic effect; excitingly, CBD is now offered as a treatment for patients with refractory epilepsy.

During my rotation in the Wollmuth lab, I worked on a project examining the M641I mutation in the GRIN1 gene. This de novo mutation was first identified in a pediatric patient with drug-resistant seizures and early-onset epileptic encephalopathy. We investigated how this mutation alters NMDA receptor function, especially on the level of a single channel, to produce such a phenotype. Mostly notably, we see that while N1/N2A-containing NDMA receptors have discrete open and closed states in the presence of glutamate, the N1(M641I)/N2A has an apparent sub-conductance state in addition to the traditional open and closed states seen in NMDA receptors. This provides some insight into how this point mutation alters the function of the N1/N2-containing NMDA receptors, providing some early evidence for how this mutation produces disease states in pediatric patients.

Publications:

Rosenberg E, Chamberland S, Bazelot M, **Nebet ER**, Wang X, McKenzie S, Jain S, Greenhill S, Salah A, Bailey S, Patra P, Rose R, Chenouard N, Sun SD, Jones D, Buzsáki G, Devinsky O, Woodhall G, Scharfman H, Whalley, B, Tsien, RW. Cannabidiol blocks a seizure-induced feedback loop driven by enhanced lipid signaling. *Neuron*. In Review.

Chamberland S, **Nebet ER**, Valero M, Hanani M, Egger R, Larsen SB, Eyring KW, Buzsaki G, Tsien RW. Brief synaptic persistently interrupts firing of fast-spiking interneurons. *Neuron*. In Review.

Matthew Obusan

Advisor: TBA

Status: 2nd Year MSTP, 2nd year Medical Student

Research Interest:

In general, I am interested in the integration of large multi-omic datasets with clinical data points to inform the development of personalized, targeted therapeutics, preventative treatments, and improved diagnostic tools. During my undergraduate years, my research focused on the influence of epigenetics on pre-mRNA splicing. During my gap years, I developed a multi-omic approach to aid in the development of cancer immunotheraputics that target cancer-specific alternative splicing events. My most recent rotation was in Dr. Ramana Davuluri's lab where I focused on exploring somatic mutations that could disrupt specific genes, leading to aberrant expression in cancer. Using somatic mutation data from the GDC (TCGA-LUAD) to identify cancer-specific mutations, I processed, analyzed, and prepared the data for subsequent analysis using the lab's deep learning model, dnaBERT.

Publications:

Leung, C. S., Douglass, S. M., Morselli, M., **Obusan, M. B.**, Pavlyukov, M. S., Pellegrini, M., & Johnson, T. L. (2019). H3K36 Methylation and the Chromodomain Protein Eaf3 Are Required for Proper Cotranscriptional Spliceosome Assembly. *Cell Reports*, *27*(13), 3760-3769.e4. https://doi.org/10.1016/j.celrep.2019.05.100

Mao, Z., Nesterenko, P. A., McLaughlin, J., Deng, W., Burton Sojo, G., Cheng, D., Noguchi, M., Chour, W., DeLucia, D. C., Finton, K. A., Qin, Y., **Obusan, M. B.**, Tran, W., Wang, L., Bangayan, N. J., Ta, L., Chen, C.-C., Seet, C. S., Crooks, G. M., … Witte, O. N. (2022). Physical and in silico immunopeptidomic profiling of a cancer antigen prostatic acid phosphatase reveals targets enabling TCR isolation. *Proceedings of the National Academy of Sciences*, *119*(31), e2203410119. https://doi.org/10.1073/pnas.2203410119

Nesterenko, P. A., McLaughlin, J., Cheng, D., Bangayan, N. J., Burton Sojo, G., Seet, C. S., Qin, Y., Mao, Z., **Obusan, M. B.**, Phillips, J. W., & Witte, O. N. (2021). Droplet-based mRNA sequencing of fixed and permeabilized cells by CLInt-seq allows for antigen-specific TCR cloning. *Proceedings of the National Academy of Sciences*, *118*(3), e2021190118. https://doi.org/10.1073/pnas.2021190118

Nesterenko, P. A., McLaughlin, J., Tsai, B. L., Sojo, G. B., Cheng, D., Zhao, D., Mao, Z., Bangayan, N. J., **Obusan, M. B.**, Su, Y., Ng, R. H., Chour, W., Xie, J., Li, Y.-R., Lee, D., Noguchi, M., Carmona, C., Phillips, J. W., Kim, J. T., … Witte, O. N. (2021). HLA-A∗02:01 restricted T cell receptors against the highly conserved SARS-CoV-2 polymerase cross-react with human coronaviruses. *Cell Reports*, *37*(13). https://doi.org/10.1016/j.celrep.2021.110167

Wang, L., Smith, B. A., Balanis, N. G., Tsai, B. L., Nguyen, K., Cheng, M. W., **Obusan, M. B.**, Esedebe, F. N., Patel, S. J., Zhang, H., Clark, P. M., Sisk, A. E., Said, J. W., Huang, J., Graeber, T. G., Witte, O. N., Chin, A. I., & Park, J. W. (2020). A genetically defined disease model reveals that urothelial cells can initiate divergent bladder cancer phenotypes. *Proceedings of the National Academy of Sciences*, *117*(1), 563–572. https://doi.org/10.1073/pnas.1915770117

Laurel Schappell

Advisor: TBA

Status: 2nd Year MSTP, 2nd Year Medical Student

Abstract / Interests

I am primarily interested in tissue engineering and mechanobiology in the context of the lungs and vasculature. My previous research focused on developing novel platforms to quantify lung mechanics during development and investigate the role of mechanical forces and external stimuli on vascular morphogenesis. Specifically, I have focused on the applications of these tools to better understand development-related pathologies such as bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH), which are known to exert deleterious effects on lung maturation, in part due to abnormalities in pulmonary vascular flow and functional lung mechanics.

Over the summer, I rotated in the Rubin lab in the bioengineering department where I was primarily focused on investigating the multisystem effects of low intensity vibration (LIV) as a potential therapeutic strategy for Duchenne muscular dystrophy (DMD). DMD is the leading genetic cause of death in males and is characterized by progressive muscle loss as well as multisystem decline affecting the bone, muscle, and nervous system. Current methods of treatment are associated with a wide range of side effects that are thought to exacerbate the progressive pathology of DMD, suggesting a beneficial role for non-pharmacologic therapies aimed at slowing the progression of disease. Exercise is known to promote the maintenance of muscle function in this population, but may not be feasible as patients decline and become more limited in mobility. Therefore, the goal is to implement LIV as a surrogate for exercise for DMD patients to slow the progression of multisystem decline. Using in vitro models of DMD, we have begun to investigate the effect of LIV on myoblast and oligodendrocyte cell maturation as an initial step in elucidating the potential of LIV to alter DMD muscle and brain pathology.

Publications:

Gilbert R, **Schappell LE,** Gleghorn JP. Defective mesothelium and limited physical space are drivers of dysregulated lung development in a genetic model of congenital diaphragmatic hernia. Development. 2021. 148(10).

Schappell LE, Minahan DJ, Gleghorn JP. A microfluidic system to measure neonatal lung compliance over late stage development as a functional measure of lung tissue mechanics. Journal of Biomechanical Engineering. 2020. 142(10): 100803.

Narayanan V, **Schappell LE**, Mayer CR, Duke AA, Armiger TJ, Arsenovic PT, Mohan A, Dahi KN, Gleghorn JP, Conway DE. Osmotic gradients in epithelial acini increase mechanical tension across E-cadherin, drive morphogenesis, and maintain homeostasis. Current Biology. 2020. 30(4): 624-633.

Kamil Taneja

Advisor: TBA
Status: 2nd Year MSTP, 2nd Year Medical Student

Abstract

Generally, I am interested in the application of genetic tools in neuroscience and cancer. In the past, I have worked in neuroimaging and eye diseases. My neuroimaging research was focused on understanding the cerebrovascular changes involved in stroke and aging. During my post-graduate years, I researched a wide range of ophthalmological diseases, such as retinitis pigmentosa, myopia, and uveal melanoma. This past summer, I studied the cellular dysfunction in the subventricular zone in Duchenne's Muscular Dystrophy in Dr. Holly Colognato's lab.

Publications

Jonathan P. Ling, Alexei M. Bygrave, Clayton P. Santiago, Rogger P. Carmen-Orozco, Vickie Trinh, Minzhong Yu, Yini Li, Jeong Han, **Kamil Taneja**, Ying Liu, Rochinelle Dongmo, Travis A. Babola, Patrick Parker, Lizhi Jiang, Patrick J. Leavey, Jennifer J. Smith, Rachel Vistein, Megan Y. Gimmen, Benjamin Dubner, Eric Helmenstine, Patric Teodorescu, Theodore Karantanos, Gabriel Ghiaur, Patrick O. Kanold, Dwight Bergles, Ben Langmead, Shuying Sun, Kristina J. Nielsen, Neal Peachey, Mandeep S. Singh, W. Brian Dalton, Fatemeh Rajaii, Richard L. Huganir, Seth Blackshaw. "Cell-Specific Regulation of Gene Expression Using Splicing-Dependent Frameshifting." *Nature Communications*. 2022. Accepted.

Karan Patel, **Kamil Taneja**, Aleem Mohamed, Sai Batchu, Hailey Hsiung, Conor Mott, Haley, Tornberg, Urvish K. Patel. "An Analysis of Epidemiological Factors in Heart Failure Outcomes." *Cureus*. 2022. DOI: 10.7759/cureus.22627

Yogita Kanan, Sean F. Hackett, **Kamil Taneja**, Mahmood Khan, Peter A. Campochiaro. "Oxidative stress-induced alterations in retinal glucose metabolism in Retinitis Pigmentosa." *Free Radical Biology and Medicine.* 2022. DOI: 10.1016/j.freeradbiomed.2022.01.032.

Monroe P Turner, Yuguang Zhao, Dema Abdelkarim, Peiying Liu, Jeffrey S Spence, Joanna L Hutchison, Dinesh K Sivakolundu, Binu P Thomas, Nicholas A Hubbard, Cuimei Xu, **Kamil Taneja**, Hanzhang Lu, Bart Rypma. "Altered linear coupling between stimulus-evoked blood flow and oxygen metabolism in the aging human brain." *Cerebral Cortex*. 2022. DOI: 10.1093/cercor/bhac057

Dong Won Kim, **Kamil Taneja**, Thanh Hoang, Clayton P. Santiago, Timothy J. McCulley, Shannath L. Merbs, Nicholas R. Mahoney, Seth Blackshaw, Fatemeh Rajaii. "Transcriptomic Profiling of Control and Thyroid-Associated Orbitopathy (TAO) Orbital Fat and TAO Orbital Fibroblasts Undergoing Adipogenesis." *Investigative Ophthalmological and Visual Sciences*. 2021. DOI: 10.1167/iovs.62.9.24

Kamil Taneja, Peiying Liu, Cuimei Xu, Monroe Turner, Yuguang Zhao, Dema Abdelkarim, Binu P Thomas, Bart Rypma, Hanzhang Lu. “Quantitative Cerebrovascular Reactivity in Normal Aging: Comparison Between Phase-Contrast and Arterial Spin Labeling MRI.” *Frontiers in Neurology*. 2020. DOI:10.3389/fneur.2020.00758

Kamil Taneja, Hanzhang Lu, Babu G Welch, Binu P Thomas, Marco Pinho, Doris Lin, Argye E Hillis, Peiying Liu “Evaluation of Cerebrovascular Reserve in Patients with Cerebrovascular Diseases Using Resting-State MRI: A Feasibility Study.” *Magnetic Resonance Imaging*. 2019. DOI:10.1016/j.mri.2019.03.003.

Trevor Van Brunt

Advisor: TBA
Status: 2nd Year MSTP, 2nd Year Medical Student

Area of interest: I am interested in studying the pathways of neuropsychiatric illnesses such as schizophrenia and the role of NMDA receptors in the modulation of these pathways.

Last summer I rotated in the Plotkin lab where I learned how to use optogenetics to target specific neurons and pathways for electrophysiological recordings. Additionally, I studied dopamine mediated long term potentiation in the striatum of OCD model mice.

Publications:

Baez, A., **Van Brunt, T**., Moody, G., Wollmuth, L. P., & Hsieh, H. (2020). Voltage dependent allosteric modulation of IPSCs by benzodiazepines. *Brain Res, 1736*, 146699. doi:10.1016/j.brainres.2020.146699

Kim, R. C., Goldberg, I., **Van Brunt, T**., Tul-Bushra, H., Batiste, R., Lane, A. H., & Hsieh, H. (2022). Juvenile Granulosa Cell Tumor Mimicking HAIR-AN in a 4-Year-Old: A Case Report. *J Clin Res Pediatr Endocrinol*. doi:10.4274/jcrpe.galenos.2022.2022-4-17

Zhao, Z., Kim, R. C., Tavernier, F., Choksi, R., **Van Brunt, T**., Davis, J. E., . . . Hsieh, H. (2022). A Young Child With Recurrent Pneumonia and Hemoptysis During the COVID-19 Pandemic. *Chest, 162*(2), e77-e80. doi:10.1016/j.chest.2022.03.053

Alice Wang

Advisor: TBA
Status: 2st year MSTP, 2st year Medical Student

Abstract/ Interests

I'm interested in studying the role of immunobiology in human diseases and identifying potential effective treatment targets. My previous research has focused on understanding inflammatory skin diseases, including sarcoidosis with clinical, scientific, and computational approaches.

Last summer, I rotated in Dr. Flaminia Talos's lab. I worked on organoid models of prostate cancer. I learned new laboratory techniques such as cell culturing and using a confocal microscope. I also analyzed a single cell RNAseq dataset from previous students to help identify future research directions.

Publications:

Damsky W., **Wang A.**, Kim D.J., Young B.D., Singh K., Murphy M.J., Clark A., Aya~~sun~~ R., Ryu C., McGeary M.K., Odell I.D., Fazzone-Chettiar R., Pucar D., Homer R., Gulati M., Miller E.J., Bosenberg M., Flavell R.A., King B., Inhibition of type 1 immunity with tofacitinib is associated with marked improvement in longstanding sarcoidosis, Nature Communications (2022)

Wang A., Fogel A.L., Murphy M.J., Panse G, McNiff J.M., Bosenberg M., Vesely M.D., Cohen J.M., Ko C.J., King B., Damsky W., Cytokine RNA in situ hybridization permits individualized molecular phenotyping in biopsies of psoriasis and atopic dermatitis, Journal of Investigative Dermatology, Innovations (2021)

Ko C.J., **Wang A.**, Panse G., Wang R., Bosenberg M., Damsky W., HPyV6- and HPyV7-negative parakeratosis and dyskeratosis in squamous cell carcinoma *in situ* and an isolated keratosis, Journal of Cutaneous Pathology (2021)

Mirza F., **Wang A.**, Damsky W., Ramachandran S., Cohen J., Dupilumab induced phenotype switch from atopic dermatitis to psoriasis is characterized by de novo IL-17A expression, British Journal of Dermatology (2021)

Singh K, **Wang A**, Heald P, McNiff J.M., Suozzi K, King B, Leventhal J, Damsky W., Treatment of angiolupoid sarcoidosis with tofacitinib ointment 2% and pulsed dye laser therapy, Journal of the American Academy of Dermatology Case Reports (2020)

Wang A, Rahman N, McGeary MK, Murphy M, McHenry A, Peterson D, Bosenberg M, Flavell R, King B, Damsky W, Treatment of granuloma annulare and suppression of pro-inflammatory cytokine activity with tofacitinib, Journal of Allergy and Clinical Immunology (2020)

Wang A, Singh K, Ibrahim W, King B, Damsky W, The promise of JAK inhibitors for treatment of sarcoidosis and other inflammatory disorders with macrophage activation: a review of the literature, Yale Journal of Biology and Medicine (2020)

Damsky W, **Wang A**, Olamiju B, Peterson D, Galan A, King B, Treatment of severe lichen planus with the JAK inhibitor tofacitinib, Journal of Allergy and Clinical Immunology (2020)

Danielle Xie

Advisor: TBD
Status: 2nd Year MSTP, 2nd Year Medical Student

Abstract

This summer I rotated in Dr. Kenneth Shroyer's lab to study prognostic proteomic signatures in pancreatic ductal adenocarcinoma (PDAC). I explored the technology of using laser capture microdissection to isolate specific tumor populations expressing Keratin-17, whose mechanistic role in promoting PDAC aggression is still being investigated. By isolating and identifying relevant proteins that are co-expressed with Keratin-17, we can begin to refine our mechanistic understanding of the role that Keratin-17 plays and design novel therapeutic approaches.

My prior research has also included immunogen development to induce broadly neutralizing antibodies against a difficult target, HIV-1, studying the enzymes implicated in mitochondrial respiratory chain disorders, and refining clinical and research models of tissue insulin sensitivity in teenagers with polycystic ovarian syndrome.

My major interests at the moment are in exploring novel therapeutic approaches for hard-to-treat cancers and the potential role of vaccine-delivered treatment modalities.

Publications:

(4) Ware, M., J. Kaar, C. Diniz Behn, K. Bartlette, A.-M. Carreau, D. Lopez‐Paniagua, A. Scherzinger, **D. Xie**, H. Rahat, Y. Garcia‐Reyes, K. Nadeau and M. Cree‐Green (2022). "Pancreatic fat relates to fasting insulin and postprandial lipids but not polycystic ovary syndrome in adolescents with obesity." Obesity 30: 191-200.

(3) Bartlette, K., A.-M. Carreau, **D. Xie**, Y. Garcia-Reyes, H. Rahat, L. Pyle, K. Nadeau, M. Cree-Green and C. Diniz Behn (2021). "Oral minimal model-based estimates of insulin sensitivity in obese youth depend on oral glucose tolerance test protocol duration." Metabolism Open 9: 100078.

(2) Carreau, A.-M., **D. Xie**, Y. Garcia‐Reyes, H. Rahat, K. Bartlette, C. Diniz Behn, L. Pyle, K. Nadeau and M. Cree‐Green (2020). "Good agreement between hyperinsulinemic‐euglycemic clamp and 2h oral minimal model assessed insulin sensitivity in adolescents." Pediatric Diabetes 21.

(1) Cree-Green, M., **D. Xie**, H. Rahat, Y. Garcia-Reyes, B. Bergman, A. Scherzinger, C. Diniz Behn, C. Chan, M. Kelsey, L. Pyle and K. Nadeau (2018). "Oral Glucose Tolerance Test Glucose Peak Time Is Most Predictive of Prediabetes and Hepatic Steatosis in Obese Girls." Journal of the Endocrine Society 2.

Dhivyaa Anandan

Understanding brain metastasis in pregnancy-associated breast cancer

Advisor: Camila dos Santos, CSHL

Status: 3rd year MSTP, 1st year Genetics graduate student

Pregnancy has been shown to have a dual effect on breast cancer risk and progression. Pregnancy is associated with increased protection against breast cancer long-term, especially with younger maternal age (<25 years). However, immediately after pregnancy, there is a transient risk of developing pregnancy-associated breast cancer (PABC) that has significantly worse survival outcomes compared to non-PABC. These worse survival outcomes are attributed to a higher incidence of metastatic disease in PABC. The physiological changes of the mammary gland during and after pregnancy and lactation result in extracellular matrix remodeling and the recruitment of macrophages to clear apoptotic debris, thereby creating an inflammatory pro-tumor microenvironment that facilitates invasion and metastasis.

Physiological changes during pregnancy also result in circulating factors secreted by the placenta, including vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) that increase blood brain barrier (BBB) permeability. Estrogen has also been shown to cause astrocytic and microglial changes that promote the formation of brain metastases. Given these physiological changes in the brain during pregnancy and the increased incidence of metastasis in PABC, we would expect to see brain metastasis occurring frequently in PABC. Interestingly, however, brain metastatic PABC is very rare, with only 6 cases being reported in the literature so far. We are interested in characterizing PABC cells and their interaction with the BBB and brain parenchyma to understand why PABC cells do not metastasize to the brain, and if there are properties of PABC cells that we can induce to non-PABC cells to confer protection against brain metastasis.

Publications

Lutze J, Kurkewich, J, Khan S, **Anandan D**, McNerney ME, Kron SJ. Multidimensional Epigenetic Analysis Reveals Transcription as a Primary Driver of Radiation Induced Double Strand Break Recognition. Blood. *Under review*.

Konecki SN, Khan S, Nam H, Bindokas V, **Anandan D**, Kurkewich J, Lutze J, Wolfgeher D, Kron SJ, McNerney ME. CUX1 cooperates with HDAC1 to facilitate nuclear condensation during terminal erythropoiesis. Blood. *Under review*.

Anandan D, Zhao S, Whigham AS. Factors Affecting Post-Anesthesia Care Unit Length of Stay in Pediatric Patients after an Adenotonsillectomy. Ann Otol Rhinol Laryngol. 2020 Nov;129(11):1071-1077.

Ghani MOA, Raees MA, Tang AR, **Anandan D**, Shannon CN, Bichell DP. Transdiaphragmatic tunneled Broviac catheters: Cost-effective perioperative central venous access in infants undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2020 May 4:S0022-5223(20)30976-4.

Khalayi Martha Aywa

Biochemical and structural characterization of human neutral sphingomyelinase 2 (nSMase2) enzyme

Advisors: Michael V. Airola, PhD and Yusuf A. Hannun, MD, Department of Biochemistry and Cell Biology, Stony Brook University

Status: 3rd year MD/PhD, 1st year Biochemistry and Structural Biology PhD Graduate Student

Abstract

Ceramide is a bioactive lipid that regulates various cellular processes such as growth arrest, apoptosis, inflammation, cell survival and differentiation. A major source of ceramide is the hydrolysis of sphingomyelin into ceramide and phosphocholine by sphingomyelinases. Neutral sphingomyelinase 2 (nSMase2) is the major neutral SMase in mammalian cells for stress-induced generation of ceramide. Although nSMase2 is widely expressed in the plasma membrane and Golgi apparatus of many mammalian cell types, its highest expression is in the brain. In particular, nSMase2 has been implicated in extracellular vesicle biogenesis as a critical regulator of exosomes that package and transfer pathogenic factors including metastasis-promoting microRNAs, tau protein and amyloid β. Here we show that we have successfully purified active human nSMase2 from *E. coli.* Going forward, we plan to crystallize and characterize effect of inhibitors on nSMase2 activity and study regulation by other phospholipids, including phosphoinositides.

Anthony Chesebro

Bridging Multiple Scales of Neural Modeling to Probe Function Under Energetic Constraints

Advisor: Lilianne R. Mujica-Parodi, PhD, Biomedical Engineering, Stony Brook University

Status: 3rd Year MSTP, 1st Year Graduate Student

Abstract

Broadly speaking, the goal of this project is to use a combination of mathematical models to leverage observations from the single neuron scale to predict functional changes within the entire brain. We are specifically interested in changes associated with insulin-resistance, which causes a decrease in glucose availability, leading to an energy deficit that causes instability in network function. Prior work in the lab has tied this instability more closely to insulin-depletion – and subsequent energy loss – by demonstrating that the administration of ketones in humans stabilizes the same networks. On-going work in the lab seeks to understand these effects at a single neuron level, where ketones are administered to brain slices during electrophysiology experiments.

Based on the preliminary results from these experiments, as well as from prior literature, we hypothesize that effect of energy depletion in the brain are predominantly caused by depleting the reversal potentials of ions, particularly Na^+, K^+, and Ca^{2+}, as these rely on ATP-driven pumps to maintain their reversal potentials across the membrane. With this in mind, we built a whole-brain model of connected neural masses, utilizing the Larter-Breakspear model (an extension of the Morris-Lecar equations), allowing us to manipulate ion gradients at a local mass level in a way consistent with our single neuron results while retaining the ability to generate whole-brain dyanmics.

This presentation focuses on probing the underlying mathematical structure of the Larter-Breakspear neural mass model under ion gradient depletion or hyperpolarization. We show that shifting the reversal potentials of Na^+, K^+, and Ca^{2+} alter the dynamics of the neural mass in ways consistent with spiking or bursting neuron models, and that specifically Na^+ and Ca^{2+} ion dynamics lie in an interesting space between two codimension 1 bifurcations (a Neimark-Sacker bifurcation and a period-doubling bifurcation, specifically), a feature has been demonstrated in small neuron ensembles as well. As this space contains inherently chaotic orbits, albeit with predictable periodicity, we then leverage these results to probe the synchronization between coupled oscillatory regions, analyzing the transition between aperiodic and periodic coupling. Having built this mathematical framework and tied it to the underlying neuronal dynamics, we can then extend it to whole-brain modeling to derive results on an EEG/fMRI scale.

Publications:
*(MSTP-supported publications indicated with an *)*

1. Lao, PJ, Boehme, AK, Morales, C, Laing, KK, **Chesebro, AG**, Igwe, K, Gutierrez, J, Gu, Y, Stern, Y, Schupf, N, Manly, JJ, Mayeux, R, Brickman, AM. Amyloid, cerebrovascular disease, and neurodegeneration biomarkers are associated with cognitive trajectories in a racially and ethnically diverse, community-based sample. *Neurobiol*. *Aging.* 2022 Sep;117:83-96.

2. ***Chesebro, AG.** *De Profundis:* Oscar Wilde's narrative of mental anguish. *Hektoen Int.* 2022 Winter; 14(1).

3. Igwe, KC, Lao, PJ, Vorburger, RS, Banerjee, A, Rivera, A, **Chesebro, AG**, Laing, KK, Manly, JJ, Brickman, AM. Automatic quantification of white matter hyperintensities on T2-weighted fluid attenuated inversion recovery magnetic resonance imaging. *Magn Reson Imaging*. 2022 Jan;85:71-79.

4. Rizvi B, Lao PJ, **Chesebro AG**, Dworkin JD, Amarante E, Beato JM, Gutierrez J, Zahodne LB, Schupf N, Manly JJ, Mayeux R, Brickman AM. Association of regional white matter hyperintensities with longitudinal Alzheimer-like pattern of neurodegeneration in older adults. *JAMA Netw Open*. 2021 Oct 1;4(10):e2125166.

5. Kreisl WC, Lao PJ, Johnson A, Tomljanovic Z, Klein J, Polly K, Maas B, Laing KK, **Chesebro AG**, Igwe K, Razlighi QR, Honig LS, Yan X, Lee S, Mintz A, Luchsinger JA, Stern Y, Devanand DP, Brickman AM. Patterns of tau pathology identified with 18F-MK-6240 PET imaging. *Alzheimers Dement*. 2021 May 31.

6. **Chesebro AG,** Amarante E, Lao PJ, Meier IB, Mayeux R, Brickman AM. Automated detection of cerebral microbleeds on T2*-weighted MRI. *Sci Rep.* 2021 Feb 17;11(1):4004.

7. Avila JF, Rentería MA, Jones RN, Vonk JMJ, Turney I, Sol K, Seblova D, Arias F, Hill-Jarrett T, Levy SA, Meyer O, Racine AM, Tom SE, Melrose RJ, Deters K, Medina LD, Carrión CI, Díaz-Santos M, Byrd DR, **Chesebro AG,** Colon J, Igwe KC, Maas B, Brickman AM, Schupf N, Mayeux R, Manly JJ. Education differentially contributes to cognitive reserve across racial/ethnic groups. *Alzheimers Dement*. 2021 Jan;17(1):70-80.

8. Gu Y, Beato JM, Amarante E, **Chesebro AG**, Manly JJ, Schupf N, Mayeux RP, Brickman AM. Assessment of leisure time physical activity and brain health in a multiethnic cohort of older adults. *JAMA Netw Open*. 2020 Nov 2;3(11):e2026506.

9. Turney IC, **Chesebro AG**, Rentería MA, Lao PJ, Beato JM, Schupf N, Mayeux R, Manly JJ, Brickman AM. APOE ε4 and resting-state functional connectivity in racially/ethnically diverse older adults. *Alzheimers Dement (Amst).* 2020 Sep 22;12(1):e12094.

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11. Domínguez-Vivero C, Wu L, Lee S, Manoochehri M, Cines S, Brickman AM, Rizvi B, **Chesebro AG**, Gazes Y, Fallon E, Lynch T, Heidebrink JL, Paulson H, Goldman JS, Huey E, Cosentino S. Structural Brain Changes in Pre-Clinical FTD MAPT Mutation Carriers. *J Alzheimers Dis*. 2020;75(2):595-606.

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BOOK CONTRIBUTION

1. Associate Author. Le, T, Bhushan, V, Sochat, M, (eds.). *First Aid for the USMLE Step 1 2023.* New York: McGraw-Hill. In Press.

Tiffany Kim

Human Cerebral Organoid Transplantation for the Treatment of Alzheimer's Disease

Advisor: Donghui Zhu, PhD, Biomedical Engineering, Stony Brook University

Status: 3rd Year MSTP, 1st Year Biomedical Engineering Graduate Student

Abstract

Alzheimer's disease (AD) is the most common cause of dementia, yet effective treatment options for AD are limited. These limitations in current treatments have led to the exploration of stem cell therapeutics as a potential treatment for AD. Stem cell therapeutics have shown promising cognitive improvements in animal models and are currently being studied in ongoing clinical trials. However, animal studies have shown that injected stem cells have a low engraftment efficiency and limited long-term survival that can likely be explained by the lack of cytoarchitecture of the delivered cells. Alternatively, we believe that implanted cerebral organoids (COs) will overcome the limited engraftment and survival rates of injected stem cells. COs are self-organized 3D cultures mimicking neurodevelopment seen in vivo. Their applications as treatments in animal models of traumatic brain injury (TBI) and strokes have shown their promise in regenerative medicine applications. Additionally, their intrinsic architecture provides them with stability to last longer in vivo than stem cells. Our central hypothesis is that implanted COs in the hippocampus of mouse models of AD will provide cognitive improvements and will have a superior engraftment efficiency and long-term survival to injected stem cells.

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Timothy Maher

The Role of Diet and Metabolism on Immunity Against Cancer

Advisor: Semir Beyaz, Ph.D., Cold Spring Harbor Laboratory

Status: 3rd Year MSTP, 1st Year Genetics Graduate Student

Abstract

Diet is one lifestyle factor that is known to play a significant role in the overall health and wellbeing of humans. Obesity increases the risk for many diseases and health complications, including some cancers. Our cells are constantly detecting changes in their environment and adapt to these signals, such as nutrients. The role of what specific diets that may lead to obesity and contribute to cancer incidence is unclear. Thus, our group has examined various high fat diets to understand the affect at the cellular and molecular level at steady state and in the context of cancer progression. Our lab has already been able to show high fat diet influences intestinal stem cells MHC-II expression, and thus alters immune cell response that contributes to increased intestinal tumorigenesis. Utilizing different high fat diets allows us to characterize the impact certain nutrients have on immune cells function in cancer immunity. In addition to in vivo models, our lab has also established various in vitro organoid models to isolate these causal mechanisms. Ongoing experiments are allowing us to identify cell-state specific gene expression and metabolic program changes in response to diet. Understanding how these immune cells alter their pathways to diet has also revealed which adaptations are important for immunity against cancer, such as specific transcriptional programs. Overall, through dietary perturbations we hope to find specific mechanisms that can be therapeutically targeted to enhance immune response to cancer.

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Cuilee Sha

A titratable mouse model of necrotizing enterocolitis

Advisor: Helen Hsieh, MD, PhD, Department of Surgery (Primary Mentor),

Lonnie Wollmuth, PhD, Department of Neurobiology and Behavior (Co-Mentor)

Department: Molecular and Cellular Pharmacology

Status: 3rd Year MSTP; 1st Year Graduate Student

Abstract

Necrotizing enterocolitis (NEC), a severe inflammatory gastrointestinal disease that commonly affects premature babies, is the leading cause of mortality in neonatal intensive care. Clinical findings with NEC include physical symptoms, such as hematochezia, emesis, and lethargy, as well as radiological findings, such as pneumatosis intestinalis, portal venous gas, and intestinal distension. NEC severity is graded with the Bell's classification system, from stage I mild NEC to stage III severe NEC. Only 50% of infants with NEC survive, and those that do experience developmental delay and neurocognitive deficits, whose severity correlates with disease severity. How NEC affects brain development and the cellular mediators required for this process remain unclear. Current murine models use a range of methods to induce NEC, including hypoxia, hypothermia, and hyperosmolar feeds. These murine NEC models, however, fail to control the severity of the induced NEC and cannot emulate mild NEC, which constitutes most surviving patients. We took advantage of a recently developed NEC model, which uses the osmolar agent dextran sodium sulfate (DSS) to induce NEC in postnatal mice. Here, we establish a novel murine NEC model that replicates various NEC stages by using DSS in the following concentrations: 0% (control), 0.25%, 0.5%, 1%, and 2%. We measured graded NEC induction by evaluating gross intestinal characteristics, such as dilation, color, and friability, and by immunostaining intestinal tissue for cell behavior with Ki-67 and cleaved caspase-3. We expanded the protocol to measure relevant clinical information during our 60-hour feed cycle, which included weight and behavior. Our NEC model demonstrated inflammatory cytokine (TNF) elevation, confirming an induced inflammatory response. Finally, we assessed the inflammatory cerebral response by qualifying microglia morphology; activated microglia were present even in the mildest NEC. Altogether, we demonstrate that our NEC model is crucial to understanding all NEC stages and advances our knowledge of mild NEC and importance of the gut-brain axis during disease progression. This tool will advance therapies to protect mild and severe NEC cases from further complications, significantly helping treatment of NEC in the NICU.

Publications:

*(MSTP-supported publications indicated with an *)*

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Sophie Shifman

Advisor: Stella Tsirka, PhD, Molecular & Cellular Pharmacology, Stony Brook University

Status: 3rd Year MSTP, 1st Year Graduate Student

Abstract

My previous research has focused on elucidating the effects of antidepressant on neurogenesis in the hippocampus of female mice across their reproductive cycle, on revealing cellular mechanisms of resistance to therapy in various cancer histologies via the MAPK and PI3K pathways, and on investigating new approaches in targeted and combinational therapies for tumors resistant to conventional treatment. Going forward, my work will focus on exploring the interactions between cancer cells and myeloid cells in the brain tumor microenvironment in glioblastoma, a malignant brain tumor with a dismal prognosis. In studying how cancer cells reprogram immune cells, such as microglia, bone marrow-derived macrophages (BMDMs), T cells, etc. in their environment to their own benefit using both human and mouse cell as well as in vivo murine models, and characterizing cancer stem cell propagation and autophagy as part of the inevitable process leading to relapse after initial treatment, we aim to shed light on mechanisms of resistance to the current standard of care of GBM and how to potentially overcome them.

Publications:

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Erin Sipple

Advisor: Michelino Puopolo, PhD, Program in Neurology, Stony Brook University

Status: 3rd Year MSTP, 1st Year Graduate Student

Abstract

Chronic neuropathic pain affects up to 60-70% of people leaving with spinal cord injury (SCI). Recent work from our laboratory showed that the increased activity of T-type calcium channels induced by the injury is responsible for driving nociceptors' hyperexcitability and for promoting the development/maintenance of SCI-induced neuropathic pain (SCI-pain) (Lauzadis et al., J Neurosci. 2020 Sep 16;40(38):7229-7240). Previous reports have shown that endocannabinoids inhibit calcium channels, raising the possibility that inhibition of T-type calcium channels in nociceptors by 2-arachidonoylglycerol (2-AG) and/or anandamide (AEA) may reduce nociceptors' hyperexcitability and SCI-pain. The goal of this work is to test the hypothesis that inhibition of endocannabinoid catabolizing enzymes *monoacylglycerol* lipase (MAGL) and fatty acid amide hydrolase (FAAH), with subsequent elevation of 2-*AG* and AEA levels, respectively, will reduce the activity of T-type calcium channels in nociceptors and rescue SCI-pain. SD rats (300-350 g) were used in this study. SCI was performed by a midline spinal cord contusion at T10 by using an Infinite Horizon Impactor (150 kilodynes, 1s dwelling time). The mechanical allodynia was assessed with the von Frey filaments by using the up-down method with the 50% threshold. The conditioned place preference (CPP) paradigm was used to assess the spontaneous pain. The action potential clamp technique was used in dissociated dorsal root ganglia (DRG) neurons isolated from SCI and sham rats to measure the interspike T-type calcium charge (sensitive to 1 µM TTA-P2) from the afterhyperpolarization of the first action potential to -50 mV before the second action potential. The 50% mechanical threshold dropped from 19.5±8.2 g (pre-injury) to 13.6±5.6 g (post-SCI). Vehicle injection changed the 50% mechanical threshold to 15.2±3.5 g. MJN110 (10 mg/kg, MAGL inhibitor) increased the 50% mechanical threshold to 37.7±10.7 g at 1-hour post-injection and to 21.4±4.7 g (n=6) at 3-hour post injection. PF3845 (10 mg/kg, FAAH inhibitor) increased the 50% mechanical threshold from 13.6±5.6 g (post-SCI) to 27.7±4.7 g at 1-hour post-injection and to 27.0±4.8 g at 3-hour post-injection. In voltage clamp experiments in nociceptors isolated from the same cohort of rats the interspike T-type calcium charge dropped from 75±14 pC/pF (n=18) in control to 39±13 pC/pF (n=14) in the presence of 5 µM MJN110 and to 9±2 pC/pF (n=12) in the presence of 5 µM PF3845. Taken together, our data suggest that inhibition of endocannabinoid catabolizing enzymes MAGL and/or FAAH reduces the activity of T-type calcium channels in SCI-nociceptors and rescues SCI-pain.

Kyungyoon (Yoon) Yoo

Characterization of Mitochondrial Changes Contributing to Age-Associated Antifungal Tolerance in C. neoformans Cells

Advisor: Bettina Fries, MD, Professor of Medicine, Microbiology and Immunology

Status: 3rd Year MSTP, 1st Year Microbiology & Immunology Graduate Student

Abstract

Cryptococcus neoformans is an opportunistic yeast that infects immunocompromised individuals; especially AIDS patients and organ transplant recipients. It is spread by inhalation of aerosolized spores, and upon infecting the host, it disseminates to the central nervous system, where it can cause meningoencephalitis. Even though the combination of proper immune response and/or antifungal therapies kills the pathogen, some *C. neoformans* cells can survive intracellularly in macrophage, replicate and persist for long periods, leading to treatment failure. This process of replication where the fungus goes through a series of asymmetric mitotic divisions is called replicative aging. In the course of these divisions, the aging mother cells increasingly manifests phenotypic changes, with older cells being more resistant to phagocytosis and antifungals. Because this resilient phenotype is selected during chronic infection, our understanding of these old cells may help identify novel targets for treatment.

Mitochondria produce the bulk of cellular ATP, and they are crucial in adapting to surrounding environments, maintaining dynamic communications with other organelles and orchestrate a range of cellular responses. In other fungi, there are age-associated mitochondrial changes that help the cell adapt to various physiological stresses and promote antifungal resistance. I have characterized various changes that occur the mitochondria in old *C. neoformans* cells. 10 generation-old *C. neoformans* cells (when compared to 1-3 generation-old cells), have decreased mitochondrial membrane potential, increased mitochondrial mass and produce more mitochondrial ROS. Additionally, while the mitochondria from young cells show a tubular morphology, the ones from old cells become clumped. Furthermore, these old cells have higher ATP levels, which is able to fuel drug efflux pumps and synthesis of ergosterol, the most important membrane sterol in fungal cells. This work highlights mitochondrial changes that could explain the enhanced resistance of old cells to antifungals.

Publications:

Moon K, Sim M, Tai CH, **Yoo K**, Merzbacher C, Yu SH, Kim DD, Lee J, Förstner KU, Chen Q, Stibitz S, Knipling LG, Hinton DM. Identification of BvgA-Dependent and BvgA-Independent Small RNAs (sRNAs) in Bordetella pertussis Using the Prokaryotic sRNA Prediction Toolkit ANNOgesic. Microbiol Spectr. 2021 Oct 31;9(2):e0004421.

Christopher Ashdown

The Effect of Low Intensity Vibration on Human T Cells

Advisor: Clint Rubin, PhD, Biomedical Engineering, Stony Brook University

Status: 4th Year MSTP, 2nd Year Graduate Student

Chimeric antigen receptor T cell therapy, also known as CAR-T therapy, is a rapidly evolving immunotherapy that has the potential to revolutionize cancer treatment. Nevertheless, autologous CAR-T therapy remains a relatively inefficient process that is confounded by prohibitively long ex-vivo expansion periods and loss of effector function upon reintroduction to the patient. Thus, strategies which speed up the manufacturing process and help maintain T cell effector function would dramatically increase the speed and efficacy of CAR-T therapy. Mammalian cells have well-conserved mechano-sensing and mechanoresponse mechanisms, the aggregate of which provide an important regulatory component for a variety of cellular responses. Our lab has spent decades developing Low-Intensity Vibration (LIV) as a mechanical regime modeled after the physiologic, high-frequency muscle contractions generated during exercise. We have previously found that in Mesenchymal Stem Cells (MSCs) LIV promotes both proliferation and differentiation. Our lab and others have identified that LIV acts on MSCs through conserved cytoskeletal components (focal adhesions and LINC complex proteins) as well as through nearly ubiquitous cell signaling pathways (AKT-GSK3b pathway). In T cells, the AKT-GSK3b pathway plays a particularly important role as it is involved in CC28 co-stimulation and subsequent activation of the T cell. My preliminary results have shown that T cells are in fact mechanosensitive to vibration. We have demonstrated that LIV applied to in-vitro culture can increase T cell number by 30% over 5 days and alter the expression of activation-associated surface receptors such as CD62L, CD69, and PD-1. Furthermore, we found that the addition of an AKT inhibitor reduced the LIV mediated growth effects by more than 60%, indicating that the AKT-GSK3b pathway does play a role in T cell mechanosensitivity. Ultimately, t*his work would represent a novel method to manipulate the growth and functionality of T cells, which would have implications for improving both the speed of CAR-T manufacturing and the efficacy of treatment*.

Publications:

(MSTP-supported publications indicated with an *)

1. ******(Submitted)* Chan M.E., Strait L.K., **Ashdown C.P.**, Pasumarthy S., Hassan A., Crimarco S., Singh C., Patel V.S., Rubin C.T., Low-intensity mechanical signal parameters promote proliferation in a cell-specific manner: Tuning a non-drug strategy to enhance tissue engineering and biomanufacturing endpoints.
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Joseph Bae

Pre-treatment CT Radiomics Predicts Survival in Chemo-Immunotherapy-treated Small Cell Lung Cancer

Advisor: Prateek Prasanna, PhD, Biomedical Informatics, Stony Brook University

Status: 4th Year MSTP, 2nd Year Biomedical Informatics Graduate Student

Abstract

The addition of checkpoint inhibitors to chemotherapy in SCLC patients provides only a modest benefit, with a median patient survival of 12 months. Development of non-invasive imaging predictors to identify patients most likely to benefit from chemo-immunotherapy would enable personalized management of SCLC.

A cohort of extensive-stage SCLC patients treated with atezolizumab, carboplatin, and etoposide were identified, and pre-treatment CT scans were curated. The axial slice at the level of the carina was identified and center-cropped. 3D radiomic features were extracted for downstream analysis. After feature selection, the most discriminative radiomic feature was used to train and evaluate a random forest machine classifier for mortality prediction using leave-one-out cross-validation (LOOCV). A baseline classifier was also trained using clinical variables. LOOCV mortality probabilities were recorded for each patient and used to stratify patient risk. Overall survival analysis was performed using Cox proportional hazards modeling.

Our results demonstrated that patient survival following chemo-immunotherapy in SCLC can be predicted using computational analysis of treatment-naive images. Studies of larger patient cohorts to further understand the relationship between imaging signatures and patient survival in SCLC could potentially leading to improved personalized disease management.

Publications: (All publications MSTP-supported)

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Santiago Espinosa de los Reyes

Identification of novel NRF2 functional binding partners in NSCLC

Rotation Advisor: Christopher Vakoc, M.D.,Ph.D
Department: Genetics
Status: 4th Year MSTP, 2nd Year Graduate Student

Abstract

Lung cancer is the leading cause of cancer death in the world. Of the two major types of lung cancer, non-small cell lung cancer (NSCLC) is the most common accounting for 80-85% of all cases. Although treatment options for this disease have improved, the 5-year relative survival rate remains low at 27%, highlighting the need for more targeted therapies. A substantial amount of evidence over the past decade has validated numerous transcription factors as strong selective dependencies in various cancers. In NSCLC, the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor, a master regulator of cellular antioxidant response, has been established as one of these selective transcriptional dependencies and a potential candidate for future small molecule targeting. To exploit this vulnerability, a better understanding of the functional protein-protein interactions between NRF2 and its cofactors is required. We, therefore, conducted a genome-wide marker-based CRISPR screen and nominated potential functional binding partners of NRF2. We aim to validate and further characterize the interaction between NRF2 and these novel binding partners to better understand how NRF2 promotes the cancer state in NSCLC.

Publications:
*(MSTP-supported publications indicated with an *)*

Gong, R., Jiang, F., Moreland, Z. G., Reynolds, M. J., **de Los Reyes, S. E**., Gurel, P., ... & Alushin, G. M. (2022). Structural basis for tunable control of actin dynamics by myosin-15 in mechanosensory stereocilia. *Science advances*, *8*(29), eabl4733.

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Sarker, M., Lee, H. T., Mei, L., Krokhotin, A., **de los Reyes, S. E.**, Yen, L., ... & Campbell, S. L. (2019). Cardiomyopathy Mutations in Metavinculin Disrupt Regulation of Vinculin-Induced F-Actin Assemblies. *Journal of molecular biology*, *431*(8), 1604-1618.

Gilmore, S. P., Gonye, A. L., Li, E. C., **de los Reyes, S. E.**, Gupton, J. T., Quintero, O. A., & Fischer- Stenger, K. (2018). Effects of a novel microtubule-depolymerizer on pro-inflammatory signaling in RAW264. 7 macrophages. *Chemico-biological interactions*, *280*, 109-116

Jakub Kaczmarzyk

Advisor: Joel Saltz (Biomedical Informatics)

Status: 4th Year MSTP, 2nd Year Graduate Student

Abstract

Population-based screening programs have improved breast cancer survival overall but have also led to the overtreatment of patients. Common treatments include surgery, radiotherapy, chemotherapy, and hormone therapy, and each has associated toxicities. Survival prognosis is an important factor in determining the aggressiveness of treatment, but current methods for prognostication of survival in breast cancer are insufficient for some patient subpopulations and disease subtypes. Without robust and generalizable methods for prognosis, personalized care of breast cancer will be greatly inhibited. Digital pathology has emerged as a rich data modality to characterize a patient's cancer. These images are the gold standard for cancer diagnosis and contain information at the patient-level, tissue-level, and cell-level. In parallel, deep learning has revolutionized image processing, and digital pathology images are the ideal data modality for deep learning algorithms. These methods, however, are prone to overfitting and learning spurious patterns. Multi-task learning has emerged as a way to attenuate overfitting and guide deep learning models to learn causal patterns in data. Despite this, multi-task deep learning has not been explored in the context of breast cancer survival. **My PhD work tests the hypothesis that incorporating prediction of morphological and molecular characteristics into a deep learning algorithm will improve the performance and generalizability of survival predictions.** This hypothesis will be addressed through the following Specific Aims. In the first aim, the effect of adding morphology characterization tasks to a survival prediction algorithm will be evaluated. In the second aim, the contribution of molecular characterization tasks in a survival prediction algorithm will be evaluated. This project utilizes digital pathology images to predict a patient's survival, while constraining the model to jointly learn a representation of the pathology predictive of cell locations, cell types, commonly mutated genes, and hormone receptor status. This research is significant because (1) it is the first to propose using multi-task deep learning for breast cancer survival prognosis, (2) it addresses the lack of reproducibility in deep learning algorithms applied to medical images, and (3) it will provide a solid groundwork for developing generalizable deep learning models for the prediction of cancer patient outcomes.

Yunyoung Kim

Cancer-associated mutations of Eph receptor tyrosine kinases

Advisor: W. Todd Miller, PhD, Physiology and Biophysics, Stony Brook University

Status: 4th Year MSTP, 2nd Year Graduate Student

Abstract

The Eph receptors are the largest family of receptor tyrosine kinases in mammals, with 9 EphA receptors and 5 EphB receptors. Our preliminary work on the EphB1 receptor has demonstrated loss-of-function mutations in colorectal cancer. There has been relatively little biochemical work on the Eph family receptors. Two other Eph receptors (EphB2 and EphA3) can be expressed at high levels in *E. coli*. The Eph receptors can have either tumor suppressive or pro-oncogenic roles in cancer. There are a large number of cancer-associated mutations in Eph family receptors that have not been characterized with respect to activity or function. We will use *E. coli* expression to produce these mutant proteins and characterize their activity as compared to their wild-type counterparts. We will also test their ability to rewire downstream signaling.

Publications:

Crooks DR, Maio N, Lang M, Ricketts CJ, Vocke CD, Gurram S, Turan S, **Kim YY,** Cawthon GM, Sohelian F, De Val N, Pfeiffer RM, Jailwala P, Tandon M, Tran B, Fan TW, Lane AN, Ried T, Wangsa D, Malayeri AA, Merino MJ, Yang Y, Meier JL, Ball MW, Rouault TA, Srinivasan R, Linehan WM. Mitochondrial DNA alterations underlie an irreversible shift to aerobic glycolysis in fumarate hydratase-deficient renal cancer. Sci Signal. 2021 Jan 5;14(664):eabc4436.

Kim YY, Tanski JM. Crystal structure of a rare trigonal bipyramidal titanium(IV) coordination complex: tri-chlorido-(3,3'-di-tert-butyl-2'-hy-droxy-5,5',6,6'-tetra-methyl-1,1'-biphenyl-2-olato-κO2)(tetra-hydro-furan-κO)-titanium(IV). Acta Crystallogr E Crystallogr Commun. 2017 Jan 1;73(Pt 1):88-91.

Steven Lewis

Investigating the relationship between the systemic response to infection and tumor progression in Brca1 breast cancer

Advisor: Camila dos Santos, PhD, Cancer Center, Cold Spring Harbor Laboratory

Status: 4th Year MSTP, 2nd Year Graduate student in Genetics

Abstract

Breast cancer (BC) is one of the most common solid tumors in women and loss-of-function mutations in the DNA repair gene, *BRCA1*, is among the most clinically relevant factors that increases BC incidence. Despite the link with BC, we cannot predict when and even if BRCA1 mutation carriers will develop BC. Therefore, identification of risk factors that initiate tumor development is needed. The dos Santos lab has found that whole body changes resulting from urinary tract infection (UTI) remodel the transcriptome of mammary epithelial cells (MECs) and the tissue microenvironment. Since UTI is one of the most common infections in women globally, it is likely that UTI and BC co-occur in millions of women. Considering the known link between infection and tumor development in other cancer types (e.g. *H. Pylori* and gastric cancer), we hypothesize that UTI, and the systemic inflammatory response, can induce BC tumorigenesis. Indeed, experimental delivery of uropathogenic *E. coli* into the bladder of *Brca1* deficient mice hastens tumor development. Analysis of pre-malignant mammary tissue from *Brca1* deficient mice with ongoing UTI by single cell RNA sequencing (scRNAseq) identified a *Krt6a*-expressing population of epithelial cells induced by UTI in *Brca1* KO mice. In addition, we found that mammary non-epithelial cells are altered by *Brca1* deficiency. Specifically, fibroblasts are enriched and further recruited to the mammary gland after UTI alongside a reduction in adaptive immune cells. In summary, this work may contribute a new appreciation of the role of infection in promoting BC and the interplay between tumor initiating epithelial cells and stromal and immune cells during tumor progression.

Publications:
*(MSTP-supported publications indicated with an *)*

Lewis, S.M., Callaway, M.K., dos Santos, C.O. *Clinical applications of 3D normal and breast cancer organoids: a review of concepts and methods*. Exp Biol Med. [accepted]*

Soldatenko, A., Hoyt, LR., Xu, L., Calabro, S., **Lewis, S.M** et al. *Innate and Adaptive Immunity to Transfused Allogeneic RBCs in Mice Requires MyD88.* J Immunol. 2022 Feb 15;208(4):991-997.

Lewis, S.M., Strano-Paul, L.A. *A COVID Service-Learning Initiative: Emotional Support Calls for the Geriatric Population*. J Am Geriatr Soc. 2020 Dec 31. doi: 10.1111/jgs.17003.*

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Harden, J.L., **Lewis, S.M.** et al. *The tryptophan metabolism enzyme L-kynureninase is a novel inflammatory factor in psoriasis and other inflammatory diseases*. J Allergy Clin Immunol. 2016 Jun;137(6):1830-1840.

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Ian Outhwaite

Maximizing Selective Inhibition of Clinically Observed MET Mutants

Advisor: Markus Seeliger, Ph.D., Department of Pharmacology, Stony Brook University

Status: 4th Year MSTP, 2nd Year Biochemistry and Structural Biology Graduate Student

Abstract

Mesenchymal epithelial transition factor (c-MET/MET), a receptor tyrosine kinase, is an oncogenic driver in non-small cell lung cancer (NSCLC) and melanomas. Some clinically approved TKIs have activity against MET (MET-TKIs); however, clinically-observed MET mutations promote resistance to certain MET-TKI subtypes that preferentially bind to active or inactive kinase conformations. *Defining which TKIs should be used to treat patients presenting with specific MET mutations is a pressing clinical need.* We recently demonstrated that combining as few as two or three kinase inhibitors with shared activity against a target of interest, it is possible to maximize on-target inhibition by diluting each inhibitor's off-target effects. In addition to maximizing therapeutic on-target effect, combinations of inhibitors with different binding modes could also decrease the probability of resistance emerging through further mutations. The *objective* of this study is to define selectivity profiles for clinically approved TKIs against clinically observed MET mutants, and calculate TKI combinations that would most selectively inhibit those mutants. The primary *rationale* for this work is that it will provide an actionable roadmap for MET mutation-specific targeted TKI therapy in clinical cohorts. Combinations of two or three clinically approved TKIs with different binding modes that have been selected to maximize on-target activity represent an actionable strategy to increase therapeutic potential and decrease the probability of further TKI resistance emerging.

Publications:

Outhwaite IR, Singh S, Chodera JD, Seeliger MA. Inhibitor Combinations Maximize On-Target Activity and Reduce Off-Target Effects. *In preparation*.

Peterson AA, Rangwala AM, Thakur MK, Ward PS, Hung C, **Outhwaite IR**, Chan AI, Usanov DL, Mootha VK, Seeliger MA, Liu DR. Discovery and molecular basis of subtype-selective cyclophilin inhibitors. *Nature Chemical Biology* (2022)

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*Hou X, ***Outhwaite IR**, Pedi L, Long SB. Cryo-EM structure of the calcium release-activated calcium channel Orai in an open conformation. *eLife* (2020) (****co-equal contribution***)

Jordan Pearson

CXCL12/CXCR4-induced Apoptosis of CD4+ T cells in the Presence of Cancer

Advisor: Douglas Fearon, MD
Status: 4th year MSTP, 2nd year Genetics Graduate Student

Cancer is able to grow and spread throughout the body by evading the immune system. In recent years, a coat made of covalently bound CXCL12 and Keratin 19 has been discovered to cover the cells in some cancers and disallow T cell infiltration. Not only does this coat keep out T cells, but it also leads to a decrease in T cell motility and ultimately T cell death. The mechanism by which this occurs is not known. Our lab believes that the interaction between CXCL12 and its receptor, CXCR4, leads to apoptosis of T cells and therefore a lack of immunogenic response to cancer cells that are coated in CXCL12 and Keratin 19. My studies will focus on how the ligation of CXCR4 by CXCL12 activates the intrinsic apoptosis pathway in surrounding T cells.

Publications:

Wang, Z., Moresco, P., Yan, R., Li, J., Gao, Y., Biasci, D., Yao, M., **Pearson, J.**, Hechtman, J.F., Janowitz, T. and Zaidi, R.M.,& Fearon, D. T. (2022). Carcinomas assemble a filamentous CXCL12–keratin-19 coating that suppresses T cell–mediated immune attack. *Proceedings of the National Academy of Sciences*, *119*(4).

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Isabel Sakarin

Characterizing the mode of action of an antimycobacterial compound after target identification by activity-based protein profiling

Advisor: Jessica Seeliger, PhD, Dept. of Pharmacological Sciences, SBU
Status: 4rd year MSTP, 2nd year Microbiology and Immunology graduate student (GS2)

Abstract

The increasing prevalence of multidrug resistant strains of *Mycobacterium tuberculosis* underscores the urgent need for novel anti-tuberculosis (TB) drugs. A major bottleneck in the discovery process for anti-TB drugs is the identification and validation of a compound's targets, which is especially difficult when multiple targets underlie biological activity. Activity-based protein profiling (ABPP) can be used to simultaneously detect all potential targets of a compound. In previous work, our lab has demonstrated the potential of ABPP in the drug development pipeline. We leveraged phenotypic screening, competitive ABPP, morphological profiling, and a structure-activity series to generate a prioritized list of targets most likely to contribute to the mode of action of our identified inhibitor, AA692 (Li and Patel et al., 2021). To further demonstrate the applicability of ABPP in drug development, we will determine the contribution of the prioritized targets to the mode of action of AA692. In this study, we focus on the target Rv3802c, an essential *Mtb* protein with a putative role in mycolic acid synthesis. We have generated autoluminescent reporter strains of *Mycobacterium smegmatis* with tunable Rv3802c expression and confirmed that Rv3802c complements the loss of the essential *M. smegmatis* homologue MSMEG_6394. To test whether Rv3802c inhibition contributes to the mode of action of AA692, we will determine how Rv3802c expression affects susceptibility to AA692. This work will provide insight into the mode of action of an inhibitor, but, more importantly, it will contribute to our understanding of how ABPP can be used in the development of novel drugs.

Publications:

DeRossi C, Bambino K, Morrison J, **Sakarin I**, Villacorta-Martin C, Zhang C, Ellis JL, Fiel MI, Ybanez M, Lee YA, Huang K, Yin C, Sakaguchi TF, Friedman SL, Villanueva, and Chu J. Mannose Phosphate Isomerase and Mannose Regulate Hepatic Stellate Cell Activation and Fibrosis in Zebrafish and Humans. *Hepatology* 2019, doi: 10.1002/hep.30677

Xun Lin, Ankita Singh, Xindi Shan, Suzanne Tawch, **Isabel Sakarin**, Tej Bahadur, Nancy McLinskey, Patricia Melville, Bettina C. Fries, Patricia K. Coyle, James Collins, Andriy Morgun, Natalia Shulzhenko, Jessica Seeliger, Timothy Hand, Linjun Xia, Olga Syritsyna and Pawan Kumar. *Akkermansia muciniphila*-mediated degradation of host mucin expands the tryptophan utilizer *Alistipes* and exacerbates autoimmunity by promoting Th17 immune responses. Submitted.

Lucia Yang

Inducing exon skipping with antisense oligonucleotides to treat diffuse intrinsic pontine glioma

Advisor: Adrian Krainer, Ph.D., Genetics, Stony Brook University/Cold Spring Harbor Laboratory

Status: 4th Year MSTP, 2nd Year Genetics Graduate Student

Abstract

Diffuse intrinsic pontine glioma (DIPG) is a deadly pediatric brain tumor for which no curative treatment option currently exists. Approximately 70-80% of all DIPG tumors are marked by a dominant heterozygous point mutation in *H3F3A*, which codes for the non-canonical histone H3.3. This toxic gain-of-function mutation replaces lysine 27 with methionine (K27M), preventing trimethylation of lysine 27 (H3K27me3) and disrupting global di- and tri-methylation on histone proteins. This mutant H3.3 histone is predicted to be a major driver of tumorigenesis in H3K27M-mutated DIPG by disrupting normal neural differentiation. Thus, the mutant *H3F3A* mRNA is a promising target for therapeutics. Antisense oligonucleotides (ASOs) offer a unique method to target mRNA through Watson-Crick base pairing with high specificity and low toxicity. For my thesis, I will develop a splice-switching ASO that reduces translation of mutant H3K27M RNA by inducing skipping of *H3F3A* exon 2, which contains the only in-frame start codon for H3F3A and the K27M mutation. I will test my hypothesis that the ASO will reduce the amount of H3K27M, limit DIPG tumor growth, and prolong survival. Additionally, I will characterize the role of the RNA-binding protein RBFOX3 in reinforcing neural differentiation and *H3F3A* exon 2 skipping following ASO injection. Methods to achieve these goals will include establishing a preclinical *in vivo* mouse model with H3.3K27M-mutated DIPG xenografts to study splicing changes of *H3F3A* and *H3F3B* through RT-PCR, protein expression of H3K27M and H3K27me3 through immunoblot, and neural cell differentiation through immunofluorescence following ASO injection. Additionally, splicing and analytical RNA-protein binding assays will be used to characterize the role and binding kinetics of RBFOX3 with *H3F3A* RNA.

Publications:
*(MSTP-supported publications indicated with an *)*

Gu X, Richman J, Langfelder P, Wang N, Zhang S, Bañez-Coronel M, Wang HB, **Yang L,** Ramanathan L, Deng L, Park CS, Choi CR, Cantle JP, Gao F, Gray M, Coppola G, Bates GP, Ranum LPW, Horvath S, Colwell CS, & Yang XW. (2022). Uninterrupted CAG repeat drives striatum-selective transcription-opathy and nuclear pathogenesis in human Huntingtin BAC mice. ***Neuron***,110(7):1173-1192.

*Kim YJ, Sivetz N, Layne J, Voss DM, **Yang L**, Zhang Q, & Krainer AR. (2022). Exon-skipping antisense oligonucleotides for cystic fibrosis therapy. ***PNAS***, *119*(3):e2114858118.

*Kim YJ, Nomakuchi T, Papaleonidopoulou F, **Yang L**, Zhang Q, & Krainer AR. (2022). Gene-Specific Nonsense-Mediated mRNA Decay Targeting for Cystic Fibrosis Therapy. ***Nat Comm***, *13(1)*:2978.

*Zhang Q, **Yang L**, Liu YH, Wilkinson, JE, & Krainer AR. (2022). Antisense therapy for H3.3 K27M diffuse midline gliomas. *In Revision, Science Translational Medicine.*

Alexander Baez

Acetylcholine Release is Pathologically Elevated in the Dorsal Striatum of SAPAP3-null Obsessive Compulsive Disorder Model Mice.

Advisor: Joshua Plotkin, PhD; Department of Neurobiology and Behavior, Stony Brook University

Status: 5th year MSTP; GS3 Program in Neuroscience

Obsessive compulsive disorder (OCD) is a neuropsychiatric disease listed as top 10 and top 15 most disabling illnesses in women and men, respectively, and has a predicted prevalence of 2.3% in the United States. SAP90/PSD95-associated protein 3 (SAPAP3) is a postsynaptic scaffold protein which is enriched at corticostriatal synapses and has been linked to OCD. The deletion of SAPAP3 in mice recapitulates aspects of OCD with biological validity (striatum hyperactivity), behavioral validity (anxiety-like behaviors and compulsive grooming), and treatment validity (reduction in compulsive behavior by chronic course of selective serotonin reuptake inhibitor). Here we show that acetylcholine (ACh) release is dysregulated in the dorsal striatum of SAPAP3-null mice. Cholinergic interneuron (CIN) soma and axonal punctae are increased in density in the dorsal striatum of SAPAP3-null mice, as determined by immunohistochemical staining for choline acetyltransferase (ChAT) and vesicular ACh transporter (VAChT). Electrophysiological recordings in *ex vivo* brain slices demonstrate that the firing rate of CINs is also increased in SAPAP3-null mice. Consistent with these findings, we found that evoked release of striatal ACh is also elevated in the dorsal striatum of Sapap3-null mice, as measured in acute brain slices using a genetically-encoded fluorescent ACh sensor. We further hypothesize that dysregulated release of ACh by CINs may shape striatal circuit dysfunctions and promote compulsive motor behaviors in SAPAP3-null mice.

Publications:

*(MSTP-supported publications indicated with *)*

* **Baez, A.**, Van Brunt, T., Moody, G., Wollmuth, L. P., & Hsieh, H. (2020). Voltage dependent allosteric modulation of IPSCs by benzodiazepines. *Brain Research*, *1736*, 146699.

* Malgady, J. M., **Baez, A.**, Jimenez, K., Hobel, Z. B., Prager, E. M., Zhang, Q., Feng, G., Plotkin, J. L. (2022). Non-synaptic alterations in striatal excitability and cholinergic modulation in a SAPAP3 mouse model of compulsive motor behavior. *Cell Reports*. (*In Revision).*

Jay Gupta

Diversity of Positive Allostery of Anti-NMDA Receptor Autoantibodies in Lupus

Advisor: Lonnie P. Wollmuth, PhD, Neurobiology and Behavior, Stony Brook University

Status: 5th Year MSTP, 3rd Year Molecular & Cellular Pharmacology Graduate Student (GS3)

Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects nearly 1.5 million Americans, disproportionately women and minorities. Up to 50% of patients with SLE experience neuropsychiatric symptoms clinically referred to as Neuropsychiatric Lupus (NPSLE) and colloquially referred to as “brain fog”. These symptoms vary greatly from patient to patient and can range from subtle (amnesia, cognitive fatigue, and impaired concentration) to severe (seizures and psychosis). The basis for this diversity is unknown, but recent studies have focused on the contributions of a subset of autoantibodies that cross react with NMDA receptors (NMDARs). These autoantibodies (DNRAbs) are identified by their affinity for dsDNA and DWEYS, a pentapeptide amino acid motif within the amino terminal domain of NMDARs. DNRAbs bind to NMDARs containing GluN2A and/or GluN2B subunits, but we recently demonstrated that G11, a patient derived monoclonal DNRAb, preferentially acts on GluN2A-containing NMDARs as a positive allosteric modulator (PAM). The PAM action of G11 increases NMDAR response to agonist and may underlie hippocampal neuron losses, microglial activation, loss of dendritic complexity and loss of spatial memory associated with DNRAbs in vivo. Other patient derived monoclonal and polyclonal DNRAbs enhance NMDAR-mediated currents suggesting they also have PAM action on NMDARs, but each has slightly different binding affinity for NMDARs. I hypothesize that different DNRAbs have different binding affinities for NMDARs, potentiating NMDARs to varying degrees, thus contributing to the wide variation in neuropathology seen in the clinic. To test this hypothesis I will use 3 patient derived monoclonal antibodies to (i) quantify DNRAb mediated differences in positive allostery of NMDARs in vitro, (ii) analyze diverse DNRAb mediated differences in neuropathology in vivo, and (iii) utilize novel NMDAR NAMs to pharmacologically oppose PAM action of NMDARs to prevent development of neuropathology. This work will enable a greater understanding of the diversity of DNRAb contributions to NPSLE.

Thomas Kim

Activity-dependent neurogenesis and functional neurovascular coupling in Alzheimer's disease mice

Advisor: Shaoyu Ge, PhD, Department of Neurobiology and Behavior, Stony Brook University

Status: 5th year MSTP, 3nd Year Graduate Student

Abstract

Alzheimer's disease (AD) is the most common form of dementia, typically presenting with progressive and irreversible neurodegeneration. Memory loss, an early symptom of AD, usually manifests as difficulty in remembering recent events or conversations. Memory loss is often due to damage in the hippocampus, which plays a very important role in day-to-day memory. It has been shown that atrophy of hippocampal areas occurs in the presence of AD. This explains the early memory impairment, especially the formation of new memories, seen in AD patients. An important aspect of structural neuroplasticity in the hippocampus is neurogenesis, the addition of newly generated neurons to existing circuits. While the occurrence, regulation, and importance of hippocampal neurogenesis in young adults have been extensively tested, very little is known about hippocampal neurogenesis in AD brains.

A recent study in our laboratory reported that microvascular blood flow rate is tightly regulated by interneuronal activity in adult mice. Several lines of evidence in AD rodent models and patients have also shown impaired vascular dynamics, especially decreased cerebral blood flow, which is essential for brain energy homeostasis. Decreased blood flow is thought to reflect neuronal dysfunction and synaptic failure, with the latter considered to be the best correlate of cognitive decline in AD. However, it is unclear which types of interneurons are affected to initiate these changes in AD. Moreover, it is unknown whether it is possible to ameliorate the declined neurogenesis via correcting interneuron activity and whether this regulation is dependent on the neurovascular pathway in AD. Therefore, I hope to determine the mechanisms underlying the declined hippocampal neurogenesis in AD, focusing on analyzing the functional neurovascular coupling (NVC), an increase in local cerebral blood flow due to an increase in local neural activity, in AD mouse models.

Publications:

(MSTP-supported publications indicated with a #)

#**Kim, T. A.**, Syty, M. D., Wu, K. Ge, S. Adult hippocampal neurogenesis and its impairment in Alzheimer's disease. *Zoological Research*, 43(3): 481-496 (2022). doi: 10.24272/j.issn.2095-8137.2021.479; PMID: 35503338; PMCID: PMC9113964.

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#**Kim, T. A.**, Chen, L., Ge, S. The Interplay of Neurovasculature and Adult Hippocampal Neurogenesis. *Neuroscience letters*, 136071. (2021) doi: 10.1016/j.neulet.2021.136071; PMID: 34147540; PMCID: PMC8683249.

Hanson, J. E.*, Ma, K.*, Elstrott, J.*, Weber, M.*, Saillet, S.*, Khan, A. S., Simms, J., Liu, B., **Kim, T. A.**, Yu, G. Q., Chen, Y., Wang, T. M., Jiang, Z., Lieder, B. M., Deshmukh, G., Solanoy, H., Chan, C., Sellers, B. D., Volgraf, M., Schwarz, J. B., Hackos, D. H., Weimer, R. M., Sheng, M., Gill, T. M., Scearce-Levie, K., Palop, J. J. GluN2A NMDA Receptor Enhancement Improves Brain Oscillations, Synchrony, and Cognitive Functions in Dravet Syndrome and Alzheimer's Disease Models. *Cell Reports*. doi: 10.1016/j.celrep.2019.12.030; PMID: 31940483; PMCID: PMC7017907. (*equal contribution)

Choi, Y. J.*, Lin, C. P.*, Risso, D.*, Chen, S., **Kim, T. A.**, Than, M. H., Li, J. G., Wu, Y., Chen, C., Xuan, Z., Macfarlan, T., Peng, W., Lloyd, K. K., Kim, S. Y., Speed, T. P., He, L. Deficiency of microRNA miR-34a expands cell fate potential in pluripotent stem cells. *Science*355, 596 (2017). doi: 10.1126/science.aag1927; PMID:22020437; PMCID: PMC6138252. (*equal contribution)

Kevin Murgas

Network Geometry In Cancer

Advisor: Allen Tannenbaum, Ph.D., Dept. of Biomedical Informatics, SBU
Status: 5th year MSTP, 3rd year Biomedical Informatics Graduate Student (GS3)

Abstract

Protein-protein interaction (PPI) networks describe how individual proteins in the cell interact with one another, thereby providing a network structure to capture the numerous interactions in a given cell. These PPI networks in turn allow one to analyze high dimensional gene expression (RNA-seq) data with respect to an underlying structure in the data, considering the relationships of each gene with other interacting genes to provide richer analysis. In fact, network-based approaches have indicated network entropy (a statistical measure of "randomness") to be an indicator of pluripotency (differentiation capacity) in stem cells and cancer.

Our research seeks to pivot from the statistical quantity of entropy to geometric properties on these interaction networks, in order to define more descriptive analysis with applications in pathway analysis and predictive modeling. Results in differential geometry directly relate the value of Ricci curvature (a geometric measure of flatness) to entropy, which in turn is also related to robustness. Based on this link, we extend the results from network entropy by applying Ricci curvature, which indeed reveals curvature can function as an indicator of pluripotency in stem cells, similarly to entropy. Further, we consider Ricci curvature in local pathway analysis in the context of melanoma data, demonstrating that known oncogenic pathways increase in curvature in tumors compared to normal tissue (i.e. increase in robustness), while conversely known tumor suppressor pathways decrease in curvature. This indicates Ricci curvature could serve as a valuable measure for assessing local network properties and pathways implicated in disease.

Publications:

*(MSTP-supported publications indicated with an *)*

*__Murgas KA__, Saucan E, Sandhu R. Beyond Pairwise Interactions: Higher-Order Dynamics in Protein Interaction Networks. In review.

Ryser MD, et al. including **Murgas KA**. Ductal Carcinoma in Situ Recapitulates Normal Breast Development. In review.

*__Murgas KA__, Saucan E, Sandhu R. Quantifying Cellular Pluripotency and Pathway Robustness through Forman-Ricci Curvature. *Proceedings of Complex Networks and their Applications*. 2021 Nov 30.

Murgas KA, Ma Y, Shahidi LK, Mukherjee S, Allen AS, Shibata D, Ryser MD. A Bayesian hierarchical model to estimate DNA methylation conservation in colorectal tumors. *Bioinformatics*. 2021 Sep 6.

Murgas KA, Wilson AM, Michael V, Glickfeld LL. Unique spatial integration in mouse primary visual cortex and higher visual areas. *Journal of Neuroscience*. 2020 Feb 26;40(9):1862-73.

Ryser MD, **Murgas KA**. Bone remodeling as a spatial evolutionary game. *Journal of theoretical biology*. 2017 Apr 7;418:16-26.

Dillon Voss

Targeting pyruvate kinase pre-mRNA as a therapy for hepatocellular carcinoma

Advisor: Adrian Krainer, PhD., Cold Spring Harbor Laboratory

Status: 5th Year MSTP, 3rd Graduate Student Stony Brook Genetics Program

Abstract

Mutually exclusive alternative splicing of exons 9 and 10 in the pyruvate kinase gene (PKM) leads to two distinct isozymes, PKM1 and PKM2. Pyruvate kinase catalyzes the last step of glycolysis, generating pyruvate and ATP. PKM1 and PKM2 differ in their ability to catalyze this reaction: PKM1 is constitutively active, whereas PKM2 is allosterically regulated. Interestingly, nearly all cancer types preferentially express the less active PKM2 isozyme. It is thought that reduced PK activity allows accumulation of upstream glycolytic intermediates that are shunted to macromolecule synthesis pathways (e.g., nucleotide and amino acid synthesis) to sustain cancer-cell proliferation. Importantly, there is also evidence of PKM2 exhibiting noncanonical functions in cancer by recruiting transcription factors to oncogenes. Our goal is to improve the understanding of PKM isozyme function in tumorigenesis, while also developing therapeutic strategies that alter isozyme expression in various cancer types. To this end, our lab utilizes antisense oligonucleotides (ASOs) that bind splicing-regulatory sequences in PKM pre-mRNA and redirect alternative splicing, leading to increased PKM1 and decreased PKM2 expression. These ASOs increase PKM1 expression, as well as pyruvate kinase activity, which induces cell-cycle arrest in hepatocellular carcinoma (HCC) cells in vitro, and significantly limits tumor growth in vivo. Stable-isotope tracing and LC-MS analysis of ASO-treated HCC cells revealed decreased incorporation of glycolytic intermediates into serine and purine synthesis pathways, suggesting a metabolically-dependent response. Follow-up studies to confirm the metabolic link between ASO-based PKM splice-switching and reduced growth in HCC can aid in identifying synergistic therapies. We are also testing whether PKM2 mutants lacking catalytic activity or nuclear localization can rescue the cell-cycle arrest phenotype in ASO-treated HCC cells, to determine if non-canonical functions of PKM2 are necessary for HCC cell growth. We have focused on HCC because ASOs preferentially accumulate in the liver when subcutaneously injected into mice. However, given that PKM2 is upregulated in many cancer types, this work provides a precedent for the use of PKM-targeting ASOs in other cancers with upregulated PKM2 and/or known sensitivity to PKM2-modulating interventions.

Publications:

# Indicates publication during MSTP training

* Both authors contributed equally to this work

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Yuejiao (Camelia) Zheng

Taste processing in a mouse model of Frontotemporal Dementia

Advisor: Alfredo Fontanini, MD, PhD, Neurobiology and Behavior, Stony Brook University

Status: 5th year MSTP, 3rd Year Neuroscience Graduate Student (GS3)

Abstract

Frontotemporal dementia (FTD) is the second most prevalent form of presenile dementia. Patients with FTD show a pathological sweet tooth and decreased ability to identify flavors. Taste perception depends on neural processing in chemosensory regions such as the insular cortex - a brain region that also contains the primary taste cortex, gustatory cortex (GC). The chemosensory deficits in FTD may be related to GC damage as insular cortex is one of the primary targets in FTD disease progression. Little is known on how circuitry changes related to FTD lead to abnormal activation of GC and to deficits in taste processing and taste-odor association in FTD. The goal of this project is to test the hypothesis that the chemosensory deficits in a mouse model of FTD are related to abnormal patterns of neural activity in GC. TDP-43 inclusions are a significant pathological feature in 50% of FTD cases, thus we use a transgenic mouse model overexpressing human transactivating response region (TAR) DNA binding protein (TDP-43) with a Q331K mutation. To assess chemosensory deficits, we relied on a taste-based two alternative forced choice (2AFC) task probing the ability to discriminate sucrose/NaCl mixtures. Analysis of psychometric functions of mutant and control mice revealed that TDP-43 Q331K mice make more mistakes and show significant deficits in the mixture discrimination 2AFC task.

To monitor neural activity, we relied on electrophysiological recordings using chronically implanted tetrodes in alert mutant and control mice. Activity in GC was probed as mice licked at different concentrations of sucrose. We observed a larger number of taste-evoked excitatory responses in TDP-43 Q331K mice compared to control mice, suggesting the possibility that GC may be abnormally excitable in TDP-43 Q331K mice.

Publications:

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Soma Kobayashi

A Computational Approach for the Histopathological Assessment of Colitis Mouse Models

Advisor: Vincent Yang, MD, PhD and Joel Saltz, MD, PhD, Biomedical Informatics, Stony Brook University

Status: 6th Year MSTP, 4th Year Graduate Student

Abstract

Inflammatory bowel disease patients have areas of their intestines that are either involved or uninvolved with disease. Colitis mouse models display a similar heterogeneity histologically. As such, spatial context may be particularly important for studying colitis mouse models, due to this simultaneous presence of colonic regions that are involved or uninvolved with disease. These regions can be identified on hematoxylin and eosin (H&E)-stained colonic tissue slides based on the presence of abnormal or normal histology. However, detection of such regions requires expert interpretation by pathologists.

Convolutional neural networks (CNNs) have shown much promise in biomedical image classification. As CNNs learn to associate visual patterns with human-defined labels, they are well-suited for application in histopathology. As such, we have trained a ResNet-34-based model to detect 'Involved' and 'Uninvolved' histological regions across three mouse models of colitis. This computational approach allows extraction of these image regions across our dataset to cluster and identify patch classes. We have found that the per-mouse proportions of these histological patch classes can be utilized to train subsequent machine learning classifiers to predict mouse model and clinical score bins in a prospectively treated cohort of mice. Reliable detection and quantification of histological findings is an important first step towards histologically grounded analysis across mouse models. Molecular approaches and mechanistic studies focusing on pathophysiology could be linked to similar and dissimilar presence of types of histological findings across different murine colitis phenotypes

For a future direction, we plan to build upon these H&E outputs using serially sectioned slides that are immunohistochemically stained for immune markers. After registering these sections to the H&E, we plan to tie immune and molecular characteristics to the histological patch classes we have identified. We will evaluate the potential for histological immune marker localization to 'Involved' and 'Uninvolved' regions to identify protective and deleterious populations. Additionally, with the hypothesis that immune cell type presence can be mapped to regional contexts defined by presence of or without specific pathologies, we will train a classifier to infer functional immune population presence from H&E alone.

Publications:

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Soma Kobayashi

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Joshua Kogan

Cortical plasticity underlying gustatory perceptual learning in behaving mice

Advisor: Alfredo Fontanini, MD PhD, Neurobiology and Behavior, Stony Brook University

Status: 6th Year MSTP, 4th Year Graduate Student

Abstract

To adapt and survive, animals must learn to discriminate overlapping stimuli predicting different outcomes. This phenomenon, known as perceptual learning (PL), has been well described in the visual, auditory, somatosensory, and olfactory systems. Specifically, improved performance on PL tasks is associated with plasticity of both sensory representations and decision related neural signals. However, few studies have addressed PL in the gustatory system. The primary sensory cortex for taste, known as the gustatory insular cortex, is known to encode both sensory and decision-related information. However, the ways that these representations might change with PL remains unknown. To address this question, we have designed a taste-based PL task modeled on a two alternative forced choice (2AFC). Mice first learn a sucrose (100mM) vs NaCl (100mM) discrimination, in which sucrose presentation at a central spout is associated with reward at one lateral spout and NaCl with reward at the other. They are then trained to discriminate between increasingly similar pairs of mixtures: 75/25 vs 25/75, 65/35 vs 35/65 and 60/40 vs 40/60 (%sucrose/%NaCl). Before and after learning, mice are tested on a battery of mixtures to establish psychometric curves. After learning, performance increased for all mixture pairs, indicating an improvement in discrimination. To assess GC plasticity, ensemble activity is monitored with two photon calcium imaging. Single neuron and population-level analysis are used to identify changes in both sensory and decision-related neural responses that occur with PL. These analyses suggest that learning is mostly associated with enhanced decision-related activity rather than shifts in sensory representations. Ongoing studies using optogenetic inhibition of GC activity will test the requirement of this activity for performance of the discrimination task.

Publications:
*(MSTP-supported publications indicated with an *)*

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Craig Marshall

Dysregulation of Transposable Elements in Amyotrophic Lateral Sclerosis

Advisor: Dr. Molly Hammell, PhD, Cold Spring Harbor Laboratories

Status: 6th Year MSTP, 4th Year Genetics Graduate Student

Abstract

Transposable elements (TEs) are autonomously replicating DNA sequences that reside within the genomes of all eukaryotes. These TEs are present in multiple copies, such that they represent highly repetitive genomic elements. The vast majority of TEs have lost their ability to replicate within the genome due to the accumulation of mutations. In addition, the host organism devotes significant resources to silencing the remaining elements. Regardless of their activity, TEs encompass a significant portion of the human genome, and dysregulation can lead to increased nascent transcription, movement of TEs throughout the genome, and genome wide instability. Human cells use a variety of mechanisms to keep these TEs dormant including histone modifications, DNA methylation, and post- transcriptional RNA degradation. TAR DNA Binding Protein 43 (TDP-43) plays many general roles in gene regulation, and additionally plays a substantial role in the silencing of TEs. TDP-43 is also known for its propensity to aggregate within the motor neurons of patients with amyotrophic lateral sclerosis (ALS). ALS is a progressive neurodegenerative disorder affecting the upper and lower motor neurons of the motor cortex and spinal cord. While some familial mutations in ALS-associated genes have been identified, the vast majority of cases are sporadic with no known mutation or family history of disease. TDP-43 aggregates are seen in motor neurons from nearly all ALS patients, yet the role of these aggregates and associated TDP-43 dysfunction is still being defined. Dr. Molly Hammell's lab recently showed that ALS patient cortex samples can be grouped into three distinct and robust clusters of patients whose transcriptome profiles nominate three dominant pathways altered in the disease: retrotransposon activation, oxidative stress, and microglial activation. Integrative genomics analysis of TDP-43 has shown that TDP-43 loss of function *in vitro* leads to retrotransposon activation, mimicking the pathways seen altered in a subset of ALS patient cortex samples. Together, this leaves open several questions regarding the interplay between TDP-43, transposon silencing complexes, and ALS pathology. My research will be to elucidate the mechanism by which TDP-43 represses TEs, with a clear focus on correlations to the molecular alterations seen in ALS patient tissues.

Publications:

Iannuzo N, Insel M, **Marshall C**, Pederson WP, Addison KJ, Polverino F, Guerra S, Ledford JG. CC16 Deficiency in the Context of Early-Life Mycoplasma pneumoniae Infection Results in Augmented Airway Responses in Adult Mice. Infect Immun. 2022 Feb 17;90(2):e0054821. doi: 10.1128/IAI.00548-21.

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Philip Moresco

Characterizing the Formation of the T Cell Excluding CXCL12 Coat

Advisor: Douglas Fearon, MD
Cancer Center, Cold Spring Harbor Laboratory

Status: 6th Year MSTP, 4nd Year Graduate Student

Abstract

The CXCL12 "coat" is a extracellular compartment that mediates the exclusion of T cells from cancer cell nests, rendering carcinomas such as pancreatic ductal adenocarcinoma (PDA), colorectal cancer, and likely breast cancer, resistant to immune checkpoint blockade (ICB). This coat is formed by the covalent coupling of CXCL12 to KRT19, which is catalyzed by the isopeptide bond forming enzyme TGM2. Our lab has shown that blocking the interaction between CXCL12 and CXCR4, the receptor of CXCL12, with a small molecule inhibitor of CXCR4, or CRISPR-mediated mutagenesis of cancer cell derived KRT19 or TGM2, renders mouse models of PDA susceptible to ICB. However, how the CXCL12 coat forms at a cell biological and biochemical level remains unknown but elucidating these mechanisms will provide the foundation to identify additional means to block its formation.

KRT19 is a classically intracellular cytoskeleton protein, and how it remains cell associated to capture extracellular CXCL12 is unknown. Using surface protein biotinylation of two human breast cancer cell lines I have shown that cancer cells externalize KRT19 along with its basic keratin binding partner KRT8. To expand upon this observation, I used live cell imaging and three-dimensional reconstruction to show for the first time that keratins assemble into intermediate filament networks on the surface of cells, reminiscent to their classic intracellular structure. Importantly, by using a combination of live cell imaging and co-immunoprecipitation I have shown that this filamentous KRT19 containing network captures extracellular CXCL12 to form the covalent CXCL12-KRT19 heterodimer, which *in vivo*, mediates T cell exclusion from cancer cell nests. Therefore, the CXCL12-KRT19 complex remains cell associated by incorporating into a keratin network on the surface of cells.

Publications:

(MSTP-supported publications indicated with an *)

*Wang Z, **Moresco P**, Yan R, Li J, Gao Y, Biasci D, Yao M, Pearson J, Hechtman JF, Janowitz T, RM, Weiss MJ, Fearon DT. (2021) Carcinomas assemble a filamentous CXCL12-keratin19 coating that suppresses T cell-mediated immune attack. MIP.

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Awards:

NIH Ruth L. Kirschstein National Research Service Award Fellowship

Daniel Radin

Current Position:

6th Year MSTP, 4th year graduate student

Advisor:

Stella Tsirka

Graduate Program:

Molecular and Cellular Pharmacology

Abstract:

Glioblastoma is the most common and aggressive primary brain tumor in adults. Median survival time remains at 16-20 months despite multimodal treatment with surgical resection, radiation, temozolomide and tumor-treating fields therapy. After genotoxic stress glioma cells initiate cytoprotective autophagy, which contributes to treatment resistance, limiting the efficacy of these therapies and providing an avenue for glioma recurrence. Antagonism of autophagy steps has recently gained attention as it may enhance the efficacy of classical chemotherapies and newer immune-stimulating therapies. The modulation of autophagy in the clinic is limited by the low potency of common autophagy inhibitors and the inability of newer ones to cross the blood-brain barrier. Herein, we leverage lucanthone, an anti-schistosomal agent which crosses the blood-brain barrier and was recently reported to act as an autophagy inhibitor in breast cancer cells. Our studies show that lucanthone was toxic to glioma cells by inhibiting autophagy. It enhanced anti-glioma temozolomide (TMZ) efficacy at sub-cytotoxic concentrations, and suppressed the growth of stem-like glioma cells and temozolomide-resistant glioma stem cells. *In vivo* lucanthone slowed tumor growth: reduced numbers of $Olig2^{+}$ glioma cells, normalized tumor vasculature, and reduced tumor hypoxia. We propose that lucanthone may serve to perturb a mechanism of temozolomide resistance and allow for successful treatment of TMZ-resistant glioblastoma.

Publications:

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Aziz M. Rangwala

Resistance to Kinase Inhibition through Shortened Target Engagement

Advisor: Markus A. Seeliger, PhD, Pharmacological Sciences, Stony Brook University

Status: 6th year MSTP, 4th year Molecular and Cellular Biology graduate student

Abstract

Protein kinase inhibitors are potent anticancer therapeutics. Imatinib, a selective inhibitor of Bcr-Abl kinase, reduced mortality in chronic myeloid leukemia (CML) by 80%, but 22-41% of patients acquire imatinib resistance. Mutations within the Bcr-Abl kinase domain (KD) are the most common cause for relapse. Some mutations are located near the imatinib-binding site and cause resistance through altered interactions with the drug. However, many resistance mutations are located far from the drug-binding site, and it remains unclear how these mutations confer resistance. Additionally, earlier studies on small sets of patient-derived imatinib resistance mutations indicated that some of these mutant proteins were in fact sensitive to imatinib in cellular and biochemical assays. These assays were performed at constant drug concentrations; however, the plasma drug concentration of patients fluctuates over time due to drug pharmacodynamics and pharmacokinetics. Therefore, dissection of the equilibrium binding constant Kd, the standard measure of a compound's efficacy, into the rate constants for drug binding to the target (k_{on}) and dissociation from the target (k_{off}) may be more relevant for non-equilibrium *in vivo* systems. Residence time, the reciprocal of the drug dissociation rate constant, describes the lifetime of the drug-target complex and has been shown to be a superior predictor of *in vivo* potency in several systems.

We hypothesized a novel general mechanism that mutations could cause resistance not by altering the equilibrium binding affinity but rather by increasing drug dissociation rates, thereby decreasing imatinib's residence time and reducing target inhibition in the non-equilibrium environment of the cell. We tested how 94 patient-derived and resistance-associated Abl mutants affected imatinib and dasatinib affinity and binding kinetics in live cells. We found that two-thirds of the tested clinically observed imatinib resistance mutations in Abl kinase significantly reduce drug affinity, whereas one-third bind imatinib with similar or tighter affinity than Abl wild-type (WT). We identified three imatinib resistance mutations, N368S, V299L, and G251E, that have similar imatinib affinity as Abl WT but increased imatinib dissociation rates.

This workflow represents the first broad-spectrum analysis of the target engagement characteristics of the full range of mutations in a clinically-relevant kinase. Mutations at these sites are present ubiquitously throughout the kinome, which suggests that kinetic resistance to structurally-selective kinase inhibitors may be a widespread mechanism. Such kinetic mutations may not be detectable in assays with constant drug concentration, and their resistance phenotype may vary from patient to patient by other pharmacodynamic and pharmacokinetic parameters. Importantly, kinetic resistance mechanisms may be circumvented by altering the treatment schedule, for example, from a single daily dose to multiple doses. We envision that this study will serve as a paradigm for further investigation of analogous mutations in other kinases such as the epidermal growth factor receptor (EGFR) and uncover a broader role for binding kinetics in drug resistance.

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Luke Torre-Healy

Molecular subtyping in Pancreatic Ductal Adenocarcinoma

Advisor: Dr. Richard Moffitt, PhD, Stony Brook University
Status: 6th Year MSTP, 4th Year Biomedical Informatics Graduate Student

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease for which potent therapies have limited efficacy. Several studies have described the transcriptomic landscape of PDAC tumors, seeking to provide insight into potentially actionable gene expression signatures to improve patient outcomes. Despite centralization efforts from multiple organizations and increased transparency requirements from funding agencies and publishers, analysis of public PDAC data remains difficult. Bioinformatic pitfalls litter public transcriptomic data, such as subtle inclusion of low-purity and non-adenocarcinoma cases. These pitfalls can introduce non-specificity to gene signatures without appropriate data curation, which can negatively impact findings. We here seek to address two aspects of subtyping in PDAC. First, we evaluate the tumor specificity of existing signatures and facilitate community exploration through the compilation, curation, and analysis of existing datasets; as well as the development of a point-and-click webtool to streamline serialized analyses. We then seek to expand molecular subtyping to Whole Slide Image (WSI) analysis by leveraging deep learning algorithms to predict transcriptomic subtypes from histology alone.

We demonstrate the effect of inappropriate sample inclusion by analyzing molecular subtype signatures in matched sample analysis, wherein scores are calculated for primary tumor samples and then again from either a matched metastasis or a cell line derived from the primary patient (PACA-AU dataset). We identified complete signature loss of the Bailey ADEX, Bailey Immunogenic, and Collison Exocrine signatures in cell lines and metastases. We then scored their expression in a variety of normal tissues (Moffitt dataset), and identified elevated PDAC signature expression for those same gene signatures in normal pancreas, liver, lung, and spleen/lymph nodes. To limit these issues in future analyses, we have created pdacR (http://pdacR.bmi.stonybrook.edu, github.com/rmoffitt/pdacR), an open-source software package and web-tool with annotated datasets from landmark studies and an interface for user-friendly analysis in clustering, differential expression, survival, and dimensionality reduction.

Following our characterization of existing signatures, we sought to train an algorithm that could extract interpretable features from WSIs of PDAC. Specifically, we implemented the DINO Visual transformer (ViT) to perform Self supervised learning (SSL) on 300+ PDAC WSI from two different public datasets (TCGA and CPTAC3). Once features were extracted, we trained an ElasticNet logistic regression classifier using 15-fold cross-validation and were able to generate a model that predicts basal-like vs classical with an Area Under the Receiver-Operator Characteristic (AUROC) of 0.91 on previously unseen WSI and an F1 score of 0.9.

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(+ denotes co-first author, * denotes program supported)

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John Yuen

Development of 5-FU-modified tumor suppressor microRNAs as a platform for novel microRNA-based cancer therapeutics

Advisor: Jingfang Ju, PhD, Department of Pathology, Stony Brook University

Status: 6th Year MSTP, 4rd Year Neuroscience Graduate Student (GS4)

MicroRNA (miRNAs) are pleiotropic post-transcriptional modulators of gene expression. Its inherently pleiotropic nature make miRNAs strong candidates for the development of cancer therapeutics, yet despite its potential, there remains a challenge to deliver nucleic acid-based therapies into cancer cells. We developed a novel approach to modify miRNAs by replacing the uracil bases with 5-fluorouracil (5-FU) in the guide strand of tumor suppressor miRNAs, thereby combining the therapeutic effect of 5-FU with tumor suppressive effect of miRNAs to create a potent, multi-targeted therapeutic molecule without altering its native RNA interference (RNAi) function. To demonstrate the general applicability of this approach to other tumor suppressive miRNAs, we screened a panel of 12 novel miRNA mimetics in several cancer types including leukemia, breast, gastric, lung, and pancreatic cancer. Our results show that 5-FU-modified miRNA mimetics have increased potency (low nM range) in inhibiting cancer cell proliferation and that these mimetics can be delivered into cancer cells without delivery vehicle both *in vitro* and *in vivo*, thus representing significant advancements in the development of therapeutic miRNAs for cancer. This work demonstrates the potential of fluoropyrimidine modifications that can be broadly applicable and may serve as a platform technology for future miRNA and nucleic acid-based therapeutics.

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Andrea Arreguin

Abnormal oligodendrogenesis in the corpus callosum of the mdx and mdx4cv mice

Advisor: Holly Colognato, PhD, Department of Pharmacological Sciences, Stony Brook University

Status: 7th Year MSTP, 5TH Year Graduate Student

Abstract

Mutations in dystrophin, the protein mutated in Duchenne muscular dystrophy (DMD), can lead to neurological dysfunction, but much is still unknown about the cell and molecular basis of these changes. The largest isoform, Dp427, connects the extracellular matrix to the actin cytoskeleton in muscle. In the brain, smaller isoforms such as Dp140 and Dp71 are more abundant, and mutations affecting the transcription of these isoforms are predicted to have worse neurological deficits. Using the *mdx* (lacks Dp427) and *mdx^{4cv}* (lacks Dp427, Dp260 and Dp140) DMD mouse models, we examined oligodendrocyte precursor cell (OPC) production and proliferation in the postnatal ventricular/subventricular zone (VZ-SVZ) and oligodendrogenesis in the corpus callosum. In the mdx mouse, at P21, there is a reduction in the density and proliferation of OPCs in both the VZ-SVZ and corpus callosum. In the mdx4cv, there is a reduction in proliferating OPCs at P8 and P21 in the VZ-SVZ and P14 in the corpus callosum. Interestingly there is a reduction in oligodendrocytes in the mdx mouse at P21 but no reduction in oligodendrocyte density in the mdx4cv mouse at any of the examined time points. These results support our previous work demonstrating myelination abnormalities in the mdx mouse and support the hypothesis that the widespread diffusion tensor imaging changes seen in patients with DMD may be indeed due to a white matter abnormality.

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Cristian Cleary

MYOD1 and E-Protein Dynamics in Rhabdomyosarcoma

Preceptor: Christopher Vakoc

Status: 7th Year MSTP, 5th Year Graduate Student

Abstract

Soft tissue sarcomas are the most common extra-cranial solid tumor type in children in the U.S. Rhabdomyosarcoma (RMS) makes up nearly 50% of soft tissue sarcomas in this demographic. RMS is a round, blue cell tumor which expresses some markers of myogenic differentiation such as MYOD, myogenin, desmin, and actin. It lacks later markers of differentiation, however, and does not form myotubes or functional muscle units. As such, this cancer is thought to represent a malignancy of muscle progenitors unable to complete the myogenic differentiation program. The standard-of-care therapy for this disease has remained unchanged for the past 50 years and utilizes mechanisms of action that are not specific to this malignancy. To find elite therapeutic targets for RMS, we have employed a negative-selection, domain-focused CRISPR/Cas9 screen of RMS cell lines to discover dependencies specific to this disease and characterize their potency. We have found MYOD1 to be the most potent RMS-specific target present in our screen. This finding is validated in a publicly available dataset of genome-wide CRISPR screens of cancer dependencies. This transcription factor has long been thought to be inactive in this cancer, given that it fails to differentiate and MYOD is a master regulator of muscle differentiation. We have performed a genome-wide screen to find regulators of MYOD expression in RMS and found that its heterodimeric partners, E-proteins, maintain its expression. As it remains unknown which E-proteins are functionally active with MYOD in this cancer, we aim to uncover the dynamics of MYOD and E-protein interaction that allow growth of this cancer without fully converting cells to muscle tissue. These findings will enhance our understanding of the pathophysiology underlying this malignancy and may reveal opportunities for novel therapeutic targets in the process.

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Alex Larkin

Understanding the mechanisms of cancer cell extravasation using a zebrafish xenograft model

Advisor: Benjamin Martin
Department: Pharmacology/Biochemistry and Cell Biology, Stony Brook University
Status: 7th Year MSTP, 5th Year Grad Student

Abstract

Cancer cell metastasis from solid tumors is a major cause of death in cancer patients. The precise way in which cancer cells leave the primary tumor, travel through the circulatory and lymphatic systems, and then invade into distant organs to grow new tumors, is still being understood. In contrast to intravasation, the process of extravasation is still mysterious. Recent studies have shown that cell cycle state may be an important factor for invasion of cancer cells through the endothelial layer[1]. Another factor is the role that macrophages play within the blood stream to aid in extravasation since they play a large role in intravasation[2,3]. One boundary to understanding this process is the difficulty of observing it *in vivo*. Using the zebrafish xenograft model overcomes this barrier by allowing high power microscopy, live cell imaging immediately after xenograft, and delayed adaptive immune system, preventing rejection. To better understand the mechanisms of metastasis I will inject breast cancer cells into the circulation of zebrafish and assess the effect of cell cycle state on extravasation as well as the relationship of circulating macrophages on this process. In this proposal I wish to increase our understanding of the different mechanisms of cancer cell extravasation. These new insights could potentially lead to new drug targets and better patient outcomes.

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Allen Lee

Analyzing NBD complex sphingolipids to reveal ceramide metabolism in the Golgi

Advisor: Yusuf A. Hannun, MD, Stony Brook Cancer Center and Dept of Medicine, Stony Brook University

Status: 7th year MSTP, 5th year Pharmacology Graduate Student

Sphingolipid metabolism is often altered in many disease states. Many sphingolipids are bioactive molecules that modulate signaling pathways including ceramide, sphingosine, S1P, and C1P. Several of the enzymes involved in sphingolipid metabolism reside in the Golgi. These enzymes are glucosyl ceramide synthase, sphingomyelin synthase 1, and ceramide kinase. These enzymes generate hexosylceramides, sphingomyelins, and ceramide 1 phosphates from ceramide respectively. Previously metabolism of these sphingolipid metabolites has been studied individually or by mass spectrometry. Using NBD-Ceramide, we can detect changes in metabolism of these sphingolipids simultaneously by HPLC. We have shown that this method will detect changes in the lipids following inhibitor and siRNA treatments of the respective enzymes. With this method we can detect major changes in sphingolipid metabolism following various manipulations and treatments. We are currently investigating the effects of doxorubicin on sphingolipid metabolism using this method as well as using the method to determine how certain pools of ceramide are trafficked to the Golgi.

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Michael A. Q. Martinez

The role of the cell cycle in establishing and maintaining invasive cell fate

Advisor: David Q. Matus, Ph.D., Department of Biochemistry and Cell Biology, Stony Brook University

Status: 7th Year MSTP, 5th Year Molecular and Cellular Pharmacology Graduate Student

Abstract

We previously identified that cell invasion and cell proliferation are mutually exclusive behaviors. To elucidate how this dichotomy between proliferation and invasion is programmed, we study the proximal stochastic fates of the *C. elegans* somatic gonad: the invasive, post-mitotic anchor cell (AC) and the proliferative ventral uterine (VU) cell. Following the Notch-mediated stochastic AC/VU decision, the AC invades the underlying basement membrane, initiating the uterine-vulval connection. The AC must be arrested in the G0 phase of the cell cycle to invade, which is controlled by an extensive gene regulatory network. To investigate how G0 is established in the AC, we examined CDK activity and the levels of the CDK-2 binding partner, CYE-1/Cyclin E, and the p21/p27 homolog, CKI-1. Our results reveal that while there is no initial difference in CDK activity, levels of CYE-1 and CKI-1 are distinct. To determine if these levels are functionally important, we ectopically expressed CKI-1 during the AC/VU decision, biasing both cells to adopt an AC fate. These results suggests that the stochastic decision that specifies AC fate is dependent on cell-cycle state. Research from multiple metazoans suggests that redundant mechanisms are in place to maintain a post-mitotic state. We find here that the G0 state of the AC is also maintained in a redundant fashion, as loss of single negative cell-cycle regulators failed to trigger AC cell-cycle entry. However, depletion of CKI-1 in null mutant backgrounds of other negative G1/S-phase regulators (*cki-2* and *fzr-1*) triggered a robust cycling AC phenotype. Together, our results delineate how initiation and maintenance of a robust cell cycle-arrested state is required for the invasive cell fate, with important clinical implications for the treatment of invasive pathologies such as cancer metastasis.

Publications:
(*denotes co-first authors; **denotes co-second authors)

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Hills-Muckey, K., **Martinez, M.A.Q.,** Stec, N., Hebbar, S., Saldanha, J., Medwig-Kinney, T.N., Moore, F.E.Q., Ivanova, M., Morao, A., Ward, J.D., Moss, E.G., Ercan, S., Zinovyeva, A.Y., Matus, D.Q., and Hammell, C.M. (2022). An engineered, orthogonal auxin analog/$_{At}$TIR1(F79G) pairing improves both specificity and efficacy of the auxin degradation system in *Caenorhabditis elegans*. *Genetics*. 220(2): iyab174.

Ashley, G., Duong, T.**, Levenson, M.T.**, **Martinez, M.A.Q.**,** Johnson, L.C., Hibshman, J.D., Saeger, H.N., Palmisano, N.J., Doonan, R., Martinez-Mendez, R., Davidson, B., Zhang, W., Ragle, J.M., Medwig-Kinney, T.N., Sirota, S.S., Goldstein, B., Matus, D.Q., Dickinson, D.J., Reiner, D.J., and Ward, J.D. (2021). An expanded auxin-inducible degron toolkit for *Caenorhabditis elegans*. *Genetics*. 217(3): iyab006.

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Joshua Steinberg

Status: 7th Year MSTP, 5th Year Graduate Student
Thesis Advisors: Robert Martienssen & Andrea Schorn, Cold Spring Harbor Laboratory

The role of RNA interference in genome stability and cancer progression

Abstract

While RNA interference (RNAi) is an essential pathway well known for gene silencing and transposon control in eukaryotes, emerging roles in chromosome and genome stability suggest a far broader function. Growing evidence supports the existence of highly conserved, Dicer-independent pathways that are involved in chromatin remodeling and DNA repair. We have observed significant fitness defects in *Dicer1* mutants in mouse embryonic stem cells (mESCs) that are independent of microRNA production. Strikingly, mutations in *Dicer1* are observed across cancer types and numerous studies have suggested a correlation between poor clinical outcome and low DICER1 expression. In parallel, fragments derived from the 3' end of mature tRNAs (3'-tRFs) are also highly abundant in cancer cell lines and may play a similar role as DICER1 in maintaining genome stability by inhibiting long-terminal repeat (LTR)-retrotransposons which use full-length tRNAs to prime reverse transcription. 3'-tRFs potentially protect many cell types in eukaryotes but are processed from full-length tRNAs under yet unknown conditions. While canonical miRNA misregulation is well-characterized in human disease, there is an urgent need to study these lesser known, non-canonical small RNA pathways and the perturbations that may occur. The significance of this project is two-fold: (i) enhancers of the *Dicer1* fitness defect may constitute novel therapeutic targets, and (ii) identification of triggers for 3'-tRF production may inform strategies against infectious LTR-retroviruses, including HIV and HTLV-1, that are also primed by tRNAs. We view these highly conserved, ancient functions of RNAi as an exciting field that remains largely unexplored but holds tremendous therapeutic potential.

Research Interests:

My current research interests are in Genetics and Molecular Biology.

Publications:

*(MSTP-supported publications indicated with an *)*

*Mo, Z. Scheben, A., **Steinberg, J.**, Siepel, A., Martienssen, R. Circadian susceptibility, sunrise time and the seasonality of respiratory infections. *Under review*. (2022).

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John Williams

Medial Prefrontal Cortex Dysfunction Mediates Working Memory Deficits in Schizophrenia

Advisor: Anissa Abi-Dargham, MD and Jared Van Snellenberg, PhD

Department: Psychiatry and Behavioral Health, Stony Brook University

Status: 7th Year MSTP, 6th Year Biomedical Engineering Graduate Student

Abstract

Schizophrenia (SCZ) is marked by deficits in working memory (WM), which predict poor functional outcome. While most functional magnetic resonance imaging (fMRI) studies of WM in SCZ focus on dorsolateral prefrontal cortex (dlPFC), recent work suggests a role for medial PFC (mPFC) in these WM deficits. We aimed to determine whether task-evoked mPFC deactivation magnitude is associated with WM performance, and whether it mediates deficits in SCZ. Additionally, we investigated associations between mPFC deactivation and cortical dopamine release in both SCZ and healthy controls (HC).

Patients with SCZ (N=41) and HC (N=40) performed a visual object n-back task during fMRI. Dopamine release capacity in mPFC was quantified with [^{11}C]FLB457 in a subset of participants (9 SCZ, 14 HC) using an amphetamine challenge. Correlations between task-evoked deactivation and performance were assessed in mPFC and dlPFC masks, and was further examined for relationships with diagnosis and dopamine release.

Deactivation was associated with WM task performance in mPFC, but no association was observed in dlPFC. Deactivation in mPFC was reduced in SCZ relative to HC and mediated the relationship between diagnosis and WM performance. Additionally, mPFC deactivation was significantly and inversely associated with dopamine release capacity across all PET participants, as well as in HCs alone, but not in unmedicated patients with SCZ.

Reduced WM task-evoked mPFC deactivation is a mediator of, and potential substrate for, WM impairment in SCZ; this reduction may be due to impairments either in elements of cognition generally related to task engagement rather or to WM specifically. We further present preliminary evidence of an inverse association between deactivation during WM tasks and dopamine release capacity in mPFC.

Publications:

Williams JC, Tubiolo PN, Luceno JR, & Van Snellenberg JX. (2022). Advancing motion denoising of multiband resting-state functional connectivity fMRI data. *NeuroImage.* 2022 Apr 1;249:118907. doi: 10.1016/j.neuroimage.2022.118907. Epub 2022 Jan 13. PMID: 35033673; PMCID: PMC9057309.

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Williams JC, Entcheva E. Optogenetic versus Electrical Stimulation of Human Cardiomyocytes: Modeling Insights. *Biophysical Journal.* 2015 Apr 21;108(8):1934-45. doi: 10.1016/j.bpj.2015.03.032. PMID: 25902433; PMCID: PMC4407252.

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Williams JC, Xu J, Lu Z, Klimas A, Chen X, Ambrosi CM, Cohen IS, Entcheva E. Computational optogenetics: empirically-derived voltage- and light-sensitive channelrhodopsin-2 model. *PLoS Computational Biology.* 2013;9(9):e1003220. doi: 10.1371/journal.pcbi.1003220. Epub 2013 Sep 12. PMID: 24068903; PMCID: PMC3772068.

Boyle PM, **Williams JC**, Ambrosi CM, Entcheva E, Trayanova NA. A comprehensive multiscale framework for simulating optogenetics in the heart. *Nature Communications.* 2013;4:2370. doi: 10.1038/ncomms3370. PMID: 23982300; PMCID: PMC3838435.

Allen Chen

Current Position: 7th Year MSTP, 3rd Year Medical Student

Advisor: Dr. Shaoyu Ge, PhD and Dr. Qiaojie Xiong, PhD

Abstract:

I am interested in studying the neural circuit and neuromodulatory mechanisms that govern cognitive-sensory behaviors, which underlie neuropsychiatric disease. My thesis research focuses on perceptual decision-making, which underlies our basic capabilities to respond to the environment with appropriate actions and is dysfunctional in multiple diseases such as Parkinson's and schizophrenia. Using in vivo calcium imaging, optogenetics, and other systems neuroscience techniques, I explored dopaminergic and striatal neural circuit function in auditory discrimination. My data indicates that dopamine regulates striatal sub-compartments for auditory discrimination. Furthermore, dopamine modulates auditory neural representation and neuronal learning within the posterior auditory striatum. Using patient-level data, I am additionally interested in using quantitative techniques to understand brain disorders at behavioral and epidemiological levels. My current clinical interests include psychiatry, neurology, and ophthalmology.

Publications:

Chen A.P., Malgady J., Chen L., Shi K., Cheng E., Zeto A. Plotkin JL, Ge S., Xiong Q. (Under Revision). Nigrostriatal dopamine pathway regulates auditory discrimination behavior.

Chen A.P., Ismail Z., Mann F.D., Bromet E.J., Clouston S.A., Luft B. (Under Revision). Behavioral impairments and increased risk of cortical atrophy among World Trade Center responders

Chen A.P., Clouston S.A., Kritikos M., Richmond L., Meliker J., Mann F.D., Santiago-Michels S., Pellechia A., Carr M., Kuan P., Bromet E.J., Luft B. (2021). A deep learning approach for monitoring parietal-dominant Alzheimer's disease in World Trade Center responders at midlife. Brain Communications. fcab145,

Chen A.P., Chen, L., Kim, T.A., & Xiong, Q. (2021). Integrating the Roles of Midbrain Dopamine Circuits in Behavior and Neuropsychiatric Disease. Biomedicines, 9(6), 647.

Kéry, R., **Chen A.P.**, Kirschen G.W. (2020). Genetic targeting of astrocytes to combat neurodegenerative disease. Neural Regeneration Research, 15(2):199-211.

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Danielle Fassler

Digital pathology-based approaches for assessing the tumor immune landscape and patient prognosis

Advisors: Richard Moffitt, PhD and Joel Saltz, MD/PhD Professor and Chair Department of Biomedical Informatics, Stony Brook University

Status: 3rd Year Medical Student

Abstract

The immune response to cancer has implications on tumor progression, prognosis, and whether patients respond to immunotherapeutic agents. For this reason, it has become increasingly important to be able to study tumor immunology. Hematoxylin and eosin-stained (H&E) tissue sections are routinely obtained for a great majority of cancer patients. H&E whole slide images can be analyzed to generate maps that characterize tumor infiltrating lymphocyte (TIL) distribution. We employed our tumor detection and TIL detection algorithms to generate tumor-TIL composite maps that clearly outline the whole tissue sample, highlighting tumor, TILs, and areas of overlap, giving a birds-eye-view of TIL distribution. We defined human-interpretable features analogous to the semantic features employed in Radiomics that could be identified at-a-glance. These spatial features, inspired by ecological concepts, include TIL forests (aggregates of TILs within tumor landscape), TIL deserts (large areas of tumor void of TILs), and lymphoid aggregates (clusters of lymphocytes outside tumor boundary); we also included scores of the degree of TIL infiltration, distinguishing between intratumoral and peritumoral TIL strength (within the tumor and around the tumor edge, respectively). We then assessed the clinical significance of these features in two independent studies. We carried out analysis of whole slide images from the TCGA breast cancer cohort and the Carolina Breast Cancer Study to explore the predictive value of quantification of TIL infiltration and of TIL semantic features. We found that TIL forests, lymphoid aggregates, and increased peritumoral TILs are protective, while TIL deserts are hazardous. Herein we provide evidence that TIL infiltration pattern is significant to patient risk assessment, and that assessing infiltration features may be a less time-consuming alternative to assessing degree of infiltration.

Publications:
*(MSTP-supported publications indicated by an *)*

*Spatial characterization of tumor infiltrating lymphocytes (TILs) and breast cancer progression. **Danielle J. Fassler**†, Luke A. Torre-Healy†, Rajarsi Gupta, Alina M. Hamilton, Soma Kobayashi, Sarah C. Van Alsten, Yuwei Zhang, Tahsin Kurc, Richard A. Moffitt, Katherine A. Hoadley, Melissa A. Troester, Joel Saltz. Cancers. 2022

*Deep learning-based image analysis methods for brightfield-acquired multiplex immunohistochemistry images. **Danielle J. Fassler**, Shahira Abousamra, Rajarsi Gupta, Chao Chen, Maozheng Zhao, David Paredes, Syeda Areeha Batool, Beatrice S. Knudsen, Luisa Escobar-Hoyos, Kenneth R. Shroyer, Dimitris Samaras, Tahsin Kurc & Joel Saltz. Diagnostic Pathology. 2020

*Utilizing Automated Breast Cancer Detection to Identify Spatial Distributions of Tumor Infiltrating Lymphocytes in Invasive Breast Cancer. Han Le, Rajarsi Gupta, Le Hou, Shahira Abousamra,

Danielle Fassler, Tahsin Kurc, Dimitris Samaras, Rebecca Batiste, Tianhao Zhao, Alison L. Van Dyke, Ashish Sharma, Erich Bremer, Jonas S. Almeida, and Joel Saltz. The American Journal of Pathology, 2020.

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*Label Super Resolution with Inter-Instance Loss. Maozheng Zhao, Le Hou, Han Le, Dimitris Samaras, Nebojsa Jojic, **Danielle Fassler**, Tahsin Kurc, Rajarsi Gupta, Kolya Malkin, Shroyer Kenneth, and Joel Saltz. arXiv 04/2019

Hyperbaric Oxygen Promotes Proximal Bone Regeneration and Organized Collagen Composition during Digit Regeneration. Mimi C. Sammarco, Jennifer Simkin, Alexander J. Cammack, **Danielle Fassler**, Alexej Grossmann, Luis Marrero, Michelle Lacey, Keith W. Van Meter, Ken Muneoka. Plos One. 2015.

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Kathryn Hill

Use of Fully Quantitative PET to Relate Biology to Behavior

Advisor: Ramin Parsey, MD, PhD, Department of Psychiatry, Stony Brook University

Status: 6th Year MSTP, 3RD Year Medical Student

Abstract

The goal of my thesis work was to advance the use of quantitative positron emission tomography (PET) towards clinically impactful tools for diagnosis and treatment of psychiatric and neurological disorders. I assessed individuals with major depressive disorder (MDD) to determine if 2-[18F]-fluorodeoxyglucose (FDG) PET, measuring glucose metabolism, could be used as a predictor of antidepressant treatment outcome. However, FDG-PET was not shown to be a predictive marker. One explanation for this could be the broad heterogeneity of symptoms and biological factors associated with MDD. I subsequently assessed mu opioid receptor dynamics through PET imaging in healthy young adults in relation to three factors associated with development of psychiatric disorders: childhood maltreatment, alcohol use, and rejection sensitivity. Assessment of young adults prior to psychiatric disorder development is critical to isolate the relationship between factors and opioidergic dynamics without including potentially confounding biological impacts of psychiatric disorders. While rejection sensitivity and childhood maltreatment were not significantly related to opioid dynamics in our cohort, increased alcohol use, specifically, binge drinking, was related to decreased mu opioid receptor density. Future investigation is needed to assess if this decreased mu opioid receptor density predicts alcohol use disorder among those with increased binge drinking. I hope to continue similar brain imaging based research as a clinician scientist in the future.

Publications:
*(MSTP-supported publications indicated with an *)*

Narayan GA, **Hill KR***, Wengler K, He X, Wang J, Yang J, Parsey RV, DeLorenzo C. Does the change in glutamate to GABA ratio correlate with change in depression severity? A randomized, double-blind clinical trial. Mol Psychiatry. 2022 Aug 18. doi: 10.1038/s41380-022-01730-4.

Hill KR*, Hsu DT, Taylor SF, Ogden RT, Parsey RV, DeLorenzo C. Mu Opioid Receptor Dynamics in Healthy Volunteers with a History of Childhood Maltreatment. Journal of Child & Adolescent Trauma, June 2022. doi: 10.1007/s40653-022-00463-4

Hill KR*, Hsu DT, Taylor SF, Ogden RT, DeLorenzo C, Parsey RV. Rejection sensitivity and mu opioid receptor dynamics associated with mood alterations in response to social feedback. Psychiatry Res Neuroimaging. 2022 Jun 6;324:111505. doi:10.1016/j.pscychresns.2022.111505.

Hill KR*, Gardus JD, Bartlett AE, Perlman G, Parsey RV, DeLorenzo C. Measuring brain glucose metabolism in order to predict response to antidepressant or placebo: A randomized clinical trial, NeuroImage: Clinical, Volume 32, 2021,102858, ISSN 2213-1582, https://doi.org/10.1016/j.nicl.2021.102858

Pillai RLI, Butchart L, **Hill K***, Lazarus Z, Patel R, Yan L, Kenyon L, Post S. You're Not Alone: Sharing of Anonymous Narratives to Destigmatize Mental Illness in Medical Students and Faculty. Academic Psychiatry. 2020; 223-226. doi: 10.1007/s40596-019-01145-4.

Hill K, Bolo N, Sarvode Mothi S, Lizano P, Guimond S, Tandon N, Molokotos E, Keshavan M. Subcortical Surface Shape in Youth at Familial High Risk for Schizophrenia. Psychiatry Research: Neuroimaging. 2017; 267, 36-44. doi: 10.1016/j.pscychresns.2017.07.002.

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Nuri Kim

Synonymous mutations and non-canonical gene expression in Mycobacteria

Advisor: Jessica C. Seeliger, PhD, Department of Pharmacology, Stony Brook University

Status: 8th Year MSTP, 3rd Year Medical Student

Clinical Specialty: Undecided

Abstract

Mycobacterium tuberculosis (*Mtb*) is the causative agent of tuberculosis, one of the deadliest infectious diseases worldwide. Previous studies have established that synonymous recoding to introduce rare codon pairings can attenuate viral pathogens. We hypothesized that non-optimal codon pairing could be an effective strategy for attenuating gene expression to create a live vaccine for *Mtb*. We instead discovered that these synonymous changes enabled the transcription of functional mRNA that initiated in the middle of the open reading frame and from which the many smaller protein products were expressed. To our knowledge, this is the first report that synonymous recoding of a gene in any organism can create or induce intragenic transcription start sites.

Selected Publications:

(MSTP-supported publications indicated with an ***** in front)

*Adikes RC, Kohrman AQ, Martinez MA, Palmisano NJ, Smith JJ, Medwig-Kinney TN, Min M, Sallee MD, Ahmed OB, **Kim N**, Liu S, Morabito RD, Weeks N, Zhao Q, Zhang W, Feldman JL, Barkoulas M, Pani AM, Spence SL, Martin BL, Matus DQ. Visualizing the metazoan proliferation-quiescence decision in vivo. (2020) *eLife* Dec;9:e63265.

*Aguirre-Chen C, Stec N, Ramos OM, **Kim N**, Kramer M, McCarthy S, Gillis J, McCombie WR, Hammell CM. A *Caenorhabditis elegans* Model for Integrating the Functions of Neuropsychiatric Risk Genes Identifies Components Required for Normal Dendritic Morphology. (2020) *G3* May;10(5):1617-28.

Kim JY, **Kim N**, Lee JE, Yenari MA. Hypothermia Identifies Dynamin as a Potential Therapeutic Target in Experimental Stroke. (2017) *Ther Hypothermia Temp Manag* Sep;7(3):171-7

Kim JY, **Kim N**, Zheng Z, Lee JE, Yenari MA. 70-kDa Heat Shock Protein downregulates dynamin in experimental stroke: a new therapeutic target? (2016) *Stroke* Aug;47(8):2103-11.

Kim JY, **Kim N**, Yenari, MA. Mechanisms and potential therapeutic applications of microglial activation after brain injury. (2015) *CNS Neurosci Ther* Apr;21:309-19

Kim N, Kim JY, Yenari MA. Pharmacological induction of the 70-kDa heat shock protein protects against brain injury. (2015) *Neuroscience* Jan;284:912-9

Kim JY, **Kim N**, Yenari MA, Chang W. Hypothermia and pharmacological regimens that prevent overexpression and overactivity of the extracellular calcium-sensing receptor protects neurons against traumatic brain injury. (2013) *J Neurotrauma* Jul;30(13):1170-6.

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Ki Oh

Coordinated single cell tumor microenvironment reinforce pancreatic cancer subtype

Advisor: Richard Moffitt, PhD, Biomedical Informatics, Stony Brook University

Status: 7th Year MSTP, 3rd Year Medical Student

Abstract

Bulk analyses of pancreatic ductal adenocarcinoma (PDAC) samples are complicated by the tumor microenvironment (TME), i.e. signals from fibroblasts, endocrine, exocrine, and immune cells. Despite this, we and others have established tumor and stroma subtypes with prognostic significance. However, the interaction of underlying signals driving distinct immune and stromal landscapes is still unclear.

Here we integrate 92 single cell RNA-seq samples from seven independent studies to build a reproducible PDAC atlas with a focus on tumor-TME interdependence. Patients with activated stroma are synonymous with higher myofibroblastic and immunogenic fibroblasts, and furthermore show increased M2-like macrophages and regulatory T-cells. Contrastingly, patients with 'normal' stroma showed M1 recruitment, elevated effector and exhausted T-cells. To aid interoperability of future studies, we provide a pretrained cell type classifier and an atlas of subtype-based signaling factors that we also validate in mouse data. Ultimately, this work leverages the heterogeneity among single-cell studies to create a comprehensive view of the orchestra of signaling interactions governing PDAC.

Publications:
*(MSTP-supported publications indicated with an *)*

*__Oh K__, Yoo YJ, Torre-Healy LA, Rao M, Fassler D, Wang P, Caponegro M, Gao M, Kim J, Sasson A, Georgiakos G, Powers RS, Moffitt RA. Coordinated single cell tumor microenvironment dynamics reinforce pancreatic cancer subtype. *Revisions* *Sep 2022 – Nature Communications*

Rao M, **Oh K**, Moffitt R, Comparative single-cell RNA sequencing (scRNA-seq) reveals liver metastasis–specific targets in a patient with small intestinal neuroendocrine cancer. *Published* *Apr 2020 – Molecular Case Studies*

***Torre-Healy LA, Kawalerski R, **Oh K**, Chrastecka L, Peng XL, Aguirre A, Rashid N, Yeh JJ, Moffitt RA pdacR: Curation and analysis of pancreatic ductal adenocarcinoma gene expression data supports a two-subtype model and enables community exploration. *Submitted* *Sept 2022 – Communications Biology*

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Deborah Rupert

Auditory Cortex Parvalbumin-Positive Interneurons Critically Depend on MeCP2 for Processing Ultrasonic Vocalizations

Advisor: Stephen D. Shea, Ph.D., Neuroscience, Cold Spring Harbor Laboratory

Status: 8th Year MSTP, 3rd Year Medical Student

Abstract

Rett Syndrome (RTT) is a pervasive neurodevelopmental disorder affecting females. RTT results from loss of function mutations in the X-linked gene Methyl CpG Binding Protein 2 (MeCP2*). MeCP2 encodes for the eponymously named protein, a ubiquitously expressed transcription factor critical for neuronal development and mature synapse maintenance. However, this pathogenesis is complicated by unequal mutation distribution; heterozygous mosaicism, one X-chromosome in each cell in lionized, results in a patchwork pattern of protein expression. Differences in the number, type, and location of MeCP2-deficient cells likely underlies the phenotype spectrum among the RTT patients. Whether some cells are more dependent on MeCP2, and therefore contribute more to clinical symptomatology or severity, is unknown. Here we explore that hypothesis in the context of impaired perceptive communication. We used Cre-lox genetic mouse lines to examine the consequences of cell-type restricted Mecp2 mutation to perception of naturally produced ultrasonic vocalizations (USVs). We employed infant pup retrieval behavior as a learned and ecologically relevant readout of auditory perception. Adult rodents naturally learn this behavior in response to pup USVs. We collected electrophysiology recordings and conducted calcium imaging to identify single neuron firing and neuronal population activity patterns in the auditory cortex during retrieval behavior and during passive playback of USVs. Cortical cell type identity dictated MeCP2 dependence for supporting auditory processing. Mecp2 mutation restricted to parvalbumin positive (PV) inhibitory interneurons (IN) impaired pup retrieval behavior. However, mutation restricted to somatostatin- or vasoactive-intestinal-peptide- positive IN had no such effect. The inability of PV-Mecp2 mutants to response behaviorally to USVs resulted from degraded stimulus-driven neuronal activity in the auditory cortex, both at the single unit and population levels. That is, PV-restricted Mecp2 mutation impaired inhibitory cortical plasticity. These findings expand our understanding of neurotypical processes of audition and the contributions of various cortical subtype populations to those processes.

Publications:
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Margaret Shevik

Neutrophil interactions with SARS-CoV-2

Advisor: Mikala Egeblad, PhD, Cold Spring Harbor Laboratory

Status: 7th Year MSTP, 3rd Year Medical Student

Abstract

Formation of neutrophil extracellular traps (NETs) is linked with COVID-19 disease severity. The causes of elevated NET formation in COVID-19 are likely multifactorial, but here I extend on previous reports showing that the SARS-CoV-2 Spike (S) protein can induce NET formation in human neutrophils. Intriguingly, I found that whereas the S protein induced NETs in neutrophils isolated from unvaccinated donors, neutrophils isolated from the same donors after COVID-19 vaccination no longer formed NETs. Similarly, neutrophils isolated from individuals before administration of a booster vaccination formed NETs, whereas they did not form NETs when isolated after booster administration. In contrast, NET formation in response to the chemical inducer PMA was unaffected by vaccination or booster status of the donors. Using a panel of chemical inhibitors, I showed that SARS-CoV-2 S protein induced-NET formation required several classical signaling molecules, including peptidylarginine deimininase 4, gasdermin D, and caspase-1. Additionally, I show that neutrophil-associated proteases and NETs can cleave the SARS-CoV-2 S protein *in vivo* and *in vitro*. Altogether, these data help elucidate the interactions occurring between the SARS-CoV-2 S protein and neutrophils during COVID-19 infection and how they contribute to disease pathophysiology.

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Lillian Talbot

Transcriptional Profiling of Cerebrospinal Fluid from Patients with Amyotrophic Lateral Sclerosis

Advisor: Josh Dubnau, PhD, Department of Anesthesiology, Stony Brook University

Status: 7th Year MSTP, 3rd Year Medical Student

Abstract

Amyotrophic lateral sclerosis (ALS) is an adult-onset, terminal disorder caused by degeneration of upper and lower motor neurons in the brain and spinal cord. In most cases, ALS progresses rapidly, and available treatments offer only minimal life extension. Biomarkers are urgently needed to shorten the diagnostic window and allow for patient stratification and drug engagement monitoring during clinical trials. As disruptions in RNA metabolism are observed in patients with ALS and in models of the disease, we profiled extracellular RNAs within cerebrospinal fluid (CSF) of ALS patients and compared them to age-matched neurologically normal controls. We identified more than 36 RNAs of multiple subtypes, differentially expressed in ALS CSF. Ferritin light chain (FTL) and ferritin heavy chain (FTH1), genes coding for the two subunits of the protein ferritin, were increased in ALS-CSF. Numerous groups have reported that elevations in ferritin at the protein level correlate with ALS. We describe elevations in 17 different transcripts coding for ribosomal proteins, many of which have been reported as elevated in transcriptomic studies of blood from ALS patients. This was notable as ribosomal proteins are known to be loaded into extracellular vesicles (EVs), suggesting EVs may be an important source of extracellular CSF RNAs. We used two RT-qPCR-based approaches to attempt to validate RNA-sequencing findings, first in the same cohort of samples used for RNA-sequencing and second in an independent cohort of ALS and control CSF. These findings provide rationale for further investigation into the utility of extracellular RNAs as biomarkers for ALS.

Publications: (MSTP-supported publications indicated with an *)

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Alex Terry

CD36 functions as a selective transporter for monounsaturated fatty acids during matrix detachment and tumor progression.

Adviser: Nissim Hay (University of Illinois-Chicago)
Year: MSTP9-MS4

During matrix detachment, tumor cells grow as multicellular clusters, and metabolism in this setting more readily recapitulates in vivo tumor metabolism. It was previously found that detached cells activate AMPK to inhibit fatty acid synthesis and induce fatty acid oxidation, which raises the question of how clustered cells maintain the integrity and biogenesis of membrane lipids. Here, we show that the fatty acid transporter CD36 is robustly induced in a p38- and AMPK-dependent manner during detachment. Preceding CD36 induction, ER stress is induced, which decreases the level of SCD1, an ER-resident desaturase that converts saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs). As a result, SFAs accumulate during matrix detachment, creating an imbalance in the fatty acid saturation index. The accumulated SFAs further activate AMPK and inhibit ACC to repress fatty acid synthesis while also exacerbating ER stress. However, the induction of CD36 maintains the fatty acid saturation index by preferentially importing MUFAs. Thus, CD36 is required to maintain lipid homeostasis and diminish ER stress during matrix detachment. Consistently, in a mouse model of breast cancer, CD36-deficiency induces ER-stress and prevents the pro-tumorigenic effect of HFD. Our results suggest that CD36 is a selective MUFA-transporter required to curb the toxicity of SFAs during tumor progression in the context of a HFD.