



IOWA

**Interdisciplinary Graduate
Program in Genetics**

2026

**Student
Retreat**

**October 7th & 8th
Coralville Public Library**

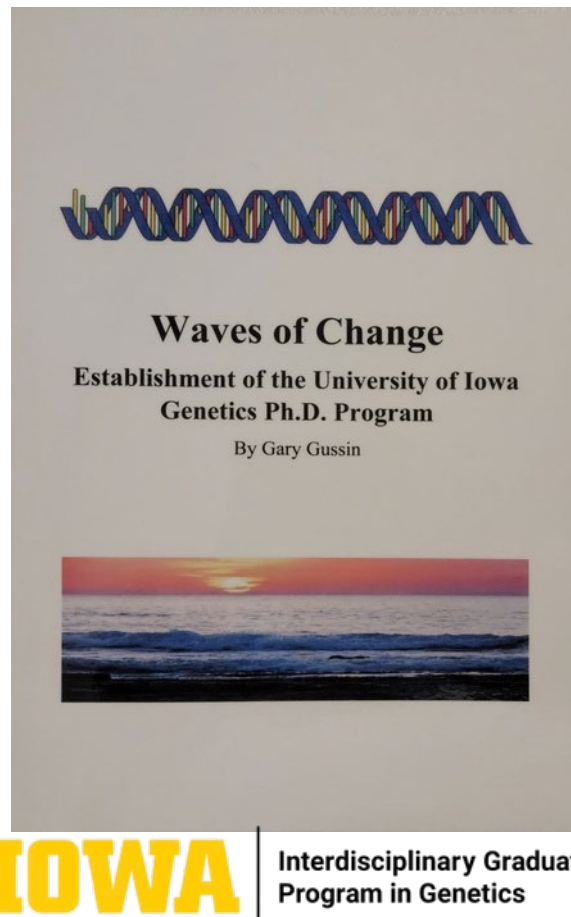


Dr. Gary Gussin
Professor Emeritus
Department of Biology

University of Iowa

Dr. Gary Gussin is a Professor Emeritus in the Department of Biology. Dr. Gussin was instrumental in the establishment of the Interdisciplinary Graduate Program in Genetics during the 1960's and was elected as the first Chairperson of the Program in 1975. Dr. Gussin published a book in 2021 titled *Waves of Change: Establishment of the University of Iowa Genetics Ph.D. Program*. The book recounts the early years of the program and successes, struggles, and contributions by the many faculty and administrators that helped develop the Program.

Wave of Change can be obtained by providing a minimum \$20 donation to the Interdisciplinary Graduate Program in Genetics.



STUDENT RETREAT



Keynote Speaker

Associate Professor

The Jackson Laboratory for Genomic Medicine

University of Connecticut

Alumni Speakers



Jacob Schillo, Ph.D. (2022)

Principal Scientist

Encapsulate



Yann Vanrobaeys, Ph.D. (2021)

Program Scientist 1/Research Scientist and Bioinformatics

BioMicro Center & Koch Institute

Massachusetts Institute of Technology

Wednesday, October 7

Public Keynote Talk—Christine Beck, PhD

2117 MERF

11:00 am Public Keynote - *"Repetitive Sequences Drive Genome Instability"*

Thursday, October 8

Coralville Public Library

9:00 am Check-in & continental breakfast

9:30 am Opening Remarks

9:40 am Student oral presentations— Session 1

- Kayla Henry (Grueter lab)
- Ellen Koufer (Schultz lab)
- Rodriguez Herrera (Potthoff lab)

10:45 am Poster session 1 (odd poster #)

11:45 am Break

12:00 pm Jacob Schillo - *"Beyond Genomics: Functional Cancer Modeling Across Earth and Space"*

12:35 pm Yann Vanrobaeys - *"From Iowa to MIT: A Bioinformatics Career Path"*

1:15 pm Lunch

2:15 pm Student oral presentations—Session 2

- Josh Ayelazuno (He lab)
- Tyler Rankin (Drack lab)
- Lucretia Shumate (Moye-Rowley lab)

3:15 pm Poster session 2 (even poster #)

4:15 pm Break

4:30 pm Keynote & Alumni Panel

5:30 pm Closing Remarks & Award Ceremony

IOWA

Interdisciplinary Graduate
Program in Genetics

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Program History

The Interdisciplinary Graduate Program in Genetics at the University of Iowa is a broad-based training program that incorporates an expansive range of techniques, model organisms, and approaches to actively address critical issues in biology, medicine, evolution, and genomics, with genetics as a common intellectual thread. Its purpose is to optimally prepare trainees to be at the forefront of genetics research and become future leaders in any area of modern genetics, from bioinformatics and omics to molecular genetics, gene discovery and mapping, cancer and medical genetics, and personalized medicine. Our mission for society is to train a diverse cohort of graduate students in the broad discipline of genetics who are highly prepared and well-equipped to educate all members of society, who will increasingly need to understand genetic aspects of their own family's health care and individualized genomes.

The Genetics Program curriculum is designed to provide a solid and broad foundation in genetics and foster strong independent critical thinking skills and multidisciplinary training to equip students to meet modern challenges. Throughout the span of their educational training, there is emphasis on rigor and reproducibility, responsible conduct and ethical, safe practices and inclusivity in the sciences. The Genetics Program also provides flexibility tailored to individual needs to ensure student success. In addition, the program offers a Computational Genetics subtrack for students who want to develop strengths in the biological aspects of genetics and computational approaches to analyzing large and diverse sets of genomic and genetic data. Students thus equipped have been extremely successful in filling a growing niche in the contemporary science workforce. Research opportunities within the program span the spectrum of genetics, from bacterial to model organism to human genetics, and from developmental genetics to evolution, from epigenetics to genomics to disease mechanisms.

After several formative years of interdisciplinary research activity in Genetics on the University of Iowa campus, the Interdisciplinary Graduate Program in Genetics was approved as a degree-granting PhD program in 1975. This program that began with 7 primary faculty has grown to currently having 73 faculty and 34 students in four colleges and 16 academic departments across our campus, with over 200 graduates. While the history of the program makes the University and the state of Iowa proud, it is the continued pursuit to change and incorporate novel ideas, modern methods, and societal needs that keeps successfully preparing our students for their scientific careers. We have a consistent track record of program completion, on-time graduation rates, publications, and awards, as well as career advancement to postdoctoral fellowships, faculty positions at research-intensive universities and primarily undergraduate institutions, and biotechnology companies. Since 1997, the Genetics Program has been supported by a T32 Predoctoral Training Grant from the National Institutes of Health, last awarded in July 2022.





Lori Wallrath, Ph.D.
Professor, Department of
Biochemistry and Molecular Biology
Director, Genetics Ph.D. Program



Bryan Phillips, Ph.D.
Professor, Department of Biology Associate
Director, Genetics Ph.D. Program



Rob DuBay
Program Administrator
Genetics Ph.D. Program



Amber Arey
Program Associate
Genetics Ph.D. Program

Genetics Retreat Chair, Aislinn Williams, MD, Ph.D.

Associate Professor, Psychiatry

The Williams lab is interested in understanding the molecular and cellular mechanisms by which genetic risk factors contribute to psychiatric disease from a developmental perspective. Her current projects focus on voltage-gated sodium and calcium channel genes, which have been linked to the risk of developing bipolar disorder, schizophrenia, depression, and autism. Her laboratory uses induced pluripotent stem cells and transgenic mouse models to study how genetic variants in ion channels alter neuronal development, neural circuit function, and behavior. Her laboratory also has ongoing projects studying the neurodevelopmental impacts of 16p11.2 CNVs. We employ a wide range of approaches, including molecular biology, live cell imaging, neuropathology, and animal behavioral assessments, to try to unravel the developmental pathways involved in neuropsychiatric disease, in the hope of identifying novel treatment targets.

**Genetics Retreat Co-chair, Anne Martin, Ph.D.**

Assistant Professor, Biology

Every thought or action we make relies upon our brain cells communicating through specialized types of connections called synapses. This fast communication can be electrical, mediated by neuronal gap junction channels, or chemical, mediated by neurotransmitters and receptors. While the structures that make up these different synapse types are distinct, we find that molecules exist to bridge their formation and seek to understand how a neuron molecularly specifies the correct type of synapse to build and support. The Martin lab is focused on investigating synapse coordination: the mechanisms that direct the assembly of electrical and chemical synapses, how these processes overlap and compete, the importance of this coordination to long-term nervous system function/behavior, and how disruptions to coordination can reveal a new understanding of neurological disorders.

Genetics Student Committee Members

Emily Fontenoy
Frank Lab
Anatomy & Cell
Biology



Renato Jensen
Mullins Lab
Ophthalmology



Interdisciplinary Graduate
Program in Genetics



Christine Beck, Ph.D.

Associate Professor

The Jackson Laboratory for Genomic Medicine
University of Connecticut Health Center

“Repetitive Sequences Drive Genome Instability”

Christine Beck, Ph.D. is a tenured Associate Professor of Genetics and Genome Sciences at the University of Connecticut Health Center and The Jackson Laboratory for Genomic Medicine. She received her Ph.D. in Human Genetics in 2012 from The University of Michigan where she studied transposable elements with John Moran. She subsequently completed a postdoctoral fellowship with James Lupski at Baylor College of Medicine studying human genomic rearrangements. In the last nine years of her independent research program, Dr. Beck has examined how repetitive elements can lead to mammalian genome variation using genome and transcriptome sequencing, molecular genetics, and the development of new computational approaches to interrogate rearrangements and their consequences. The Beck lab uses genome assemblies to identify variation that can affect disease outcomes, to examine the mechanisms of human variation, and to interrogate the impact of variation on gene regulation and evolution.

Alumni 2022 Jacob Schillo, Ph.D.

Principal Scientist
Translational Oncology & Tumor Biology
Encapsulate

*"Beyond Genomics: Functional Cancer Modeling
Across Earth and Space"*



Jacob Schillo, PhD. is Principal Scientist at Encapsulate, a biotechnology company developing microfluidic platforms for functional precision oncology. He received his doctorate in Genetics from the University of Iowa in 2022, where he trained under the mentorship of Dr. Adam Dupuy and focused on identifying co-occurring mutations that drive therapeutic resistance in melanoma. He subsequently completed postdoctoral training at Yale University in the laboratories of Dr. Katerina Politi and Dr. Don Nguyen, investigating epigenetic mechanisms underlying lung cancer progression and metastasis. Prior to his scientific career, Dr. Schillo served in the United States Air Force as a Nuclear Weapons Specialist, supporting Department of Defense and Department of Energy missions.

At Encapsulate, Dr. Schillo leads the development of patient-derived organoid and tumor-on-a-chip platforms designed to predict individual therapeutic response and advance precision oncology. His experiences in both military service and biomedical research have shaped his interest in building technologies that translate complex biological data into actionable decisions. His work also extends beyond Earth through a NASA-supported Metastasis-on-a-Chip program being evaluated aboard the International Space Station to investigate how microgravity influences cancer biology and metastatic progression.



Alumni 2021

Yann Vanrobaeys, Ph.D.

Program Scientist 1/Research Scientist and
Bioinformatics

BioMicro Center & Koch Institute Massachusetts
Institute of Technology

"From Iowa to MIT: A Bioinformatics Career Path"

Yann Vanrobaeys, Ph.D. is a Bioinformatics Research Scientist at the MIT BioMicro Center and Koch Institute for Integrative Cancer Research, where he collaborates with research groups across MIT on computational analyses spanning cancer biology, neuroscience, and genomics. He earned his Ph.D. in Genetics from the University of Iowa in 2024, where he worked in Ted Abel's laboratory developing cutting-edge single-cell and spatial transcriptomic approaches to map activity-dependent gene expression in the brain, resulting in multiple first-author publications in *Nature Communications*. Prior to Iowa, he completed graduate training in biochemistry at the Université de Sherbrooke and holds undergraduate degrees in biotechnology from the University of South Brittany, France. At MIT, Yann develops and applies computational frameworks for bulk and single-cell RNA seq, spatial transcriptomics, and Oxford Nanopore long-read sequencing, with an emphasis on reproducible, containerized workflows and publication-ready analyses. His work has contributed to submitted manuscripts from the Gehrke, Straehla, and Anderson laboratories, spanning Zika virus neuropathogenesis, blood-brain-tumor barrier biology, and cancer immunotherapy. He is also an active contributor to the Breakthrough Cancer program, where he applies long-read sequencing and epigenomic analyses to glioblastoma research.

Student Oral Presentations

Session 1: 9:40 am-10:40 am

Kayla Henry

"Cdk8 and Cdk19 exhibit a synthetic rescue that maintains basal cardiac homeostasis in cardiomyocytes"

Ellen Koufer

"Site-specific N-glycosylation regulates ER retention and trafficking of I1061TNPC1"

Maria Alejandra Rodriguez Herrera

"Ketone body sensing in hypothalamic neuronal population"

Session 2: 2:15 pm-3:15 pm

Joshua Ayelazuno

"Glucose limitation and amino acid metabolism define a pH-modulating transcriptional program underlying candida glabrata phagosomal persistence"

Tyler Rankin

"Defining meaningful clinical endpoint for BBS10-associated retinal degeneration"

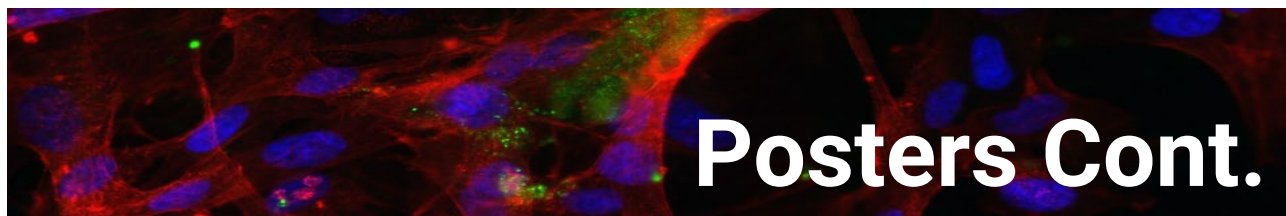
Lucretia Shumate

"Chemical molecule screening by luciferase reporter construct for inhibitors of CDR1 expression in azole-resistant pathogenic Candida glabrata"

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1. Cdk8 and Cdk19 exhibit a synthetic rescue that maintains basal cardiac homeostasis in cardiomyocytes

Kayla M. Henry^{1,2,3}, Ella M. Riniker^{2,3}, Katharine Estep^{2,3}, Robert Weiss², Chad E. Grueter^{1,2,3}.

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2 Department of Internal Medicine, Division of Cardiovascular Medicine, Francois M. Abboud Cardiovascular Research Center, University of Iowa, Iowa City, IA, USA

3 Fraternal Order of Eagles Diabetes Research Center, University of Iowa, Iowa City, IA, USA

Synthetic rescue is a genetic phenomenon in which the detrimental effects of one mutation are offset by a second mutation, restoring cellular function and survival. While this concept has emerged primarily from cancer biology, its relevance in the heart remains unknown. To our knowledge, our lab has identified the first example of a synthetic rescue in cardiomyocytes involving paralogous Mediator kinase subunits, Cdk8 and Cdk19. The mediator complex is responsible for modulating signal-dependent transcription and has been implicated as essential in maintaining basal cardiac function, yet the roles of Cdk8 and Cdk19 have not been defined in cardiomyocytes. To determine their functions in vivo, we generated a cardiomyocyte specific knockout Cdk8 mouse model (Cdk8cKO), a germline Cdk19 knockout (Cdk19KO), and a double knockout (Cdk8/19dKO). Cdk8cKO mice developed progressive cardiac dysfunction, dilated cardiomyopathy, increased fibrosis, and premature lethality by 9 months of age. Unexpectedly, simultaneous deletion of Cdk19 completely rescued these phenotypes, with Cdk8/19dKO mice maintaining normal cardiac structure, function, and survival through 12 months of age. RNA sequencing suggests in the absence of Cdk8, Cdk19 promotes activation of pathways associated with heart failure, whereas a loss of both Cdk8 and Cdk19 prevents maladaptive transcriptional responses and preserves cardiac homeostasis. Ongoing studies are aimed at deciphering the underlying mechanism for synthetic rescue through distinct Cdk8 and Cdk19 substrate identification. Together, these findings uncover a previously unrecognized genetic compensation mechanism in the heart and establish Cdk8/19 synthetic rescue as a novel regulator of basal cardiac function.

2. Site-specific N-glycosylation regulates ER retention and trafficking of I1061T-NPC1

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² Stead Family Department of Pediatrics, University of Iowa, Iowa City, IA

³ Department of Chemistry, College of Liberal Arts and Sciences, University of Illinois, Chicago, Chicago, IL

Niemann-Pick disease type C1 is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in NPC1, which encodes a lysosomal membrane protein required for cholesterol export. The most common pathogenic variant, I1061T, retains cholesterol transport activity when properly localized to lysosomes but is predominantly retained and degraded in the endoplasmic reticulum (ER) before reaching its functional destination. Although NPC1 is extensively N-glycosylated, the contribution of individual N-linked glycans to NPC1 folding, ER quality control, and trafficking remains poorly understood. Here, we investigated the role of site-specific N-glycosylation in regulating the trafficking of wild-type and I1061T-NPC1. Using mass spectrometry, we profiled N-glycosylation of wild-type and I1061T-NPC1 and identified broad differences in glycan maturation associated with the I1061T variant. Notably, we identified N-glycosylation at N1064, located only three amino acids from the pathogenic I1061T substitution. To determine whether glycosylation at this site influences NPC1 trafficking, we disrupted the N1064 glycosylation sequon by introducing an N1064Q substitution and assessed NPC1 maturation using Endoglycosidase H sensitivity assays and immunoblotting. Loss of N1064 glycosylation did not alter trafficking of wild-type NPC1. In contrast, introduction of N1064Q into I1061T-NPC1 partially restored acquisition of Endoglycosidase H resistance, indicating increased trafficking beyond the ER. Together, these findings identify a site-specific N-glycan that selectively influences the proteostasis of I1061T-NPC1 and supports a model in which glycan-dependent ER quality control contributes to retention of the mutant protein. Targeting interactions between site-specific glycans and ER quality-control machinery may therefore provide a strategy to promote trafficking of functionally competent I1061T-NPC1.

3. Ketone body sensing in hypothalamic neuronal populations

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² Harold Hamm Diabetes Center, University of Oklahoma, Oklahoma City, OK

³ Department of Biochemistry and Physiology, University of Oklahoma, Oklahoma City, OK

Mammals possess a range of nutrient-responsive pathways for adapting to changes in energy availability. One example is ketone bodies, which are lipid-derived metabolites that are produced from the liver during physiological states of low glucose availability. Ketones circulate through the bloodstream to reach extrahepatic tissues where they are ultimately taken up and oxidized into ATP for energy. A major consumer of ketones is the brain, which uses ketone bodies to sustain its high energetic demand. Interestingly, interventions that increase the production of ketone bodies (e.g., dietary restriction, fasting, ketogenic diet) beneficially enhance metabolic health and cognitive protection. One of the best-known therapeutic applications for drug resistant epilepsy is the use of a ketogenic diet. The anti-convulsant effects of ketones are thought to involve the modulation of neuronal firing through the regulation of ion flux across the plasma membrane. However, it is still unclear whether ketone bodies signal to the central nervous system (CNS) to improve central and peripheral health beyond their metabolic function. Here, we find that the CNS can rapidly sense ketone bodies. Hypothalamic neurons are activated by the peripheral administration of ketones in wild-type mice. Furthermore, using acute slice imaging of the genetically encoded calcium sensor GCaMP we have dissected the dynamics of ketone-induced neuronal activation in the paraventricular nucleus of the hypothalamus (PVH). Our data suggests that the hypothalamus dynamically senses ketone bodies, similar to how it senses changes in other nutrients (i.e., glucose), which may be critical for nutrient and energy homeostasis.

4. Glucose limitation and amino acid metabolism define a pH-modulating transcriptional program underlying *Candida glabrata* phagosomal persistence

J A Ayelazuno¹, B Z He^{1,2}

¹ Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA

² Department of Biology, University of Iowa, Iowa City, IA

Candida glabrata can persist within macrophages despite harsh conditions in the phagosome. Previous studies suggest that during host infection, *C. glabrata* may adapt to nutrient limitation by utilizing alternative carbon sources, including amino acids. Amino acid catabolism requires removal of amino groups, generating ammonia that can raise environmental pH. This alkalization counteracts the acidification that is part of the maturation process for phagolysosomes; since the acidic pH is crucial for the activity of the proteases to breakdown the fungal cell walls, the alkalization could help create a permissive intracellular niche for fungal persistence and survival. These observations suggest that nutrient availability directly influences pH modulation and may contribute to macrophage survival. However, the transcriptional program linking amino acid utilization to pH modulation remains unresolved. We hypothesized that glucose limitation activates an amino acid-responsive transcriptional state that supports alkalization and may contribute to phagosomal persistence.

To define this program, we performed RNA-seq on *C. glabrata* grown in %1 casamino acid medium from pH 4.0, sampled at baseline, t7.5hrs, and t11.5hrs, alongside glucose-supplemented controls. Principal component analysis separated baseline, casamino acid, and glucose-supplemented samples, indicating that growth on amino acids as alternative carbon sources induces a distinct transcriptional state. Differential expression analysis identified casamino-specific genes by requiring significant changes relative to baseline and matched glucose controls. The response was predominantly inductive. The casamino-specific gene trends were largely recapitulated in two published, asynchronous *C. glabrata* macrophage infection datasets—RNAPII ChIP-seq and RNA-seq—indicating that the alternative-carbon source transcriptional program captures biologically relevant response that are also engaged during macrophage adaptation.

GO enrichment of sustained upregulated genes highlighted amino acid and nitrogen metabolism, transport, mitochondrial/TCA-associated metabolism, lipid and sterol biosynthesis, and cell wall-associated processes.

Together, these data define a nutrient-responsive transcriptional program linking glucose limitation, amino acid metabolism, and pH modulation in *C. glabrata*. Ongoing functional studies will test whether prioritized candidates contribute to alkalization and macrophage survival.

5. Defining meaningful clinical endpoints for BBS10-associated retinal degeneration

Tyler J. Rankin^{1,2}, Wanda Pfeifer^{1,*}, Ethan Brandauer¹, Giulia Del Valle^{1,#}, Samuel Tadros¹, Megan Smith¹, Valencia Potter¹, and Arlene V. Drack^{1,2}

¹ Department of Ophthalmology and Visual Sciences, University of Iowa

² Interdisciplinary Graduate Program in Genetics, University of Iowa

* current address: Bascom Palmer Eye Institute, Palm Beach Gardens, Florida

#current address: Hospital de Olhos do Paraná, Curitiba, Paraná, Brazil

Bardet-Biedl syndrome type 10 (BBS10) is an inherited ciliopathy characterized by progressive retinal degeneration and severe vision loss. As therapeutic approaches for inherited retinal diseases advance toward clinical trials, a major challenge is identifying outcome measures that are sensitive to disease progression while also reflecting meaningful changes in visual function. Our work aims to define these endpoints in individuals with biallelic BBS10 variants and validate complementary measures of functional vision for future interventional trials.

We longitudinally characterized retinal degeneration in ten individuals with BBS10-associated disease over 6-12 months. Despite the progressive nature of the disease, several conventional measures of visual function demonstrated variability or limited change over this short interval. However, retinal structure on OCT showed a significantly measurable progression. Manual foveal thickness significantly decreased between visits and with increasing age, while automated foveal thickness decreased with age, supporting its utility as a sensitive marker of short-term disease progression. Interestingly, progressive outer retinal degeneration was accompanied by significant thickening of the inner retina between visits, potentially reflecting structural remodeling secondary to photoreceptor loss. Flash visual evoked potential amplitude also declined with age, supporting its potential utility as an objective functional measure.

A virtual reality mobility course, using patented software on a standard gaming device, was studied as an exploratory endpoint. Pilot testing in individuals with BBS10-associated retinal degeneration demonstrated feasibility and differences in functional performance. We are now validating this approach in a larger cohort which includes patients treated with an investigational gene therapy to determine its reproducibility and relationship with established measures of retinal structure and function. Together, these studies identify measurable structural changes associated with BBS10 disease progression, reveal potential remodeling of the surviving retina, and provide a framework for integrating these biomarkers with assessments of real-world visual function for future clinical trials.

6. Chemical molecule screening by luciferase reporter construct for inhibitors of CDR1 expression in azole-resistant pathogenic *Candida glabrata*

L Shumate^{1,2}, T Conway¹, S Beattie³, D Krysan³, WS Moye-Rowley^{1,2}

¹ Department of Molecular Physiology and Biophysics, University of Iowa, Iowa City, IA

² Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA

³ Department of Pediatrics, University of Iowa, Iowa City, IA

Candida glabrata is an opportunistic yeast which causes infections in immunocompromised patients and is the second most common species responsible for *Candida* infections with a 40% crude mortality rate.

These infections are often treated with azole drugs, such as fluconazole. Azoles target the ergosterol biosynthesis pathway, specifically inhibiting an enzyme encoded by the ERG11 gene. Azole resistant isolates are often found to have a hyperactive allele of a transcription factor encoded by PDR1, such as D1082G PDR1. Pdr1 stimulates the expression of a membrane transporter protein called Cdr1 that is thought to act as a drug pump, exporting azole drugs out of the cell. Strains containing the D1082G PDR1 hyperactive allele show a tenfold increase in Pdr1 activity compared to wild-type, increasing the azole resistance of the hyperactive strain.

Azole resistance is a serious problem because only three classes of drugs are available to treat fungal infections.

In order to reduce azole resistance complications, we aim to identify small molecule compounds which will reduce the activity of the hyperactive isoforms of Pdr1. We have screened a library of 52K compounds with a hyperactive D1082G PDR1 strain of *C. glabrata*, which contains a luciferase reporter gene under the control of the CDR1 promoter to identify compounds which reduce the activity of Pdr1 and thus reduce CDR1 induction. Through this we have identified several compounds which reduce CDR1-LUCIFERASE induction in our high-throughput screen and in low-throughput secondary testing. Additionally, these compounds have reduced fluconazole-mediated induction of native CDR1 expression and lower the concentration of fluconazole necessary to inhibit growth. These results indicate these compounds increase azole susceptibility of strains containing hyperactive PDR1 alleles, potentially increasing the number of ways we could combat *C. glabrata* infections. We would ultimately want to determine if these compounds could treat azole-resistant *C. glabrata* infections in vivo.

7. Evolution of pioneer factor activity between orthologous transcription factors

B Bruce^{1,2}, E O'Brien¹, B He^{1,2}

¹ Department of Biology, University of Iowa, Iowa City, IA

² Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA

Pioneer Factors (PFs) are a special class of Transcription Factors (TFs) that can bind DNA motifs embedded in nucleosomes. This then leads to the opening of the chromatin and allows for downstream gene expression. Pioneer factors were initially identified and have been primarily studied in mammalian development and for their roles in cell-fate specification. This led to the focus on a small number of well-characterized PFs, leaving important questions unanswered, such as; whether PFs function in other biological processes and how PF activity varies and evolves among homologous TFs. Emerging evidence suggests that PF activity is not an invariant property of particular TFs but a quantitative trait that can differ among homologs. In preliminary studies, we found strong evidence supporting such variation between two orthologous TFs in the related yeast species. In the baker's yeast *Saccharomyces cerevisiae*, the basic Helix-Loop-Helix TF, Pho4 (ScPho4), fails to induce a reporter gene when the promoter contains only a nucleosome-occluded motif. By contrast, the orthologous Pho4 in the related yeast, *Candida glabrata* (CgPho4), is capable of inducing the same mutant promoter. In vivo chromatin profiling reveals that CgPho4 occupies nucleosome-occluded and exposed binding sites at comparable levels. At promoters containing occluded sites, CgPho4 promotes reduced nucleosome occupancy and expansion of the nucleosome-depleted region through interactions with chromatin remodelers. This leads to productive gene activation, while ScPho4 fails to induce to significant levels. Domain-mapping chimera experiments further implicate an intrinsically disordered region immediately N-terminal to the bHLH DNA-binding domain in conferring this activity in CgPho4. Several additional Pho4 orthologs exhibit similar activity, establishing the Pho4 family as a comparative model for investigating the molecular evolution of pioneer function.

8. Dissecting synapse development and pruning in the neurofibromatosis type 1 *Drosophila* model

Cole Collins^{1,2} and Seth Tomchik^{1,2,3}, PhD

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² Department of Neuroscience and Pharmacology, University of Iowa, Iowa City, IA

³ Department of Neuroscience and Pharmacology Pediatrics, University of Iowa, Iowa City, IA

Synaptic development and refinement (pruning) during critical periods is vital to neurodevelopment. Disruption of these processes contributes to neurodevelopmental disorders (NDDs), which alter cognition and behavior. Neurofibromatosis type 1 (NF-1) is a monogenic multisystem disorder resulting from mutations in the Neurofibromin 1 gene (NF1). NF-1 is a NDD that presents cognitive and behavioral differences in patients along with higher rates of psychiatric comorbidities such as autism spectrum disorder and intellectual disability, and it is unknown how these differences are shaped by changes in synaptic development.

Loss of the NF1-encoded neurofibromin protein (Nf1) in *Drosophila* results in behavioral alterations, including increased grooming frequency. Further investigation revealed that Nf1 expression is required during a developmental critical period for normal grooming behavior. This suggests that Nf1 is required during development for normal adult behavior. Therefore, it is necessary to identify the irregular neurodevelopmental mechanism during critical periods under Nf1 control responsible for this difference.

Because *Drosophila* Nf1 protein is conserved, as is function of its downstream pathways, it is an exceptional model for NF-1. *Drosophila* have also been used to understand neurodevelopmental mechanisms, further increasing their value to fill this knowledge gap.

To investigate whether loss of Nf1 affects synapse development and pruning, we examined synapse formation and elimination in the *Drosophila* antennal lobe. By applying RNAi knock down of Nf1 in flies with a well-established olfactory exposure paradigm, we present a powerful tool to illustrate neurodevelopmental irregularities brought about by Nf1 protein loss. Preliminary results suggest that loss of Nf1 affects pruning in the ethyl butyrate-responsive VM7 glomerulus of the antennal lobe. By determining the neurodevelopmental mechanism underlying the learning and behavior differences in NF-1 models we can apply the same experimental design to investigate downstream pathways of Nf1 protein as well as other genes related the NDDs.

9. Genetic drivers of MEK inhibitor resistance in low-grade serous ovarian cancer

I Edwin^{1,2}, R Peplinski¹, A Polio³, JD Riordan², M Goodheart³, AJ Dupuy^{1,2}

¹ Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA

² Department of Anatomy and Cell Biology, University of Iowa, Iowa City, IA

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Low-grade serous ovarian cancer (LGSOC) is a rare subtype of epithelial ovarian cancer accounting for 5-10% of cases. A defining characteristic of LGSOC is activation of the mitogen-activated protein kinase (MAPK) pathway, which follows a RAS-RAF-MEK-ERK signaling cascade. Approximately half of LGSOC patients harbor RAS or RAF mutations in KRASG12V/D, NRASQ61R/K, or BRAFV600E. Even after cytoreductive surgery and chemotherapy, ~80% of patients experience recurrence. Recently, clinical trials have demonstrated that inhibiting MEK or MEK along with a focal adhesion kinase (FAK) prolongs progression free survival for recurrent disease. However, patients eventually succumb to disease, highlighting unidentified mechanisms of therapeutic resistance. The objective of this work is to uncover genetic drivers of therapeutic resistance and understand how these drivers mechanistically promote LGSOC progression.

To investigate this, we utilized LGSOC cancer cell lines: ES2 (BRAFV600E), VOA7681 (KRASG12V), and PM-LGSOC-01(KRASG12V). We performed Sleeping Beauty mutagenesis, a low-bias forward genetic screen, in ES2 cells and RNA-sequencing in all three cell lines after MEK inhibition (MEKi) to identify drivers of resistance and conserved gene expression changes. We further analyzed immunohistochemistry and RNA-sequencing from LGSOC patient tumors to understand if the same genes/pathways were being altered clinically.

Our ES2 screen identified ETV1 and ETV5 among the top 10 drivers of MEKi resistance. RNA-sequencing demonstrated that MEKi reduced ETV1, ETV4, and ETV5 expression in all three cell lines. Finally, patient tumors showed that ETV4 trended with LGSOC progression and ETV1, ETV4, and ETV5 transcriptional levels were elevated in LGSOC compared to patients with other epithelial ovarian cancer subtypes. These results suggest that ETV1, ETV4, and ETV5, members of the PEA3 transcription factors, may be involved in promoting MEKi resistance in LGSOC. Currently, my focus is understanding how overexpression of ETV1, ETV4, and ETV5 and deactivation of their transcriptional repressor, Capicua (CIC), are contributing to MEKi resistance.

10. Identification of expression-modulating variants encompassing LOXL1

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Genome wide association studies of exfoliation syndrome have identified polymorphisms in LOXL1 associated with increased risk of disease. The mechanisms by which polymorphisms in or near LOXL1 affect disease risk is unknown. We and others hypothesize that LOXL1 contains one or more expression modulating variants (emVars) that influence disease risk by altering expression of nearby genes. Therefore, we evaluated polymorphisms encompassing the LOXL1 region to identify polymorphisms displaying allele-specific regulatory effects.

We conducted a massively parallel reporter assay to identify emVars associated with increased risk of developing XFS. Hundreds of oligonucleotides were designed, each containing alleles for one or more polymorphisms in the LOXL1 region. These oligonucleotides were cloned into an expression vector to create a plasmid library and transfected into HEK-293T and HLE-B3 cells. From each replicate of transfected cells, DNA and RNA were extracted. NGS libraries were created, pooled, sequenced, and aligned to the human reference genome. The regulatory effect of each polymorphism was determined by computing the relative allelic prevalence of each polymorphism in the libraries.

We identified 11 putative emVars in HEK-293T and HLE-B3 cells. To assess the biological relevance of the emVars, we annotated each emVar based on observed eQTL association in GTEx. The database JASPAR was used to screen for transcription factor binding motifs overlapping our putative emVars.

In summary, we have identified putative emVars that may modulate transcription of LOXL1, which may affect risk of developing XFS. The emVars will be validated with RT-PCR to confirm the observed allele-specific changes in expression. We will confirm allele-specific changes in protein binding and verify the identities of the proteins that bind our emVars. We aim to identify regulatory mechanisms revealing therapeutic targets that may lead to treatments that prevent or delay blindness caused by XFS-related glaucoma.

11. Factors that control synaptic homeostasis maintenance also support sleep

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The brain and all the tissues that it excites govern animal behavior. To keep behaviors controlled, nervous system output needs to stay within physiological bounds. At the levels of neurons, synapses, or circuits, this means that homeostatic forms of regulation are needed. One model synapse where this form of regulation is studied is the *Drosophila* neuromuscular junction (NMJ). Our lab and others have found that at the NMJ, a small group of factors has been identified as critical for the long-term maintenance of synaptic homeostasis. These factors can respond to acute challenges to the synapse but cannot maintain synaptic homeostasis with long-term challenges.

The idea of homeostatic regulation has been extended to specific behaviors like sleep. The synaptic homeostasis hypothesis (SHY) in the sleep field posits that sleep is used as an off-line period to restore the brain's capacity for plasticity that is needed during wakefulness. If the general concept of SHY is correct, perturbations that disrupt sleep would affect synaptic homeostasis, and likewise, disruptions to synaptic homeostasis would also affect sleep. Previous research has shown that disruptions in a subset of canonical sleep genes can also cause disruptions to synaptic homeostasis. I compared the 23 maintenance factors to wild type and found that 12 showed abnormal sleep phenotypes in adult *Drosophila*. Four of these factors show decreased sleep when knocked down pan neuronally. These factors are *Src64B* (Src family kinase), *Pyramus* (FGF ligand), *Stumps* (adaptor), and *Ephexin* (Rho-type GEF). I am currently working to determine the specific neurons where these genes work in sleep. Once I have identified the neurons where these genes function in sleep I will work on determining how these factors control sleep behavior.

12. Periderm-like cells are present on the surface of *Irf6* knockout mouse embryos

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The main function of the epidermis of the skin is to form an effective barrier protecting the body. The epidermis originates from the single-layered ectoderm, when cells delaminate to establish the basal and periderm layers between embryonic day (E) 9.5 and 12.5. As the epidermis stratifies (E12.5 to E17.5), the periderm stays superficial to the developing layers until it sloughs off starting at E17.5. Many molecules are required for epidermal differentiation including Interferon Regulatory Factor 6 (IRF6). Specifically, *Irf6*-null embryos show absence of terminal epidermal differentiation and of barrier function. Since the periderm is part of the epidermal differentiation process and that this process is impaired in *Irf6*-null embryos, we asked whether the periderm is affected by *Irf6* levels. To answer this question, we analyzed the superficial layers of wildtype and *Irf6*-null embryos. At E10.5, E12.5 and E14.5, we observed that most periderm cells are polygonal in shape with bundles of microvilli marking their borders and fewer microvilli dispersed throughout their surface. Interestingly, periderm shape and abundance of microvilli vary along the cranial-caudal axis, suggesting regional influences in periderm morphology in wildtypes. In *Irf6*-null, however, microvilli are more disorganized than in the wildtype and superficial cells show indistinguishable cell borders by E14.5. They also lacked the characteristic electron-dense feature of wildtype periderm cells by transmission electron microscopy. However, despite these morphological differences, both wildtype and *Irf6*-null superficial cells show the presence of Keratin (K) 17 and K6, hallmarks of periderm cells. Collectively, although superficial cells of the *Irf6*-null exhibited distinct morphological features compared to wildtype periderm, they shared key markers of wildtype periderm, demonstrating the presence of periderm-like cells in *Irf6*-null epidermis. **NSF (MD), T32 (GG)**

13. Cell surface complement complexes and gene expression at the single cell level in human eyes and hiPSC-derived endothelial cells

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Age-related macular degeneration (AMD) is characterized by early dropout of endothelial cells in the choriocapillaris and increased deposition of the complement cascade's membrane attack complex (MAC). Accordingly, we are interested in learning about the potential role of complement inhibitors and the MAC in endothelial cell health in early AMD.

To study this, we used a single-cell RNA sequencing-based approach with simultaneous cell surface protein detection. Using oligo-barcoded antibodies against the assembled MAC, we can get transcriptomic and surface complement detection at single cell resolution. We used this technique to assay single cell preparations from human donor eyes and human serum-treated hiPSC-derived endothelial cells. Analysis of our human donor eye single-cell data revealed cell clusters with expected gene expression profiles and antibody-based detection of cell surface proteins. The MAC was detected in highest quantities on the surface of immune cells, smooth muscle cells, and pericytes. In our cultured cell single cell data, MAC was detected on a significant fraction of recovered cells. Complement activity appeared to contribute to a variety of gene expression changes on cultured endothelial cells.

Our data showcases this multi-omic approach as a valuable new tool to analyze gene expression and surface complement on cells from human donor eyes and cultured cells. Our findings suggest that the MAC is deposited on an unexpectedly wide variety of different cell types in vivo, and surface complement deposition can alter gene expression of hiPSC-derived endothelial cells.

14. Enhanced glucagon receptor signaling supports pancreatic β -cell compensation in response to nutrient stress

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Type 2 diabetes (T2D) accounts for roughly 90-95% of diabetes cases worldwide. T2D is defined by hyperglycemia and is caused by both resistance to the hormone, insulin, and importantly, insufficient release of insulin by the pancreatic β -cells. Early in response to insulin resistance, β -cells adapt by increasing insulin secretion to preserve glucose homeostasis, termed β -cell compensation. This adaptation acts as the primary defense against the transition from insulin resistance to overt diabetes. Despite the importance of this adaptation, the mechanisms by which β -cells compensate remain incompletely understood. We hypothesize that α -cell to β -cell communication through proglucagon-derived peptides, glucagon and glucagon-like peptide-1 (GLP-1), is a major component of compensation. While the importance of GLP-1 signaling in β -cells is well documented, the role of glucagon signaling in β -cell function is less well understood. Using an ex vivo model of β -cell compensation, exogenous glucagon significantly increased insulin secretion in compensating β -cells relative to controls, while GLP-1 stimulation did not. Additionally, pharmacological inhibition of glucagon receptor (GCGR) signaling, but not GLP-1 receptor (GLP-1R) signaling, greatly reduced insulin secretion in this compensation model. We further found that endogenous glucagon levels were not significantly different between compensating β -cells and controls. Collectively, these findings suggest that during β -cell compensation, there is a reweighting of receptor input from GLP-1R to GCGR that supports increased insulin secretion. Future work will define changes in downstream signaling of GCGR during compensation, including cAMP production and PKA activity, as well as alterations to the trafficking of GCGR after ligand binding. These findings will allow us to better understand how β -cells defend against insulin resistance in the prediabetic stage and potentially uncover strategies to prevent the transition to overt T2D by enhancing β -cell compensation through GCGR signaling.

15. Cyclin C regulates Drp1-dependent mitochondrial fission in response to metabolic and cardiac stress

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Cardiovascular disease remains a leading cause of death worldwide, with mitochondrial dysfunction contributing to both acute injury and chronic progression. Mitochondrial fission, driven by the dynamin related GTPase Drp1, is a central stress response mechanism. Prior work has established that cyclin C translocates from the nucleus to the cytoplasm following cardiac stress and promotes mitochondrial fragmentation in vivo. However, the precise mechanisms by which cyclin C regulates Drp1 activity, and its role in acute metabolic and adrenergic stress responses, remain incompletely defined. We investigated cyclin C's role in mitochondrial dynamics across complementary cellular and in vivo models. Co immunoprecipitation in HEK293 cells revealed a direct association between Drp1 and cyclin C. In mouse embryonic fibroblasts, cyclin C deficiency blunted palmitate induced mitochondrial fragmentation, indicating that cyclin C plays a role in metabolic stress evoked fission. In mice with a cardiomyocyte specific deletion of cyclin C, isoproterenol injection failed to induce the expected increase in total and phospho Drp1 in knockout hearts, and knockout animals displayed altered cardiac remodeling as reflected by increased heart weight to body weight ratios. Together, these findings extend prior observations by identifying cyclin C as a direct Drp1 interacting factor required for acute mitochondrial fission in response to metabolic and adrenergic stress. By linking stress signaling to Drp1 activation, cyclin C emerges as a novel regulator of mitochondrial dynamics with implications for cardiac adaptation and injury responses. These results highlight cyclin C as a potential therapeutic entry point for modulating mitochondrial remodeling in cardiovascular disease.

16. Network based stratification of known microdeletion and duplication syndromes to improve interpretation of variants of unknown significance

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In USA, about 17% of children under 17 years of age have one or more developmental problems with many having neurodevelopmental disorders (NDD) and intellectual disabilities (ID). Given the complexity of NDD and ID patient data, there is a need for bioinformatic approaches that integrate genotype and phenotype information to identify and prioritize pathogenic variants.

Copy number variants (CNVs) are a major genetic cause of NDD and ID, yet patients with strikingly similar phenotypes frequently carry CNVs at entirely different loci. Advances in genomic testing including chromosomal microarrays (CMA) and whole genome sequencing (WGS) led to the identification of an increasing number of "variants of uncertain significance (VUS)". In this project, we hypothesize that specific protein-protein interaction networks are common between established microdeletion / microduplication syndrome (MMS) syndromes and VUS CNVs in patients with similar phenotypes.

To investigate this hypothesis, we used CMA data from over 2000 pediatric patients seen at the University of Iowa. Using network-based stratification (NBS) of CNV gene content together with Human Phenotype Ontology (HPO) semantic similarity, we defined significant MMS PPI networks and resolved patients into $K = 32$ optimal genotype- and phenotype-based clusters. We identified 23 VUS CNVs whose genes connect to MMS networks in STRING DB and further analyzed them for various parameters including tissue expression and established neurodevelopmental disease links. Of these, 13 VUS are enriched in our patient dataset using 2 independent data sets (Chi square test; p value < 0.05): (1) the UIHC Whole Genome Sequencing (WGS) dataset and (2) the All of Us Research Program dataset.

For functional validation, we identified *Drosophila melanogaster* (fly) orthologs for XX of the 13 candidate genes. We will model CNV dosage directly, using RNAi knockdowns and assess learning and memory by T-maze olfactory associative conditioning.

This combined genotype and phenotype approach identifies novel candidate genes affecting cognition and memory and provides a framework for VUS interpretation.

17. Mapping verbal fluency to polygenic risk and diagnostic status

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One in six American children and adolescents have a developmental disability. Early detection and intervention improves outcomes and quality of life for these children. However, we lack efficient and accurate screeners to identify these children. If accessible and accurate screeners were available, children at-risk could be detected earlier and given the support they need to succeed. One possible approach to do this is through the automated screening of language ability. Language difficulties have frequently been shown to have strong comorbidity with developmental disabilities; consequently, evaluating language data via machine learning approaches offers promising results for automated screening development.

Tools like the Controlled Oral Word Association Test (COWAT), a verbal fluency task, offer a widely accessible way to collect quantitative language data to investigate and validate predictive linguistic features. As a preliminary step to evaluate linguistic data as a reliable proxy for developmental disability risk, this study utilized an adult dataset to map COWAT performance to polygenic risk scores ($n = 2,121$) and diagnostic status ($n = 1,087$).

Total word count for the COWAT task tracked significantly with educational attainment ($R^2 = 0.0154$, $p = 9.694 \times 10^{-9}$) and cognitive performance ($R^2 = 0.0181$, $p = 4.987 \times 10^{-10}$) polygenic risk scores. Preliminary investigation also revealed that several clinical diagnoses showed a measurable impact on an individual's total word count, with ROC curve analysis able to predict better than random chance ($AUC = 0.641$) whether an individual had a diagnosis of intellectual disability. These results establish that COWAT performance captures genetically grounded, clinically relevant signal, highlighting its strong potential for the development of accessible automated screening tools for developmental disabilities.

18. Repopulation of human choroid endothelial cells ex vivo

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Age-related macular degeneration (AMD) is characterized by the early loss of choriocapillaris endothelial cells, which can precede degeneration of the RPE and photoreceptor cells. In this study we explored strategies for replacing lost or damaged endothelial cells in the human choroid for AMD therapy and prevention.

Endothelial cells were generated from human iPSCs using a commercial protocol (StemCell Technologies). Punches of human RPE/choroid were flash frozen and subjected to a “decellularization” protocol to remove cells from the tissues. The efficacy of the decellularization was assessed with a protein concentration assay, western blotting, and transmission electron microscopy. Decellularized choroid tissues were mounted to a cell culture plate in the middle compartment of a three-welled divider using Matrigel (Corning) with iPSC-derived endothelial cells plated flanking the decellularized choroid. Once the cells were confluent, the divider was removed to allow the cells to migrate into and “recellularize” the choroid. Time lapse phase contrast microscopy was used to image the migration of endothelial cells co-cultured with choroids. Choroids were embedded for transmission electron microscopy or immunohistochemistry to image intact, decellularized, and recellularized choroid tissues with probes directed against extracellular matrix (including Collagen IV), endothelial cells (UEA-I lectin), and nuclei (DAPI). Bulk RNA-sequencing was performed on endothelial cells that entered choroid tissue and those that did not.

Decellularized human donor choroid tissues contain few soluble proteins and preserved vascular basal laminae. Immunofluorescence imaging showed that iPSC-derived endothelial cells can infiltrate and occupy the decellularized choroid, including collagen IV-bounded lumens. Endothelial cells that repopulate choroid tissue upregulate genes related to ECM remodeling.

Repopulation of endothelial cells within the human choroid is possible ex vivo. This platform will be useful for identifying factors involved in successful revascularization. Repairing the damaged choroid has potential for addressing progression of disease in individuals that suffer from AMD.

19. Metabolic changes in human RPE/choroids in aging and age-related macular degeneration

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Age-related macular degeneration (AMD) is a leading cause of vision loss in older adults with a complex etiology involving environmental and genetic risk factors. Metabolic disturbances are implicated in AMD pathogenesis, but investigations of metabolism in disease relevant human tissue are difficult to undertake.

In this study, extramacular tissue from 87 eyes (86 donors) covering young (n=8), aged control (n=37), early/intermediate AMD (n=21), geographic atrophy (n=7), and macular neovascularization (n=14) were analyzed using LC-MS metabolomics profiling. The largest and most significant differences were found between young and aged control tissue, rather than between aged controls and any disease state or between disease states. Several metabolites elevated in aging are uremic toxins, including trimethylamine N-oxide (TMAO) and uric acid. TMAO was also elevated in tissue from eyes with macular neovascularization compared to aged controls. N-acetylneuraminic acid, an important glycan moiety for endothelial cell function, was elevated in early/intermediate AMD tissue.

Functional and molecular effects of TMAO and uric acid were assessed using wound healing assays with C166 mouse endothelial cells and bulk RNAseq on primary human choroidal endothelial cells. Wound healing was significantly slower in cells treated with 200 µg/mL uric acid. No difference was observed with 100 µg/mL uric acid, 500 µM TMAO, or 1 mM TMAO. Bulk RNAseq revealed significant decreases extracellular matrix genes and gene ontology (GO) terms for both metabolite treatments, including decreased CD34 with TMAO treatment. Uric acid also negatively impacted glycoconjugate binding and plasma membrane signal transduction functions, while TMAO showed increases in several transcription and translation related GO terms.

This study is the first to assess metabolic disturbances in intact disease relevant human tissue for AMD. The LC-MS and bulk RNA-seq results pointed to previously implicated pathways (glycan biology) and new pathways (uremia induced endothelial dysfunction) which both warrant further investigation.

20. APOE and self-reported cognitive symptoms (“brain fog”) during illness in the All of Us Research Program

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Brain fog describes a state of transient cognitive dysfunction that occurs secondary to a primary stressor, which can include stress, poor sleep, or illnesses. The dysfunction of brain fog is characterized by difficulty concentrating, slow thinking, and memory lapses. Previous research has shown an increase of amyloid beta (A β) accumulation during illnesses, such as COVID-19. The accumulation of A β is also notably a key feature of neurodegenerative diseases, such as Alzheimer’s disease, which also display a negative cognitive phenotype. We sought to answer the question whether germline variation in genes governing A β biology is associated with susceptibility to cognitive symptoms during illness.

Using short read whole genome sequence data from the NIH All of Us Research Program, we compared APOE genotype and allele frequencies, and the burden of coding variants in APP, PSEN1, and PSEN2, between participants who reported cognitive symptoms during illness (n=476) and participants who reported illness without such symptoms (n=3911). The brain fog phenotype was ascertained from the COVID-19 Participant Experience (COPE) survey. Variant deleteriousness was scored using CADD.

This study identified the APOE3 allele as significantly underrepresented (p=0.0046), and the APOE4 allele trending towards significant overrepresentation (p=0.0247) in the cohort that did experience brain fog after multiple testing correction. In addition, there were significantly more severe PSEN1 variants identified in the cohort that did not experience brain fog when compared to the cohort that did experience brain fog (p=0.0217). Finally, the analysis on APP found that the cohort that did not experience brain fog had a significantly higher burden of potentially deleterious variants, measured by CADD-Raw score, than the cohort that did experience brain fog (p=6.627e-06).

These findings suggest a potential genetic predisposition to neurological cognitive symptoms during illness, in turn, elucidating possible mechanisms behind the common cognitive symptom known as brain fog.

21. Ectoderm-mediated patterning of the mandible during mouse development

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Embryonic development requires partitioning homogenous tissues into distinct domains; disrupting this causes patterning defects. We recently identified an opposing functional network establishing the oral-aboral axis of the mandibular epithelium. Initially overlapping, the transcription factors (TFs) SOX2 and TFAP2 (AP-2 α and AP-2 β) resolve into complementary expression domains within the mandibular ectoderm. Functionally, loss of aboral TFs expands oral programs aborally, producing ectopic teeth in skin-fated epithelium. While previous studies focused on the mesenchyme, our discovery of early ectodermal partitioning reveals an unexplored mechanism for mandibular patterning, where downstream ectodermal TFAP2 impinges on the SHH axis—potentially via WNT signaling—to reinforce these programs.

Ongoing studies aim to determine: 1) how these networks are initially established, 2) how they mutually repress each other, and 3) which downstream factors drive domain specification. To address these questions, we are utilizing mouse genetics to conditionally force the expression of putative aboral programs (Tfap2b and WNT) within the oral domain, subsequently assessing mandibular development via multiomics, in situ hybridization, and immunofluorescence. Furthermore, we have conducted CUT&RUN profiling of the mandibular epithelium for key oral and aboral TFs across critical developmental stages. To evaluate the functional significance of these bound non-coding regulatory elements, we are pairing luciferase-reporter assays with lentiviral transductions of the relevant TFs.

Ultimately, this competition between opposing ectodermal networks drives mesenchymal organization, illuminating the gene regulatory mechanisms behind mandibular patterning and craniofacial anomalies.

22. The effect of UV damage on transcription factor binding

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Transcription factors (TFs) bind specific DNA motifs, with different sequences altering TF function. Surprisingly, high sequence variation is found within TF binding sites (TFBS), suggesting that TF binding is inherently mutagenic. Two mechanisms may contribute to this high frequency of variation at TFBS by increased frequency of unrepaired damage. First, TF binding enhances DNA damageability by altering its structure. Second, TF binding to damaged DNA occludes recognition of the damage by the repair proteins, attenuating repair. There is evidence for both models in cell-based assays measuring accumulation and repair of UV damage. Focusing on the occlusion of repair model, I hypothesize that TFs can retain sufficient affinity to UV lesion containing DNA and compete with repair proteins (e.g., UV-DDB). Although cell-based assays indicate that repair is repressed at the TF binding loci and that position contributes to competition with the repair proteins, it is still not clear how the sequence context and/or identity of damaged bases have an impact. To understand the effect of UV lesions throughout TFBS on its affinity, we use specificity measured by sequencing (Spec-seq). We first measured the relative affinity of two TFs, Ets-1 and the glucocorticoid receptor (GR), to thousands of sequences accounting for possible single, paired, triplet, and quadruplet variations across their binding sites. We then validated Spec-seq relative affinities using Biolayer Interferometry (BLI). We found that the relative affinities from Spec-seq were remarkably accurate for the high-affinity monomeric Ets-1. For the lower affinity dimeric GR, Spec-seq relative affinities were also validated by BLI with more variability. This work shows that Spec-seq can measure even fine differences in affinities of sequence pools that span two orders of magnitude or more, indicating that Spec-seq can be used to detect the effect of UV lesions on TF affinity.

23. Aberrant NRG1-ERBB signaling leads to strong remodeling in chronic lung disease

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Airway remodeling, such as squamous cell metaplasia, is a hallmark of chronic lung disease, yet the upstream signals driving this phenotype remain poorly understood. In a porcine model of primary ciliary dyskinesia (PCD), we observed airway surface epithelial layer thickening and loss of terminal differentiated goblet and ciliated cells, which are early phenotypes of squamous cell metaplasia. Preliminary Ki-67 staining and EdU incorporation analysis indicate increased basal cell proliferation in the remodeled PCD airways vs. WT. To explore cellular and molecular causative mechanisms, we performed single-cell RNA sequencing (scRNA-seq) of airway epithelial tissues from WT and PCD pigs across postnatal development. Pseudo-bulk differential expression analysis of older PCD versus WT airways revealed 275 significantly upregulated genes enriched for cell proliferation, and the ERBB signaling pathway. Neuregulin-1 (NRG1) emerged as one of the most strongly induced genes in the remodeled PCD airways. Analysis of public human lung scRNA-seq datasets demonstrated elevated NRG1 expression in many chronic lung conditions. This indicates that increased NRG1 is a conserved feature of chronic airway disease.

NRG1 is an EGF-family growth factor that induces cell proliferation through ERBB receptors. scRNA-seq reveals that airway basal cells express NRG1 and its expression is higher in the basal cells of old PCD vs. WT. ERBB2 and ERBB3 are expressed in multiple airway epithelial cell types including basal cells, secretory cells, and ciliated cells. We propose an elevated autocrine NRG1-ERBB2/3 signaling disrupts the balance of basal cell proliferation and differentiation in the airways, resulting in squamous cell metaplasia in old PCD pigs.

Next steps include confirming our preliminary data, defining the NRG1-ERBB pathway in surface epithelial thickening, mapping downstream transcriptional programs that drive metaplasia, and testing whether targeted inhibition of NRG1 signaling can prevent this hallmark phenotype. These mechanistic studies will clarify how crosstalk shapes remodeling across chronic lung diseases.

24. Elucidation of intercalated disc transcriptomes implicates an essential role for Adenomatous Polyposis Coli protein in RNA trafficking and cardiac viability

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Background: RNA localization in cardiomyocytes (CMs) has gained interest with recent evidence of local RNA enrichment and translation at sarcomeres and intercalated discs (ICDs), with microtubule-dependent mRNA localization appearing to be required for cardiac hypertrophy. To date, the identities of ICD-localized mRNAs has remained largely unknown, as no transcriptome-wide unbiased approaches have been used to spatially profile RNAs at ICDs; in addition, few efforts have been made to identify the specific RNA-binding proteins (RBPs) and/or trafficking machinery that mediate ICD RNA localization.

Methods: We developed an “ICD-seq” protocol to isolate and sequence RNAs enriched at ICDs using laser-capture microdissection from wildtype (WT) mouse heart tissue sections (n=10). This required troubleshooting to preserve RNA integrity. ICDs were laser-captured with a 5 µm margin, and control regions were captured either from areas within individual CMs sparing ICDs or as large sectional areas of CM dense regions. HCR-FISH was performed to validate ICD-localization of “top-hit” mRNAs. Bioinformatic tools were used to identify enriched sequence motifs and candidate RBPs. We studied CM-specific APC knockout (cApc^{-/-}) mice by injecting AAV:Tnnt2-Cre virus into 4-week-old Apcfl/fl BL6J mice and WT littermates (n=10 each) and assessed survival and cardiac function.

Results: We identified ~800 ICD-enriched transcripts. Functional classification by pathway analysis yielded terms related to cardiac growth and structure as well as intriguing enrichment of transcriptional regulators. We found significant 4-fold enrichment of G/AG-rich motifs, consistent with high abundance of RNA G-quadruplex structures (rG4s) among ICD-enriched transcripts. We also noted that ICD RNAs were enriched for those known to be trafficked by APC/KIF1C pathway, and notably, cApc^{-/-} mice develop severe dilated cardiomyopathy and early death.

Conclusion: We developed a working ICD-seq protocol and found specific pools of ICD-enriched transcripts, with a significant portion likely trafficked and localized by rG4- and APC/KIF1C-dependent mechanisms essential for normal cardiac structure and function.

25. Uncovering hidden seizures in a large autistic cohort

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Childhood absence epilepsy (CAE) is a common yet frequently underrecognized form of epilepsy in school-aged children, characterized by brief, recurrent lapses in consciousness that significantly disrupt academic, social, and psychological functioning. This diagnostic challenge is particularly pronounced in autistic children, whose absence seizures are often misattributed to core neurodevelopmental behaviors, such as daydreaming or inattentiveness. Left untreated, these frequent, covert seizures can impair learning and exacerbate long-term developmental and mental health challenges. Despite evidence that epilepsy affects up to 46% of individuals with autism spectrum disorder (ASD), the prevalence and genetic architecture of CAE within autistic populations remain unknown.

This project addresses this critical gap by investigating the prevalence, biological signatures, and behavioral characteristics of undiagnosed absence seizures in autistic children using data from the Simons Powering Autism Research (SPARK) cohort. Specifically, this study utilizes the empirically validated Pediatric Seizure Questionnaire (PSQ) to estimate undiagnosed seizure prevalence and compares PSQ-identified cases with participants who hold formal CAE diagnoses. Preliminary analyses from ~1,970 autistic children reveal that one in four exhibit undiagnosed, clinically significant seizure features. Furthermore, these high-risk, undiagnosed individuals show a significantly higher family history of suicide (OR = 1.84, 95% CI = 1.21–2.74, $p = 0.003$). These findings demand urgent attention, as untreated seizures threaten developmental trajectories and signal shared genetic susceptibility to severe psychiatric outcomes.

We hypothesize that undiagnosed absence seizures are far more pronounced in autistic children than current diagnostic rates suggest, and that integrating genetic, medical, and behavioral data reveals distinct, identifiable signatures unique to ASD/CAE comorbidity. Identifying these empirical markers provides the foundation for an accessible screening tool, enabling earlier diagnosis and preventing long-term developmental and psychiatric impairment in a deeply vulnerable population.

26. Identifying redundant functions of AP-2 α and AP-2 β in epidermal development

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Ectodermal dysplasias are rare genetic disorders marked by the abnormal development of multiple ectodermal structures. The AP-2 transcription factor family has strong links to ectodermal development, including early expression in ectoderm-derived tissues, like the neural crest and epidermis. In humans, mutations in TFAP2A or TFAP2B cause significant anomalies in these structures, most notably the craniofacial complex. While previous studies have established a role for AP-2 α in embryonic epidermal development, both Tfap2a and Tfap2b are highly expressed in the epidermis. Their combined role, however, remains unknown. To investigate potential redundancy between AP-2 α and AP-2 β during epithelial development and appendage formation, we are leveraging conditional mouse genetics, basic histology, RNAscope, immunofluorescence, and single-cell multiome sequencing. Initial findings reveal that the combined ectodermal loss of AP-2 α and AP-2 β completely arrests the formation of ectodermal appendages, including hair follicles, mammary buds, and vibrissae. It also results in severely defective epidermal development. Ongoing work focuses on mapping high-resolution expression dynamics of Tfap2a/AP-2 α and Tfap2b/AP-2 β across key stages of epidermal stratification and differentiation. Furthermore, we are identifying the shared regulatory targets of AP-2 to uncover the molecular mechanisms driving this pathology. Ultimately, this work will detail AP-2's essential role in epidermal biology, providing a broader framework to understand the pathogenesis of ectodermal dysplasias.

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27. Canonical Wnt reception in lung fibroblasts regulates alveolar homeostasis

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The alveolus is the functional unit of the lung, where specialized epithelial cells interface with the capillary plexus to enable gas exchange. Maintenance of this structure requires coordinated signaling among alveolar epithelial cells, endothelial cells, and fibroblasts. Fibroblasts have been demonstrated to be a key source and recipient of Wnt signals within the alveolar niche. Canonical Wnt signaling is a highly conserved pathway in which the binding of Wnt ligands to their receptors stabilizes beta-catenin, allowing translocation to the nucleus and regulate transcription of target genes. How Wnt signaling within fibroblasts regulates alveolar homeostasis remains poorly understood.

To determine how reception of Wnt signaling in fibroblasts influences the alveolar niche, we generated complementary mouse models that allow inducible manipulation of beta-catenin in *Pdgfra*-expressing fibroblasts. Conditional deletion of *Ctnnb1* (gene encoding beta-catenin protein) disrupts beta-catenin signaling (Wnt-LOF), whereas deletion of exon 3 from *Ctnnb1* generates a stabilized form of beta-catenin and constitutively activates the canonical Wnt pathway (Wnt-GOF).

Preliminary analysis of the lungs from Wnt-GOF mice revealed a reduction in alveolar type 2 (AT2) cells in the tissue compared to wildtype animals, suggesting that dysregulation of canonical Wnt signaling in fibroblasts alters epithelial homeostasis. We next performed scRNA-seq from the lungs of Wnt-GOF mice which demonstrated broad transcriptional changes in fibroblasts which propagated to changes throughout other cell types in lung, including decreased expression of Hepatocyte Growth Factor (*Hgf*), an important regulator of epithelial growth and regeneration. Ongoing studies are comparing Wnt-GOF and Wnt-LOF models to determine how the direction of Wnt reception in fibroblasts alters their niche functions, including regenerative capacity and signaling with neighboring alveolar cells.

Together, these studies will define how beta-catenin-dependent Wnt signaling regulates fibroblast function and determine how disruption of this pathway reshapes the cellular interactions required to maintain the alveolar niche.

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