From the Director

This Fall the Center for Human Genetics will welcome three new faculty members, Dr. Kelsey Witt-Dillon, Dr. Shyamalika Gopalan and Dr. Aaron Masino.

Dr. Witt-Dillon joins us from Brown University. She studies the genomics of past populations using ancient DNA, with special interests in domestication, admixture, and using computational methods to analyze low-coverage genomic data. Part of her research has elucidated the genetic signatures of dog domestication concomitant with human dispersal out of Africa.

Dr. Gopalan joins us from Duke University. She is an evolutionary geneticist interested in investigating population history and mechanisms of phenotypic variation. Her research combines data and approaches from population genetics, quantitative genetics, epigenetics, and anthropology. Her most recent work has focused on human demographic history during the Holocene and building epidemiological-evolutionary genetic models of *Plasmodium vivax*.

Dr. Aaron Masino joins us from the Children's Hospital in Philadelphia. His research includes machine learning model development for sepsis prediction, utilization of wearable device data to recognize stress in individuals with autism, natural language processing applications for information extraction from clinical text, and deep learning methods to detect latent concepts in electronic health record data.

We are pleased that Dr. Anurag Chaturvedi, who spent six months with the Center as a visiting scholar, will come back to us from the University of Birmingham (UK) to join the Mackay-Anholt laboratory as a postdoctoral research associate. After earning her doctoral degree this Fall semester, Maryam Nasiri, who spent a year at the Center for Human Genetics as a visiting student from the University of Guadalajara in Mexico, will also remain with us as a postdoctoral research associate.

Rebecca MacPherson, a graduate student in the Mackay-Anholt laboratory, defended her doctoral dissertation on *Drosophila melanogaster* models of rare and common neurodevelopmental disorders and has taken a temporary position as lecturer in the Department of Genetics and Biochemistry where she will teach an undergraduate course in comparative genomics before pursuing a career in medical genetics.

Dr. Trudy F. C. Mackay, FRS, is the Self Family Endowed Chair of Human Genetics. She is a Fellow of the Royal Society of London, a member of the National Academy of Sciences of the USA, a member of the American Philosophical Society, and recipient of the 2016 Wolf Prize.

Tori Gyorey has left us for a technical staff position at Stanford School of Medicine. We are delighted to welcome Elisabeth Howansky as a research technician in the Drosophila Core Facility and Sidney Angner as a research technician in the Genomics Core Facility. We also welcome Madeline Santana who joins us as an M.S. student.

The Spring semester featured again an outstanding series of distinguished lectures in Human Genetics. The highlight was the Science and Music event that featured Nobel laureate and former President of the Royal Society, Dr. Venki Ramakrishnan, who gave an inspiring account of his work that led to solving the structure of the ribosome, with musical interludes by his son, cellist Raman Ramakrishnan and concert pianist Benjamin Hochman. Another highlight was our successful summer symposium with a large turn-out and a record number of poster presentations.

This Fall, we are looking forward to distinguished lectures by Drs. Yoav Gilad from the University of Chicago, Gene Robinson from the University of Illinois at Urbana-Champaign, and Tom Maniatis from Columbia University. I also invite everyone to attend the annual retreat of the Center for Excellence in Biomedical Research in Human Genetics, which will be virtual this year via Zoom on October 12.

Finally, I am excited to inform you that after much preparation the Clemson University Precision Medicine Initiative (CUPMI) is ready to start this September. The CUPMI is a collaboration between Clemson University, Rymedi, Inc., and Self Regional Healthcare to collect genome sequences from volunteers that can be connected to their electronic health records to establish a database for future studies aimed at predicting disease risk based on genetic information. The CUPMI stands apart from other databanks since we will sequence the whole genome including coverage of the non-coding segment of the genome. The use of saliva samples will also enable us to obtain information about variation in oral microbiome, and the use of families in addition to unrelated individuals will provide an opportunity to assess environmental effects. In addition, different ethnicities and rural populations will be represented. An initial pilot study of 200 individuals will be expanded to ultimately collect information from at least 100,000 South Carolinians.

The Center of Biomedical Research Excellence in Human Genetics

2023 Summer Symposium
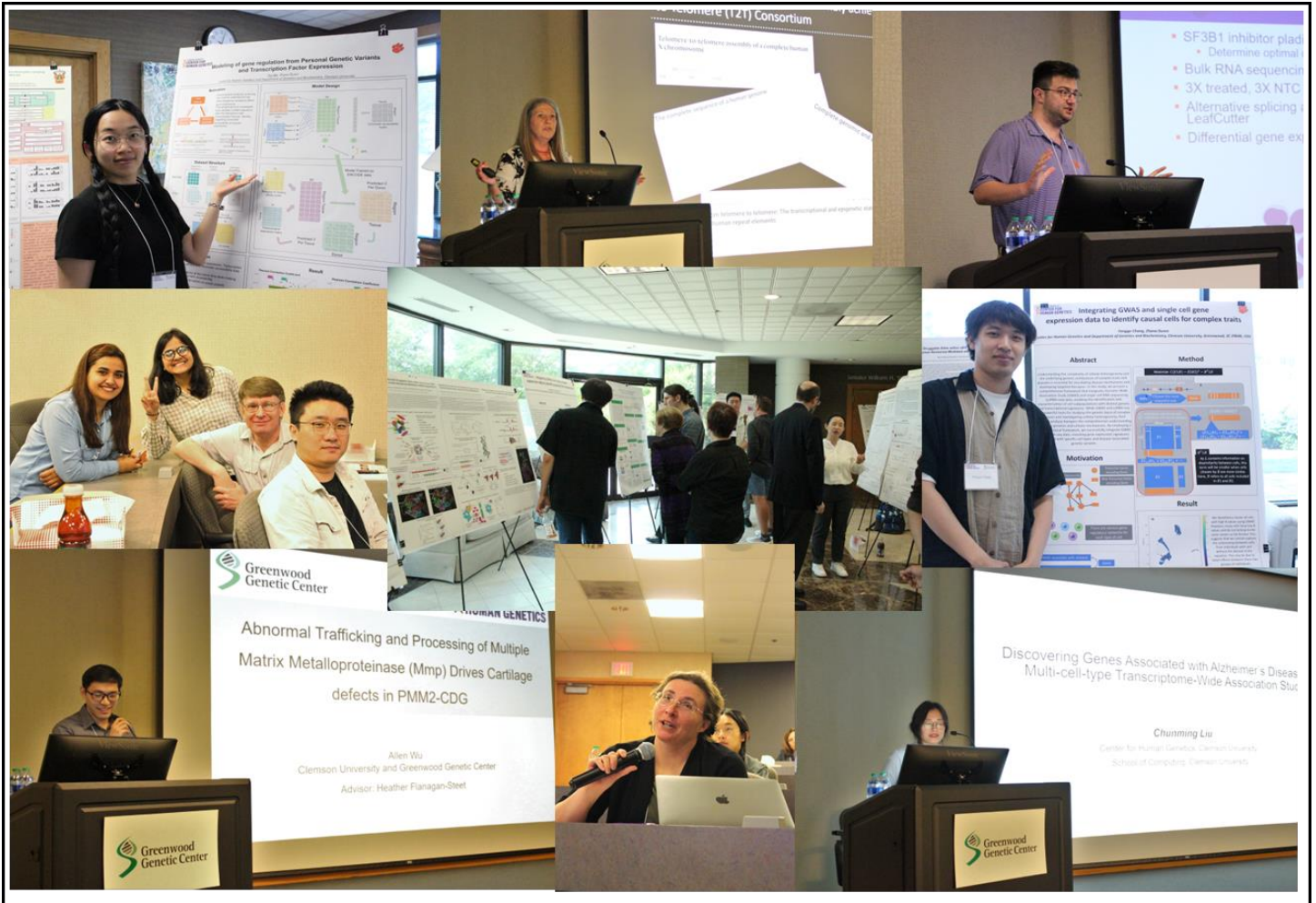
The 2023 summer symposium of the Center for Biomedical Research Excellence in Human Genetics was held on May 10, 2023, with a record attendance of 80+ participants and 40 posters. The theme of the meeting was "Experimental and Computational Approaches to Precision Medicine." The meeting featured plenary speakers and student oral and poster presentations.

Dr. Richard Steet from the Greenwood Genetic Center addressed the problem of the large number of variants of uncertain significance associated with rare diseases and described a collaborative effort that resulted in the characterization of missense variants in the kinase NEK8 as a new cause for polycystic kidney disease.

Dr. Yi Xing from the Children's Hospital of Philadelphia presented ESPRESSO, a computational tool for robust discovery and quantification of transcript isoforms from error-prone long reads and used ESPRESSO to identify aberrant transcripts isoforms among tumor suppressor genes in 40 breast cancer cell lines.

Dr. Beth Sullivan from Duke University discussed the recent completion of the human genome by the Telomere-to-Telomere Consortium and insights derived from that endeavor regarding centromere variation and chromosome stability.

Finally, Dr. Rachel Karchin from the Johns Hopkins University presented computational methods for predicting immunogenic neoepitopes in cancers.

The symposium was highly interactive with a lively poster session and animated discussions throughout the day. Thanks to Sharon Lattimore for her expert assistance in organizing this event. Many thanks also to the Greenwood Genetic Center for hosting the event in their auditorium and for providing breakfast and lunch.

For information about the Center of Biomedical Research Excellence (COBRE) in Human Genetics visit:

https://scienceweb.clemson.edu/cobre/

All About RNA

by Maria E. Adonay

The Clemson University Center for Human Genetics (CHG) hosted its inaugural "RNA-seq Retreat" from July 12 to 14 this year. The 3-day retreat was presented in collaboration with the Clemson University Genomics and Bioinformatics Facility (CUGBF) and gave an in-depth overview of transcriptomics, from experimental design to analysis and interpretation. Participants attended the retreat free of charge in the Roy Muldrow Cooper Library at Clemson University. This was possible due to sponsorship from New England Biolabs, QIAGEN, and PacBio, as well as endorsement from The RNA Society, support from COBRE Grants P20GM139767 and P20GM146584, and the 2023 CU-MRI: Boosting Computational Infrastructure for Multidisciplinary Big Data Analyses Grant awarded to Dr. Trudy Mackay.

Of the 45 applicants for the retreat, 24 were selected to attend. The selected applicants included 19 Clemson affiliates (3 staff scientists, 5 postdoctoral scholars, 2 masters graduate students, 9 PhD graduate students) and 5 members of the Greenwood Genetic Center (2 postdoctoral scholars, 3 staff scientists).

The retreat focused heavily on the theory behind the analyses, while also incorporating a variety of demonstrations and hands-on exercises. "I love being able to have real-life applications of what [transcriptomic] data looks like and what it would look like if there were red flags," one participant remarked, "This is one of the most helpful and applicable workshops I have ever been to." After reflecting on the retreat, another participant said: "I feel like I have a greater understanding of how to analyze RNA-seq data and I am excited that this knowledge can be applied to my future RNA-Seq projects and other sequencing projects."

Dr. Vijay Shankar provides one-on-one instruction to participants in the RNA-seq retreat.

All instructors were bioinformaticians under the direction of Dr. Trudy Mackay (CHG: Dr. Vijay Shankar, Maria E. Adonay, Dr. John Poole) and Dr. Chris Parkinson (CUGBF: Dr. Rooksie Noorai, Dr. Max Ortiz). To expand the event's scope, RNA-seq Retreat organizers plan to modularize retreat topics and incorporate molecular lab exercises into future iterations.

The RNA-seq Retreat will be offered on an annual basis in the summer.

Maria Adonay is a bioinformatician in the Center for Human Genetics at Clemson University.

Congratulations to Dr. MacPherson!

by Kristin Bussey

On May 31st, 2023, Rebecca Anne MacPherson successfully defended her PhD dissertation and joins the ranks of Mackay-Anholt laboratory alumni.

Rebecca gained a strong foundation in research skills during her undergraduate years by participating in Honors research at Clemson University. During her summers she worked as an intern with the Greenwood Genetics Center Molecular Diagnostic Laboratory, thus fostering her interest in the field of clinical genetics. She originally graduated from Clemson University with a bachelor's degree in Genetics before applying to Dr. Trudy Mackay and Dr. Robert Anholt's lab at the Center for Human Genetics (CHG) for a PhD. She was the first graduate student to study under Trudy and Robert since their transition from North Carolina State University.

Early on, Rebecca stated her interest in utilizing *Drosophila melanogaster* as a model system for diseases, both rare and common diseases. Her dissertation covered a range of topics from common disorders, alcohol use disorder and Fetal Alcohol Spectrum Disorder (FASD), to rare disorders of the cohesion (Cornelia de Lange syndrome) and SWI/SNIF complexes (SWI/SNF-related intellectual disability disorders, SSRIDD, Coffin-Siris syndrome).

Her comparative genetics approaches relied on evolutionary conservation of fundamental biological processes. Genetic mutations that give rise to Coffin-Siris syndrome affect chromatin modification, a process that is conserved between humans and flies. Rebecca used targeted RNA interference to study genes that correspond to their human pathogenic counterparts and characterized behavioral effects on startle behavior, a proxy for sensorimotor behavior, locomotion and sleep patterns, as well as morphological changes in the mushroom bodies, brain structures associated with sensorimotor integration and experience-dependent modulation of behavior.

Through her work she was able to establish Drosophila models of rare diseases, identify new functions for a previously unknown gene, *Uhg4*, which encodes a long noncoding RNA associated with alcohol sensitivity and fitness phenotypes, and explored candidate modifier genes for the rare diseases she studied. At the completion of her PhD, her work demonstrated the success of taking a quantitative genetics approach to study single gene disorders with variable clinical phenotypes and how powerful *Drosophila melanogaster* can serve as a model for translational research of rare human disorders.

Her work over the past five years at the CHG has been exceedingly productive, resulting in 5 publications, three of which are first author or co-first author. Clemson University has bestowed several awards on Rebecca, including the Outstanding Senior in Genetics and Outstanding Graduate in Discovery Awards. She was accepted into the Cold Spring
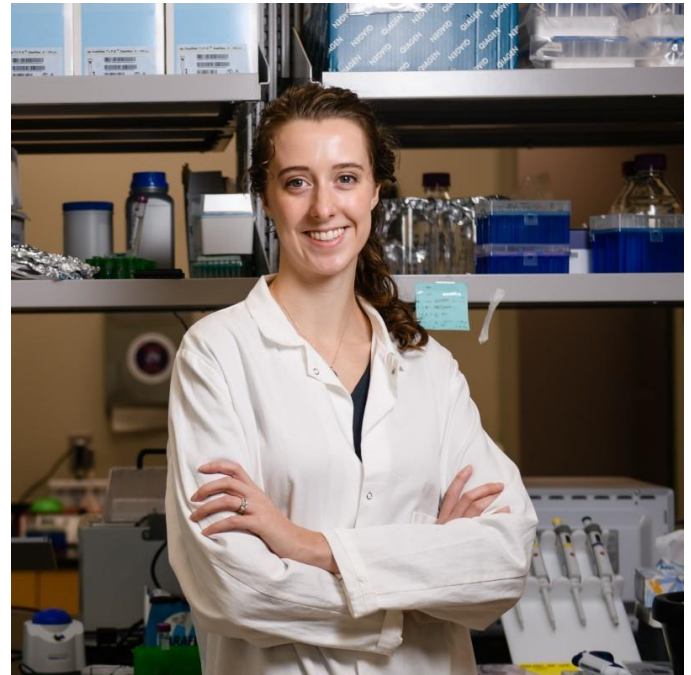
Rebecca MacPherson

Harbor Laboratory summer course on "Statistical Methods for Functional Genomics", which is an intensive residential course on handling large datasets and learning the R programming environment. She is also the recipient of an NIH F31 grant. She presented her work at several national conferences, including the annual meeting of the American Society for Human Genetics and the annual *Drosophila* Research Conference.

Outside of the lab, Rebecca continues to serve her community in many ways. Over the past few years, she has been heavily involved in the Greenwood Genetics Center education division to help create laboratory demonstrations for high-school students to foster early interest in science.

Additionally, she has served as a science fair judge for elementary schools in the past 3 years. She also served as a workshop co-chair for ComSciCon, a science communications conference. She has been a pillar of support for the graduate students at the CHG, offering guidance to new incoming graduate students in both laboratory skills and bioinformatics. Under her tutelage many have flourished and continue the cycle of peer mentoring for others.

Now, as a successful PhD graduate and new mother, Rebecca and her husband will be settling back in Anderson, SC. Alongside raising her son, Rebecca's long-term career goals are to obtain a postdoctoral fellowship in Clinical Genetics and Genomics to one day direct her own clinical diagnostic laboratory of rare disease.

Kristin Bussey is a graduate student in the Center for Human Genetics at Clemson University.

Bach, Chopin, and Gene Machine
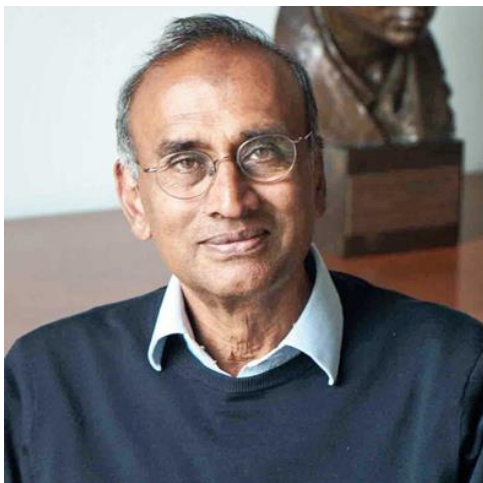
Dr. Venki Ramakrishnan


Raman Ramakrishnan

Benjamin Hochman

A remarkable event occurred at Clemson University on March 9, 2023. Nobel laureate, Venki Ramakrishnan, visited Clemson University to tell the story of his discovery of the structure of the ribosome in a Science and Music event in which his lecture was accompanied by music played by his son, renowned cellist Raman Ramakrishnan, together with family friend, concert pianist Benjamin Hochman. Ramakrishnan has received numerous prestigious awards in addition to the Nobel prize. He was elected to the US National Academy of Sciences and the American Philosophical Society as well as the German Leopoldina society. He served as President of the Royal Society of London, was knighted by Queen Elizabeth, and received the Order of Merit from King Charles. It was an honor for Clemson to host this remarkable scientist. Venki's wife, Vera Rosenberry, accompanied him during the visit. Vera is an accomplished artist and illustrator of children's books.

The event began with a flawless performance of the beautiful Johann Sebastian Bach's Sonata 2 in D Major for piano and viola da gamba. This performance in which the cello and piano came together in complete harmony set the stage for an inspiring presentation by Venki Ramakrishnan about his quest to solve the structure of the ribosome. The lecture, titled "Gene Machine", was a masterful tour-de-force in which Ramakrishnan described the history of the discovery of the ribosome, explained the composition of polypeptides and the mechanism of protein synthesis as well as methods of X-ray diffraction crystallography in an engaging and lucid manner that was targeted to be understandable to a broad audience. He recounted how several laboratories had been in competition to cross the finish line in deciphering the structure of the ribosome at atomic resolution and how he managed to walk away with the prize, the Nobel Prize, that is. In addition to his scientific exploits, Venki expressed profound appreciation for his wife Vera who, while taking care of two young children, was unwaveringly supportive when his scientific ambitions made him move from Ohio to

San Diego, from San Diego to Yale, from New Haven to Long Island, from Long Island to Tennessee, from Tennessee to Utah, and ultimately across the pond to the University of Cambridge. The lecture accentuated the human cost, resilience, perseverance, and commitment that are inherent in the quest for knowledge.

Ramakrishnan's lecture was followed by a rendition of a contemplative piece by Gabriel Fauré, Après la Rêve (After the Dream). After this brief musical interlude, Robert Anholt engaged Venki in a conversation on stage where they both reminisced about their days when they were in graduate school together, discussed to what extent Venki's parents, both well known scientists had influenced his life, whether music had been an important aspect for Venki, whether Venki had any regrets about his life (he did not have any), and advice he could give to young scientists.
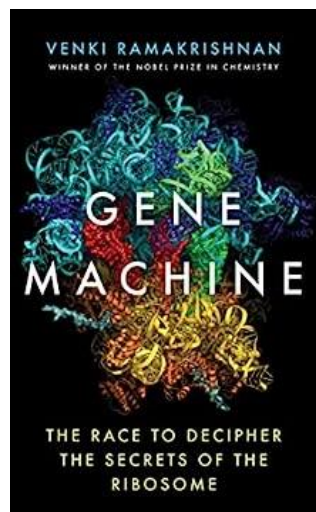
The event concluded with a rousing rendition of Chopin's Introduction and Polonaise Brillante in C Major, a gruelingly difficult piece for the piano where Hochman displayed his mastery of the Steinway and a virtuosity about which the New York Times had commented that "classical music does not get any better than this."

The performance was followed by a reception and book signing. Venki's book *"Gene Machine: The Race to Decipher the Secrets of the Ribosome"* broke the record for book sales of all book signings at Clemson. Many students now own a piece of history, a book, signed by Venki Ramakrishnan.

The Genetic Complexity of Colorectal Cancer Development

by Alp Ummet

On January 27th, 2023, the Clemson University Center for Human Genetics welcomed Dr. David Threadgill, the Tom and Jean McMullin Chair and Professor in Genetics at the Department of Biochemistry & Biophysics, Texas A&M University, as the esteemed speaker for the Distinguished Lectures in Human Genetics series. The lecture titled "The genetic complexity of the EGFR/ERBB signaling axis in colorectal cancer development and therapy" provided valuable insights into his recent research, cutting-edge approaches in cancer therapeutics, and the influence of genetic background on cancer development.

Dr. Threadgill's academic journey began with a Bachelor's degree in Zoology and a Ph.D. in Genetics from Texas A&M University, followed by postdoctoral research at Case Western Reserve University. Subsequently, he served as the Head of the Department of Genetics at North Carolina State University for five years before returning to Texas A&M. He is the Founding Director of the Texas A&M Institute for Genome Sciences and Society, boasting an extensive research portfolio spanning cancer genetics, genetics of environmental response, and systems genetics. His laboratory primarily employs mouse models to investigate the impact of genetic factors, including specific gene families and alleles, on individual variations in health and disease.

During the lecture, Threadgill delved into his recent research using mouse models to study genes and molecular pathways implicated in gastrointestinal cancer. He discussed the different mouse models utilized in cancer research and their relevance to human tumor development. Notably, he highlighted the significance of the EGFR (epidermal growth factor receptor) gene, a member of the ERBB gene family, which consists of four genes producing receptors and ligands on the cell surface. This gene family constitutes a major focus of Threadgill's investigations.

A pivotal aspect of his research centered around the ERBB gene family, particularly the EGFR gene. Through targeted silencing of EGFR, he discovered its vital role in homeostasis and survival, as its suppression proved to be lethal. Interestingly, the outcome varied significantly when the same experiment was conducted on different mouse strains, suggesting the influence of genetic background on the gene's impact on survival. Recognizing EGFR's potential significance in gastrointestinal cancer research, Threadgill continued exploring its effects on gastrointestinal polyps and cancer establishment.

Threadgill's lecture emphasized the complexity of cancer research, revealing that targeting the EGFR gene in mouse models significantly reduced polyps in their colons but paradoxically accelerated tumor growth rate. This observation highlighted pleiotropic effects of a single gene in a complex disease.

Dr. David Threadgill

In his subsequent work, Threadgill turned his attention to the ERBB3 gene, a lesser-studied member of the ERBB gene family. Initially, his research demonstrated the gene's involvement in gastrointestinal cancer, directly influencing polyp size and numbers. However, when he revisited the experiment in 2021, his lab yielded different results, illustrating the challenges of scientific research.

To further elucidate the complexities, Threadgill targeted both the EGFR and ERBB3 genes in mouse models with different genetic backgrounds. This resulted in diverse outcomes depending on the genetic context. He highlighted that much preclinical cancer research had been conducted on homogenous single genetic backgrounds, potentially yielding inaccurate results when translating research data into clinical applications.

Addressing the challenges faced in the field, Threadgill concluded the lecture with thought-provoking questions on designing preclinical studies to ensure research findings translate effectively to clinical applications without adverse outcomes.

Threadgill continues to investigate the effects of genetic background on different genetic backgrounds of cancer and seeks potential therapeutic targets that can offer new insights into cancer therapy. His lecture provided a compelling glimpse into the intricate world of cancer genetics and the importance of considering genetic diversity in preclinical studies and clinical applications.

Alp Ummet is a graduate student in the Center for Human Genetics at Clemson University.

Genomic Signals to Stabilize Cell Identity

by Kristin Bussey

The Clemson University Center for Human Genetics invited Dr. Adrian Bird, esteemed professor at the University of Edinburgh to give a lecture on February 10, 2023. Sir Adrian Bird possesses several high honors including the Buchanan Medal of the Royal Society (2018), Foreign Associate of the National Academy of Sciences (2016), and the Gairdner Foundation prize (2011) which is considered one of the most prestigious medical honors in the world, for his ground-breaking research in the field of DNA methylation and gene expression regulation. His talk "Proteins that Interpret Genomic Signals to Stabilize Cell Identity" delved into the topics of DNA methylation with examples of MeCP2 and SALL4 to provide support for mechanisms by which transcription in the mammalian genome is regulated. Bird received his PhD from the University of Edinburgh. He has contributed tremendously to the field of methylation and gene expression regulation through the discovery and characterization of MeCP2 and CpG islands. He is the MeCP2 gene expert, a gene responsible for Rett Syndrome, an X-linked disorder, when mutated. In 2007, Bird and his group published evidence of phenotypic rescue of Rett Syndrome in mouse models. He also serves on the board of the Rett Syndrome Research Trust, a nonprofit organization focused on finding a cure for Rett syndrome.

A central theme of the talk was how epigenetic signals reinforce differentiation according to individual cells' needs and how these chemical modifications within our genomes switch gene expression. His first example highlighted proteins that switch off expression by negatively affecting transcription. He explained his work on MeCP2 mouse models to study Rett Syndrome and neurological phenotypes. MeCP2-null mice mimicked human phenotypes closely. Males exhibited exaggerated phenotypes compared to females. MeCP2-null males lived for a few weeks and died while null females had a normal lifespan but exhibited a chronologically similar delay in neurological function compared to humans. His experiments showed that MeCP2 is highly abundant and essential for maintenance in the brain, but not for neurodevelopment. Additionally targeted knockdown in the brain produced the same phenotype as ubiquitous knockdown and rescue experiments restored normal functionality. In the context of rare neurological diseases, to see such a drastic reversal and improvement of a neurological disease is extremely rare and Bird emphasized how important this study was to support the idea of Rett Syndrome as a candidate for gene therapeutics.

His work on MeCP2 also revealed two conserved domains in the gene known as the Methyl Binding Domain (MBD) and the NCor/SMRT interaction Domain (NID). These domains are responsible for the basic MeCP2 function and gave rise to Rett Syndrome when mutated. To test the importance of these domains, he created MeCP2 "mini-genes", which contained only the MBD and NID domains and cassettes to disrupt the mini-gene function. Mutations in the MBD showed that MeCP2 could no longer bind to DNA while NID mutations indicated that the mutant protein cannot interact with its corepressor complex to repress transcription. Furthermore, when MeCP2 is perturbed many genes in the organism are affected.

Dr. Adrian Bird

The lecture transitioned from MeCP2 to his second topic, proteins with positive effects on transcription. Bird wanted to understand how short sequences may modulate expression of genes through epigenomics. He hypothesized there are proteins which can recognize runs of A/T pairings that amplify subtle differences in the base composition in chromosomes, which can serve as genomic signals. One candidate AT binder at AT-rich motifs was the gene SALL4.

SALL4 restrains precocious differentiation of embryonic stem cells and is involved in many physiological processes and neuronal development. SALL4 is important for organismal survival; SALL4-null mice died at the implantation stage. SALL4 interacts with the Nucleosome Remodeling and Deacetylase (NuRD) co-repressor complex, which is responsible for transcriptional repression when recruited to target genes. Also, SALL4 contains a zinc finger motif (ZFC4) which mediates binding to AT-sequences in the genome. Mutation of this ZFC4 results in a sharp decrease in AT-rich DNA motifs. Furthermore, inactivation of ZFC4 in mice mimics SALL4 knock-outs. This results in neuronal hyper-differentiation and embryonic lethality. In essence, the ZFC4 motif is critical for the binding capabilities of SALL4, which regulates gene expression through transcriptional repression. In its absence, transcription of specific target genes skyrockets due to loss of repression.

Both examples of MeCP2 and SALL4 are critical for supporting the notion that epigenetic signals play an important role in cell differentiation and how a simple point mutation in a critical gene can cause severe, widespread defects in an organism. Through mechanistic understanding of how these genes bind to DNA to modulate transcription, it opens a dialogue to investigate the potential of gene therapeutics for rare diseases. This is a brilliant example for the use of model organisms and translational studies to identify potential targets for future therapeutic intervention.

Kristin Bussey is a graduate student in the Center for Human Genetics at Clemson University.

Unraveling the Mysteries of the Human Genome with Advanced Sequencing Technology

by Naqing

On Friday, March 31, 2023, Dr. Evan E. Eichler, an esteemed investigator at the Howard Hughes Medical Institute and a prominent Professor of Genome Sciences at the University of Washington School of Medicine in Seattle, presented an enlightening seminar titled "Complex Structural Variation in a Complete Human Genome" at the Strom Thurmond Institute of Clemson University as part of the Distinguished Lectures in Human Genetics series. Eichler's seminar was the first in-person lecture after the COVID-19 pandemic.

Eichler is widely recognized for his contributions to the study of human genome evolution, genome variation, and their implications in diseases, earning him accolades such as the 2008 Curt Stern Award from the American Society of Human Genetics and membership in the National Academy of Science. Together with his team, he has dedicated his efforts to understanding structural variations in the human genome.

During the seminar, Eichler highlighted the transformative impact of long-read sequencing technology on our understanding of human genomes and their structural variations. He emphasized that traditional sequencing methods, such as Illumina whole genome sequencing, have limitations in characterizing a significant portion of structural variations, with approximately 75% remaining uncharacterized. However, the advent of long-read sequencing, particularly HiFi sequence data and linking read technology like Strand-seq, has offered a much more comprehensive view of intermediate-sized structural variations. He emphasized the critical importance of completing the human genome project by sequencing the previously skipped regions, as the information gained from these regions is essential for understanding fundamental biological processes, genomic disorders, human adaptation, and brain function.

One of the key insights shared by Eichler was the successful sequencing and assembly of phased genomes spanning approximately 6 gigabases (6Gbp) by combining HiFi sequence data and parental Illumina whole genome sequencing. These efforts have yielded complete telomere-to-telomere assemblies of human chromosomes, enabling a detailed understanding of complex structural variations within the genome. The integration of long-read technologies, such as Oxford Nanopore Technologies (ONT) and HiFi PacBio, has been instrumental in achieving haploid-equivalent genome assemblies and unraveling the mutational processes associated with structural variations.

Eichler also highlighted the groundbreaking work of a former student, who discovered a method to identify and study duplicate genes using long-read sequencing. This discovery sheds new light on the importance of duplicate genes in human biology and further advances our understanding of gene function. In addition, Eichler and his team delved into the study of centromeres, essential parts of the human genome responsible for maintaining chromosome stability. Long-read sequencing enabled them to delve deeper into the structure of centromeres and uncover new repeat sequences, unveiling new insights into genomic organization.
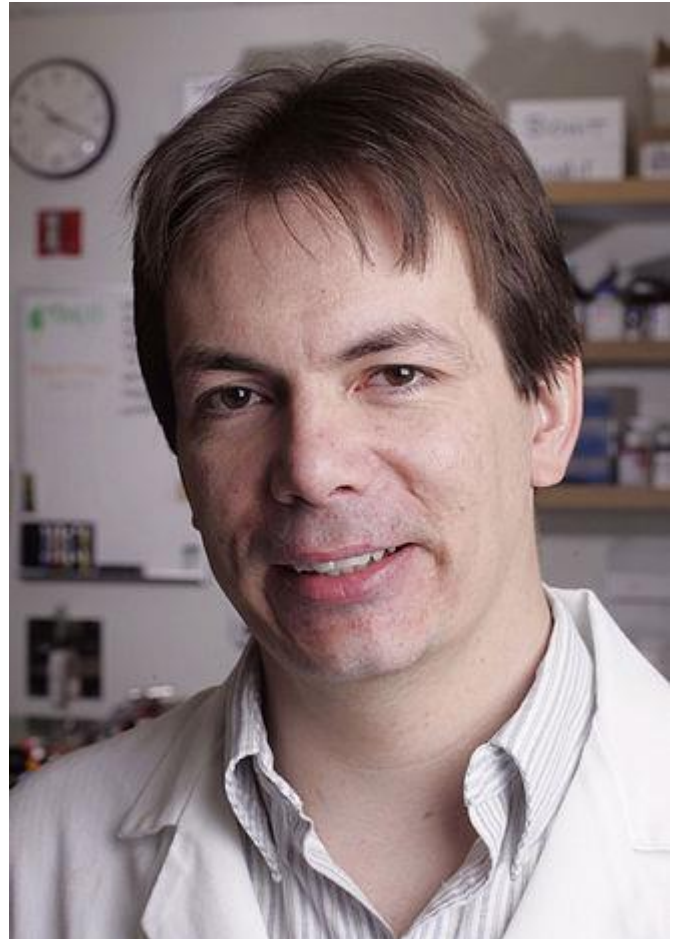
Dr. Evan Eichler

This seminar was a great opportunity for students and faculty to engage with a leading expert in the field and gain insights into the cutting-edge research being conducted at the intersection of genomics, genome evolution, and human diseases. Eichler's presentation underscored the remarkable potential of long-read sequencing technology to revolutionize our understanding of the human genome and its implications for human health and disease. His research and discoveries, along with the contributions of his dedicated team, are driving the field forward, promising to shape the future of genomic medicine and personalized healthcare.

Naqing is a graduate student in the Center for Human Genetics at Clemson University.

Visit the Clemson University Center for Human Genetics website at
https://scienceweb.clemson.edu/chg/

A Conversation with Miriam Konkel

Could you briefly describe your research program?

My research centers upon genomics with an emphasis on transposable elements. Specifically, my group is interested in the evolution of transposable elements and their impact on the host's genome. With each insertion and rearrangement mediated by transposable elements, the architecture of the genome changes. Thus, over time, transposable elements shape each genome uniquely.

Furthermore, transposable elements can carry transcription factor binding sites to different locations in a genome, which can modify gene regulation. To investigate this, my group focuses on primates with emphasis on humans, though I am always open to engaging other species (as I have done for the platypus and zebra finch consortia).

Recently, my group's research has expanded to investigate the role of extracellular RNA and their modification in intercellular and interkingdom communication. Here, my group is particularly interested in the impact of transposable element-derived sequences on extracellular RNA and its function.

Lastly, I have been working on the development of genomic interfaces for data manipulation and science communication. Our interdisciplinary team developed an interactive kiosk and workstation, Fargates, that was shown at the ACCelerate Festival in the Smithsonian's National Museum of American History in Washington D.C. and at Artisphere in Greenville, South Carolina in 2022.

What led you to focus your research program on characterizing transposable elements in primates?

As a trained physician, human genetics has always been a central interest. In order to fully understand human genetic diversity and phenotypic variation, I think it is important to extend to a whole genomics view and to elucidate findings in the context of evolution. In addition, I find the diversity of primates fascinating.

Transposable elements remain understudied and not fully understood. At the same time, they are major contributors to genetic diversity as they continue to propagate in most species. In humans, approximately one new transposable element insertion occurs per 20 live births. Some of these insertions cause monogenetic disorders such as hemophilia, neurofibromatosis type 1, or cystic fibrosis. The combination of direct human genetic impact and evolution has intrigued me.

What is the most important discovery your lab has made?

I think our most important discoveries are related to our recent Y chromosome studies. The Yq12 heterochromatin region, which is only partially assembled in the human reference genome, is highly size variable between males. This region is comprised of two repeats, one of which harbors transposable element sequence of the most active transposon in humans, the *Alu* element. Despite the interindividual variation, the ratio between the two repeats remains roughly 1:1.

What do you see as the greatest challenge in human genetics?

I am not sure that there is one greatest challenge in human genetics. From a clinician's view, I think identifying the underlying cause of genetic disorders, especially rare diseases, is a major challenge. While it can be challenging for monogenetic disorders, for complex diseases, where often multiple genetic variants in conjunction with the environment result in a certain phenotype, we are only now starting to scratch the surface. It is also becoming more evident that variants outside the coding region and genomic structural variation are major contributors to phenotypic diversity and can cause genetic disorders. From a basic science perspective, bringing the knowledge of the field to the clinical bedside is a major challenge, especially given the speed the field has been advancing in the last several decades.

What advice would you give young investigators who aspire to academic careers in research?

This is not an easy question to answer. Perhaps my main thought is, stay true to yourself and do not try to fit a mold that is (or you perceive to be) expected. Everyone and every research endeavor is unique. When you are encountering challenges, remind yourself of the excitement of pursuing research and the opportunity to walk unbeaten paths. Building a network of mentors has been transformative. I highly encourage identifying mentors and building a network in parallel to starting a research program.

How do you spend your time away from the lab?

In my time away from the lab, I like to cook and bake. I also like to visit museums when I get a chance to travel.

Miriam Konkel is an Assistant Professor in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

Viewpoint

Standing on the Shoulders of Dwarfs

by Robert Anholt

We are all aware of the competitive nature of grant reviews. No matter how well-written a proposal is or how timely the concept, when a reviewer describes it as "incremental" it is dead in the water. There is an unreasonable expectation that all our scientific endeavors must be "transformative."

The heroes of our scientific heritage are the Nobel laureates, scientific giants who advanced scientific concepts by leaps and bounds. Yes, the development of the polymerase chain reaction, the discovery of the structure of DNA, CRISPR technology, and many other major discoveries were certainly transformative. But these discoveries were not made in a vacuum. They built on previous work by lesser folks, dedicated scientists, unsung heroes, whose work would have been considered incremental: the dwarfs of science.

Take for example the polymerase chain reaction, which revolutionized molecular biology. In the 1960s two microbiologists from Indiana University, Thomas Brock and Hudson Freeze, isolated a new species of bacterium from the Mushroom Spring in the Lower Geyser Basin of Yellowstone National Park. They named it *Thermus aquaticus*. This remarkable bacterium could survive under temperatures up to 80ºC and reproduce happily at temperatures that would be lethal to other bacteria.

This intriguing adaptation was studied extensively. In 1976, Chien, Edgar and Trela reported the isolation of the *T. aquaticus* DNA polymerase in a publication in the *Journal of Bacteriology*. Few people will remember their names. The discovery of a new bacterial species, however interesting, might not have been considered a transformative event in the broader picture of science. Nor was the isolation of its DNA polymerase. It was Kary Mullis and his colleagues at Cetus Corporation who caught on to the concept that the heat stable properties of this enzyme could be used to amplify DNA.

Mullis got the Nobel prize in 1993. This would not have happened without the "incremental" contributions of Brock, Freeze, Chien, Edgar, Trela and others. Mullis stood on the shoulders of dwarfs.

The polymerase chain reaction (PCR) enabled the discovery of odorant receptors for which Linda Buck and Richard Axel received the Nobel Prize in 2004. But it was not just the application of the PCR reaction, it was the choice of the right degenerate primers, corresponding to conserved regions of G protein-coupled receptors that was critical. Documentation of these sequences depended on studies from many laboratories. Individually reporting a sequence of yet another member of this family of receptors might have been considered incremental. Yet, the availability of many sequences enabled the identification of conserved regions.

Similar stories, in which painstaking incremental discoveries laid the groundwork for brilliant minds to create major transformative insights, can be found for almost all significant, so-called "transformative" advances in science. Venki Ramakrishnan, who received the Nobel prize for elucidating the structure of the ribosome wrote in his book *Gene Machine*: "I don't subscribe to the heroic narrative of science. Rather, some of us are fortunate enough to be the agents of important discoveries that would have been made anyway, sometimes not even that much later."

If Watson and Crick would not have reported the structure of DNA in 1953, would we today still not know its structure and mode of replication? The lesson is that all of us contribute to the quest for knowledge in different ways and on different scales. All of us add pieces to the puzzle, but he who adds the last piece to complete the picture gets the fame. Yes, the history of science is replete with giants, but let's not forget the incremental dwarfs.

The images from top to bottom show Thomas Brock, Alice Chien and John Trela. Chien was a Master's student.

Robert Anholt is the Provost's Distinguished Professor of Genetics and Biochemistry and Director of Faculty Excellence in the College of Science at Clemson University.

Grants

Jeffrey Hatfield received a two-year $95,388 Ruth Kirschstein National Research Service Award from the National Institute on Drug Abuse to study systems genetics of cocaine preference in *Drosophila melanogaster*. He also received a $500 travel award to attend the annual meeting of the International Behavioral Association for Neurogenetics in Galway, Ireland.

Jessica Larsen received a two-year $404,643 R21 exploratory grant from the National Institute on Neurological Disorders and Stroke to study nanoparticle distributed intravenous enzyme replacement therapy (NanoDIVERT).

Xinyi Li is Co-principal Investigator of a one-year $19,075 Faculty Excellence Interdisciplinary Enhancement Program grant, titled "DECAL: Data sECurity and mAchine Learning - When theory meets practice."

Seminars

On Friday, **September 15**, at 2:30 pm, **Dr. Yoav Gilad**, Professor of Medicine, Chief of the Section of Genetic Medicine, Vice Chair for Research, and Dean for Biomedical and Health Informatics at the University of Chicago, will present a seminar titled "No cell left behind: Using new *in vitro* system to study dynamic eQTLs in all cell types." The seminar will be delivered virtually via zoom, https://clemson.zoom.us/j/93021202510.

On Monday, **October 2,** at 2:00 pm, **Dr. Gene Robinson**, University Swanlund Chair and Director of the Carl R. Woese Institute for Genomic Biology at the University of Illinois at Urbana-Champaign, will present a seminar titled "Pillars of the social brain: Lessons from the honeybee." The seminar will be a joint Discover Science lecture of the College of Science and will be held in the auditorium of the Watt Family Innovation Center.

On Monday, **November 13**, at 2:00 pm, **Dr. Tom Maniatis**, Director of the Columbia University Precision Medicine Initiative and Scientific Director and Chief Executive Officer of the New York Genome Center at Columbia University, will present a seminar titled "The genomic organization and functions of large human gene clusters: β-globin and the clustered protocadherins." The seminar will be delivered via zoom, https://clemson.zoom.us/j/95474602403.

Symposia

On Monday, **September 18**, the College of Science hosts the **2023 Rising Star Symposium** featuring new assistant professors from departments across the college. The symposium will be in the auditorium of the Watt Family Innovation Center from 1:30 pm to 4:30 pm.

On **October 12**, the Center of Biomedical research Excellence in Human Genetics hosts its annual retreat. The retreat will be virtual via Zoom from 10:00 am-4:00 pm EST, https://clemson.zoom.us/j/99869680480.

Publications

(affiliates of the Center for Human Genetics are in bold font)

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Out and About

Robert Anholt was an invited symposium speaker at the South Carolina Autism and Neurodevelopmental Disorders Research Symposium at the University of South Carolina, Columbia, SC. He also served on an NIH Special Emphasis Panel to review applications for the Innovative Programs to Enhance Research Training (IPERT) and the MOSAIC (Maximizing Opportunities for Scientific and Academic Independent Careers) program.

Robert Anholt and **Trudy Mackay** presented seminars at the University of Toronto and Grand Rounds at the Georgia Cancer Center of Augusta University in Augusta, GA. They also represented Clemson University at the 2023 Bio International Convention in Boston, MA.

Zhana Duren was an invited speaker at the international workshop, "Single-Cell Plus – Data Science Challenges in Single-Cell Research," organized by The Banff International Research Station for Mathematical Innovation and Discovery (BIRS) in Alberta, Canada, where he presented the latest research from his group on modelling gene regulation via integrative analysis of single-cell multi-omics data. He also served on the BDMA study section at NIH and has been named a member of the Editorial Board of Genome Biology.

Heather Flanagan-Steet and **Richard Steet** gave presentations at the 44th Annual David W. Smith Workshop on Malformations and Morphogenesis in Southbridge, MA.

Jeffrey Hatfield gave oral presentations at the annual Genetics and Epigenetics Cross-Cutting Research Team meeting of the National Institute on Drug Abuse in Bethesda, MD, and the annual meeting of the International Behavioural and Neural Genetics Society (IBANGS) in Galway, Ireland. He also presented a poster at the COBRE in Human Genetics meeting in Greenwood, SC, and gave a seminar in the Department of Biology at Presbyterian College, Clinton, SC. He received a second-place award of $2,000 in the Clemson iGRADS scientific video competition.

Miriam Konkel attended the Human Genome Structural Variation Consortium meeting in Glasgow, Scotland.

Jessica Larsen was appointed Carol and John Cromer '63 Family Endowed Associate Professor in Chemical and Biomolecular Engineering at Clemson University.

Xinyi Li presented a departmental colloquium in the Department of Statistics at the University of Virginia, Charlottesville, VA, and a Functional Data Analysis seminar at the Department of Statistics at North Carolina State University, Raleigh, NC. She also attended the 6th International Conference on Econometrics and Statistics, the the International Chinese Statistical Association in Chengdu (virtual), the 2023 China Conference, the International Chinese Statistical Association 2023 Applied Statistics Symposium, Ann Arbor, MI, and the 36th New England Statistics Symposium, Boston, MA.

Qing Liu gave a presentation on transcriptional regulation of mitochondrial biogenesis as it relates to drug-induced cardiotoxicity at the Department of Pharmaceutical Sciences at Wayne State University, Detroit, MI.

Trudy Mackay presented seminars at the University of Georgia in Augusta, GA, and the University of South Carolina in Columbia, SC. She also gave a presentation at the Advance '23 Sanfilippo Community Conference via Zoom. She has been named a member of the Class 2 Committee on Membership of the American Philosophical Society.

Rebecca MacPherson attended the American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting, Salt Lake City, UT, and presented a poster at the Genetics Society of America Annual Drosophila Research Conference. She received a best poster award at the 2023 Center of Biomedical Research Excellence in Human Genetics symposium and the Outstanding Graduate in Discovery Award in Genetics from the Department of Genetics and Biochemistry at Clemson University.

Fabio Morgante attended the Joint Statistical Meeting in Toronto, Canada.

Qiuyue ('Kaya') Yuan attended the International Symposium on Circuits and Systems (ISCAS 2023) in Monterey, CA.

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