CLEMSON UNIVERSITY
CENTER FOR HUMAN GENETICS

The Transcript

Newsletter of the Center for Human Genetics at Clemson University
Fall, 2024

From the Director

I am pleased to welcome Dr. Tara Doucet-O'Hare, who has joined the Center for Human Genetics as an Assistant Professor in the Department of Genetics and Biochemistry. Dr. Doucet-O'Hare is returning to her roots. She received her B.A. degree from Clemson in 2010. Following her doctoral period at the Johns Hopkins University School of Medicine, she worked as a postdoctoral fellow at the National Institutes of Health. Dr. Doucet-O'Hare joins us from the National Cancer Institute where she studied the role of endogenous retroviruses in cancer, a line of research she will continue to pursue with her research team in Greenwood.

I am also pleased to welcome Dr. Shahid Mukhtar, who joins us from the University of Alabama as Professor in the Department of Genetics and Biochemistry. Having started his successful career working on Arabidopsis and bacteria, Dr. Mukhtar will apply his computational skills to human genetics. His interests lay at the intersection of multiomics analyses, single-cell sequencing, large-scale protein-protein interactions, and genome-wide association analyses, with a primary focus on addressing precision medicine and health disparity-related questions.

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.

Dr. Renée Cottle has also joined the Center for Human Genetics. She is an Assistant Professor of Bioengineering at Clemson University and specializes in gene editing and nonviral delivery strategies. Her research group develops new cell-based gene therapies for liver-related genetic diseases.

The Center for Human Genetics also welcomes Dr. Gavin Arno who joined the Greenwood Genetic Center as Associate Director of Research from University College London (UK). Dr. Arno's laboratory studies ophthalmic genetics and genomic analysis of inherited eye diseases.

I want to congratulate Jiamutai on completing his M.S. thesis on regulation of mRNA polyadenylation under the direction of Dr. Lela Lackey. We also welcome our new graduate students, Kathryn Howe and John McCoy (Doucet-O'Hare lab), Brianna Dyer (Farrell lab), Yuxuan Sum (Morgante and Mackay labs) and Ranga Baminiwatte, Kazi Jewel Rana and Jordyn Brooks (Masino lab).

Special congratulations to Dr. Vijay Shankar who received the 2024 inaugural Center of Human Genetics Award of Excellence for his outstanding service as Director of Bioinformatics at the Center for Human Genetics. In addition to efficiently handling numerous projects for members of the Center, Dr. Shankar designed and maintains our powerful high performance computer cluster for rapid large scale data processing by multiple users. He also provides invaluable statistical support for the Clemson University Precision Medicine Initiative and organizes popular educational summer workshops that teach the nuts and bolts of RNA-sequence analyses. Dr. Shankar is a topnotch scientist who always seeks to improve statistical methodology and constructs new analytical pipelines.

Dr. Rachel Lyman, who has directed our genomics service facility, is leaving to take a position at the National Heart Lung and Blood Institute of the National Institutes of Health in Bethesda, MD. We wish Rachel success in her new position.

We are looking forward to another exciting Fall semester with distinguished lectures by Drs. Rasmus Nielsen (University of California at Berkeley), Rodolphe Barrangou (North Carolina State University) and Jonathan Pritchard (Stanford University). The seminar of Dr. Barrangou is also a Provost's Distinguished Lecture and will focus on applications and implications of genome editing technologies.

I hope to welcome all members of the Center for Human Genetics to the annual retreat of the Center for Biomedical Research Excellence (COBRE) in Human Genetics on October 25 at the JC Self Research Institute of the Greenwood Genetic Center in Greenwood.

I also encourage everyone to attend the lecture on the role of graduate education in science and its impact on society by Dr. Holden Thorp, who is the Editor-in-Chief of *Science* magazine. His seminar will be on November 7 at the Strom Thurmond Institute on the Clemson University campus.

In the Fall semester we will continue our weekly Advances in Human Genetics discussions and our monthly lunch-and-learn sessions via Zoom. These events are always informative and enjoyable. I look forward to seeing everyone on the screen.

As we continue our journey together, I wish each of you a great Fall semester! Go Tigers!

The Center of Biomedical Research Excellence in Human Genetics 2024 Summer Symposium

by Gianni Martino and Allen (Chia-Lun) Wu

The 2024 Summer Symposium of the Center for Biomedical Research Excellence (COBRE) in Human Genetics was held on May 17th, 2024, at the J.C Self Research Institute, Greenwood Genetic Center. This year's topic was "Gene Regulatory Mechanisms in Health and Disease." The program included four keynote speakers and eight 5-minute oral presentations selected from 32 poster presentations, which gave us new insights in how gene regulation might drive the pathogenesis of human diseases.

Dr. Robert Anholt from the Clemson University Center for Human Genetics gave a presentation on systems genetics of substance use disorders in *Drosophila melanogaster*. He demonstrated the fruit fly, Drosophila, as a powerful animal model and used the Drosophila Genetic Reference Panel to identify SNPs and genetic interaction networks associated with variation in cocaine preference and sensitivity to alcohol. His study on fetal alcohol spectrum disorder showed that alcohol-induced changes in gene expression in the brain may contribute to Fetal Alcohol Spectrum Disorder.

Dr. Francesca Telese from the University of California at San Diego presented her impressive work on gene regulatory mechanisms in substance use disorders. To better understand the cellular complexity and susceptibility in the brain, her study focused on unraveling the dynamic regulatory genomic landscape in the brain. Her research also aims to employ the genetic diversity of an outbred population of rats with a drug self-administration system to identify the cell type-specific gene regulatory network that is essential for substance use disorders like cocaine and opioid addiction. By using RNA-seq and ATAC-seq, she profiles gene expression and chromatin accessibility from low and high addiction indices in rats' brains and found that GABA-ergic transmission increases in rats with a high addiction index.

Opening the afternoon session, Dr. Anita Corbett from Emory College of Arts and Sciences presented her functional genomic research exploring the pathogenic mechanisms of mutations in the RNA exosome complex subunits. Consisting of ten essential subunits encoded by EXOSC genes, the RNA exosome demonstrates a “garbage disposal-like” function for RNA turn-over and its dysfunction is often associated with pontocerebellar hypoplasia (PCH). This autosomal recessive disorder results in underdevelopment of the cerebellum leading to significant developmental delays.

Through her interaction with clinicians, Corbett began working with a girl with a missense mutation in the EXOSC4 subunit, not described previously in the literature. Yeast knockout models were used to demonstrate that the affected amino acid residue was conserved. The mutation resulted in a buildup of precursor ribosomal RNA (rRNA), inhibiting ribosomal function in a tissue-specific manner. This accumulation resulted from the introduction of a proline in place of a lysine residue that prevented proper association of the subunit to the complex. From here the question remained, “Are there any currently approved therapeutics that could serve to remedy this child’s ailments?” Through

exhaustive interactions with clinicians, Corbett came across a case of two siblings treated for EXOSC3 mutations using a proteasome inhibitor. The goal of this treatment was to boost the quantity of functional RNA exosome proteins by inhibition of protein turnover. To date, this generalized treatment has improved the quality of life of the young girl dramatically and may serve as a viable treatment for other EXOSC gene disorders.

The final distinguished speaker, Dr. Greg Carter from the Jackson Laboratory, described his inquiries into the genetics of gene expression in metabolic health through a series of experiments in genetically diverse mice. Carter’s asked if epigenetics can explain variation in gene expression. He implemented a comprehensive sequencing approach including the use of RNA-seq for expression, bisulfite-seq for methylation, and chromatin immuno-precipitation sequencing (ChIP-seq) for histone modification analysis. These data allowed for an extensive search into the epigenetic mechanisms that may underlie differential gene expression at particular loci. He demonstrated that chromatin accessibility, single nucleotide variations, and methylation patterns play a role in explaining differential gene expression. Finally, Carter’s investigations into the impact of these epigenetic characteristics in relation to their location in topological space indicated that variations anywhere within a topologically associated domain (TAD) are always correlated to some degree. Considering that a TAD boundary is roughly one megabase in size, this puts the complexity of the mechanisms of genetic variation into a humbling perspective!

Shannon Lattimore, program coordinator of the COBRE in Human Genetics, was recognized for her exceptional service. Dr. Vijay Shankar, director of the bioinformatics core of the Center for Human Genetics, received the Center’s inaugural Award for Excellence.

Gianni Martino and Allen (Chia-Lun) Wu are doctoral students in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

From Darwin to Deep Space: Evolutionary Biology Concepts in Science Fiction

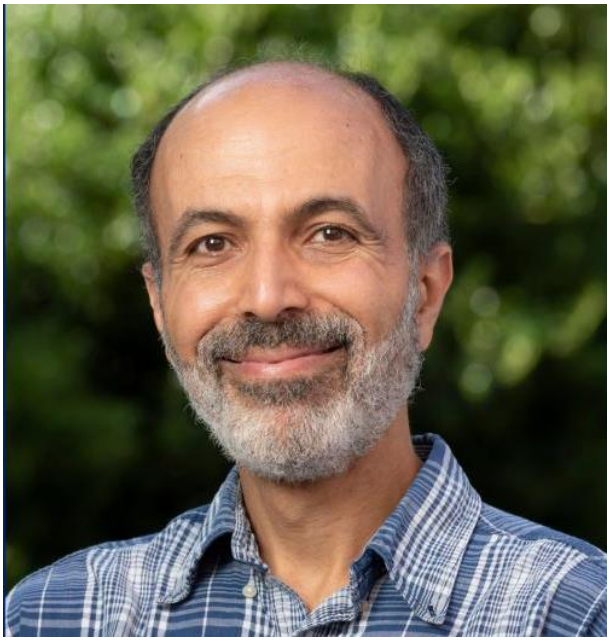
by Prakrit Subba

On Monday, February 12th, 2024, Dr. Mohamed Noor, Professor of Biology and Interim Vice-Provost of Academic Affairs at Duke University, delivered the 2024 Darwin Lecture. The lecture, titled “Using Science-Fiction Depictions to Teach Real-World Evolution Concepts,” marked the 215th birthday of Charles Darwin and the 165th anniversary of Darwin’s seminal work, "On the Origin of Species." This special occasion was appropriately chosen for an accomplished evolutionary biologist like Dr. Noor, who comes from the academic lineage of Theodosius Dobzhansky, Thomas Hunt Morgan, and Jerry Coyne, and is a recipient of the prestigious Darwin-Wallace Medal from the Linnean Society of London. Dr. Noor is a “Trekkie” who is passionate about teaching biology concepts using depictions from science fiction series like *Star Trek*, a franchise for which he also serves as a science consultant.

Dr. Noor’s teaching and science communication work has been driven by the central question: “How and why do people learn about biology?” He argues that the average person learns science through more accessible means like science-fiction movies rather than esoteric books. In his talk, he leveraged people’s interest and exposure to sci-fi to get them interested in learning science, using *Star Trek* as a “case study.” In fact, he has authored a book titled “*Live Long and Evolve: What Star Trek Can Teach Us about Evolution, Genetics, and Life on Other Worlds*,” and delivered numerous talks and courses to introduce evolutionary concepts and to challenge his students to think scientifically. First, Noor explained and provided evidence for evolutionary biology concepts, including topics like natural selection, shared traits and common ancestry. Next, he used his *Star Trek* case study to test three hypotheses about whether and how we could see “life as we know it” outside Earth.

Noor described the ideas of life beginning from a common ancestor, the sharing of traits, and the classification of species to explain the relationships between different taxa in the tree of life. For this, he employed deductive reasoning and examples from our daily lives, such as the similarity of traits between siblings and cousins, as well as basic genetics. He addressed common misconceptions, like the idea that humans descended from chimpanzees. He explained Darwin’s discovery of evolution by natural selection and how it can contribute to convergent evolution, using relevant examples from nature.

An astute “Trekkie” who has watched all 900-plus episodes, Dr. Noor used a short video clip from the series to test three hypotheses about the existence of “life as we know it” outside Earth. His first hypothesis, from Star Trek: The Next Generation’s episode titled “*The Chase,*” stated that life on Earth and outside were variants of panspermia—that is, raw materials of life or seed codes exist all over space and entered Earth and other planets, resulting in convergent evolution. However, he rejects this hypothesis because of two inconsistencies: (i) the conditions on both planets may not be the same, and based on Stephen Jay Gould’s idea of



Dr. Mohamed Noor

the “tape of life,” this hypothesis minimizes the role of random chance events and their impact on prevailing conditions, such as multicellularity arising from the endosymbiotic acquisition of mitochondria by a prokaryote being a random chance event that had a big impact on earth; (ii) that seed codes cannot persist across the universe and will change due to mutations. Next, the second hypothesis, from Star Trek: The Original Series episode “*Return to Tomorrow,*” stated that modern humans descended from ancient aliens, or humanoids (likely *Homo erectus*), who visited Earth 600,000 years ago. However, he rejected this hypothesis because it assumes that we are not related to chimpanzees and other extant life on Earth when there is DNA evidence and fossil records to support this relatedness. Finally, Noor transitioned to his third hypothesis from Star Trek: The Original Series episode "*The Paradise Syndrome,*" where some life on Earth was taken to space by the “preservers” for the conservation of primitive cultures. Dr. Noor argues that there is good reason to support this hypothesis because life on Earth has indeed gone to space (e.g., the Mars Rover), and an Earth humanoid could be taken to another world and evolve into the modern Trek aliens with similar physical and genetic features (which remains a testable prediction). This hypothesis also explains the presence of hybrids, especially because modern humans still contain genes from Neanderthals and/or Denisovans.

Overall, Noor proposes using testable hypotheses based on science fiction to understand the world we live in or a world that might exist somewhere else.

Prakrit Subba is a doctoral student in the Department of Biological Sciences and the Center for Human Genetics at Clemson University.

Mapping Genetic Networks Using Systematic Genetics

by Amy Bergmann

On Friday, January 19th, Dr. Brenda Andrews, Charles Best Chair of Medical Research, Director of the Donnelly Center for Biomolecular Research and Professor of Molecular Genetics at the University of Toronto delivered a Distinguished Lecture in Human Genetics describing her influential research with long-time collaborator Dr. Charles Boone in mapping genetic networks using the yeast system. Andrews is a Fellow of the Royal Society of Canada, the American Academy of Microbiology, the American Association for the Advancement of Science, and the National Academy of Science of the USA.

Andrews' lecture, titled "Mapping Genetic Networks using Systematic Genetics", described how she used the budding yeast model system to map genetic interaction networks to explain not only the relationship between genetic interactions but to use these interactions to explain the genotype to phenotype relationship. Using yeast models, Andrews and colleagues created computational methods and algorithms which can then be applied to larger systems.

A previously created variety of yeast mutant arrays was used to delete the approximately 6000 genes in the yeast genome. The phenotype of each deletion was examined, and out of the ~6000 genes, ~5000 were deemed non-essential. The phenotypic consequences of mutations of the remaining ~1000 genes can then be studied. The team looked at single loss-of-function mutations, as well as consequences of deletion of multiple genes at one time using an assay termed synthetic genetic array (SGA). SGA allows them to determine if the genetic interaction occurring between the two alleles of the double mutants causes an unexpected phenotype.

To generate interaction maps, Andrews quantified the genetic interactions between wild type, single mutants, and double mutants. The easiest assay to measure deviation in phenotype is colony size/growth rate in yeast spot tests. Using a multiplicative model, her team determined the fitness of each strain, and phenotypic deviations versus wild type. A negative interaction, such as synthetic lethality will have a fitness score less than wild type, while a positive interaction will have a fitness score closer to wild type. In some cases, the double mutants can grow better than the wild type. Interestingly, some of the synthetically lethal mutations have been used to target cancer and create chemotherapeutics. An example given was BRCA deficient tumors that can be treated with PARP inhibitors, which was shown by a double mutant of BRCA and PARP which decreased cell growth. Several years ago, Andrews and her team published the complete genetic interaction map of budding yeast. Using the SGA assay, they tested the approximate 6000 genes in budding yeast for pairwise genetic interactions, which led to the identification of nearly 1 million interactions. Of those interactions, they discovered ~555,000 negative interactions and ~350,000 positive interactions, which span nearly 90% of all yeast genes. To map the interactions, they select one gene, and connect the interactions using both negative and positive correlations. The map can then be used to predict both gene and protein functions based on the different genetic profiles and connectivity to other genes in the network. Those genes with less correlation to other genes can still be compartmentalized into cellular compartments, and even biological processes, even if the phenotypic consequences cannot be determined.

Dr. Brenda Andrews

The use of CRISPR-Cas9 enabled testing loss-of-function mutations in human cell lines. Andrews utilizes CRISPR-Cas9 and a guide RNA library for genome-wide screens in a single genetic background, using the haploid cancer cell line, HAP1, to create a human scaffold map. It was previously discovered that there are 1528 essential genes out of the ~20,000 genes present in the genome. Using the yeast map, Andrews was able to narrow down the list to ~100-200 genes to mutate, score the interactions and create a network of genetic interactions for human cell lines. They were able to generate networks that represent - among others - DNA replication, cell cycle progression, and mRNA processing. This information allows us to make predictions of phenotypic consequences of genomic mutations.

Andrews' research has shown that the principles of genetic interactions are conserved from yeast to humans. This will be useful for mapping reference genetic networks in higher eukaryotic systems. Such maps can give a better understanding of the organization of cells and biological functions, as well as help to explain the relationship between the genotype to the phenotype. It has already been proven to be useful in cancer therapies and can pave the way for diagnostics and treatments for many diseases caused by mutations in the human genome.

Amy Bergmann is a doctoral student in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

Exploring Global Genomic Diversity with Complete Telomere-To-Telomere (T2T) Assemblies

by Kassandra Roemer

Dr. Karen Miga presented a seminar in the series of Distinguished Lectures in Human Genetics that highlighted the importance of expanding studies of global genomic diversity with the help of complete Telomere-to-Telomere (T2T) assemblies. Miga serves as an Assistant Professor of Biomedical Engineering at the University of California, Santa Cruz, and is also the Associate Director at the UC Santa Cruz Genomics Institute. She was named as one of TIME's 100 most influential people in 2022 and Nature's One to Watch. She was presented with the 2023 Early Career Award from the American Society of Human Genetics. Her laboratory focuses on studying the genomic and epigenetic architecture of human centromeric and heterochromatic regions, with a particular interest in satellite DNA, repetitive structures, their regulation, and changes over time, as well as their contributions to diseases.

Dr. Karen Miga

Until 2022, the human genome was incomplete, with large regions missing from the reference genome. These missing segments contain long repetitive regions such as satellite DNA, heterochromatic sequence and centromeric regions, accounting for approximately 8-10% of the genome.

The Telomere-to-Telomere consortium recently achieved a groundbreaking milestone by releasing the first complete telomere-to-telomere assembly of the human genome. This ambitious project has introduced an additional 200 million base pairs into scientific knowledge, representing a significant leap forward in our understanding of the human genome. This advancement has enabled researchers to examine previously unresolved structures of the human genome in unprecedented detail.

The success of the T2T consortium can be largely attributed to the long-read sequencing revolution. Long-read sequencing technologies, such as those developed by PacBio and Oxford Nanopore Technologies, have transformed genomic research by allowing for the generation of reads that are hundreds of kilobases to even megabases long. This capability has facilitated the accurate assembly of complex regions of the genome, which were previously challenging to resolve. PacBio's HiFi sequencing, in particular, has been instrumental in achieving high accuracy and long-read lengths, while Oxford Nanopore's technology offers the advantage of ultra-long reads, making it possible to span entire repetitive regions.

By leveraging the advancements in long-read sequencing and the complete genome assemblies, scientists can now examine these critical regions, such as centromeric structures, in greater detail than ever before. Furthermore, researchers can now explore questions related to chromosome structure, chromatin organization, gene expression, and the evolution of transposable elements. Understanding the role of these elements in the genome, particularly in repetitive regions, is crucial for elucidating their contributions to genomic diversity and evolution.

Responding to the NIH's call to better represent human diversity in reference genomes, the goal is to build a comprehensive pan-genome database. By including genomes from a wide range of populations, scientists aim to create a reference that better reflects the genetic diversity of the human population. This effort is crucial for advancing precision medicine, as an open database representing the genomic diversity of the population would improve our understanding of medically relevant variants in challenging loci, structural variations between individuals, and their implications for disease risk and treatment personalization.

The creation of a comprehensive pan-genome database also has important implications for understanding human evolution. Comparing genomes from different populations scientists enables tracing the history of human migration and admixture, uncovering patterns of genetic diversity that can provide valuable insights into the genetic basis of traits that vary among populations.

The Human Pan-Genome Project is a global initiative under the Global Alliance for Genomic Health, which involves collaborations with international research groups and bio banks, emphasizing the need for equitable and transparent partnerships to ensure diverse representation. The project also addresses ethical considerations and data sovereignty, ensuring that decisions benefit a broad range of populations. This includes developing tools and resources that support global genetic diversity and equitable healthcare.

In conclusion, Miga's work and the T2T consortium, along with the efforts to create a comprehensive pan-genome database, marks a new era in genomics, opening up new possibilities for understanding genetic variation and its implications for health and disease.

Kassandra Roemer is a doctoral student in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

Transgenerational Epigenetic Inheritance

by Bhoomi Mirani

The Clemson University Center for Human Genetics hosted Dr. Victor Corces on April 5 as part of its Distinguished Lectures in Human Genetics series. Corces, a professor in the Department of Human Genetics at Emory University School of Medicine, has made significant contributions to understanding how environmental factors induce changes in the epigenome that are inherited across generations. His work has focused on understanding the mechanisms by which chromosomes are folded in the three-dimensional nuclear space. Corces studies how environmental factors affect the epigenome, leading to heritable changes that can result in disease. His research explores how these epigenetic changes respond to genetic variation in the non-coding genome. Elected to the National Academy of Sciences in 2020 for his pioneering work in epigenetics, genomics, and computational biology, Corces presented his findings in a seminar titled "Mechanisms of Transgenerational Epigenetic Inheritance in Mammals." His work highlights the significant impact of environmental effects on the epigenome, with implications for diseases such as metabolic disorders and autism.

Corces' work elucidates how environmental exposures, such as chemicals like Bisphenol A (BPA), can affect the epigenome, leading to heritable changes that influence disease susceptibility. BPA, an estrogen-like compound, binds to nuclear hormone receptors, triggering signaling pathways that alter transcription. His studies on mice exposed to BPA during pregnancy demonstrate significant alterations in the epigenome of the germline, leading to inherited metabolic and behavioral disorders in the offspring. Offspring from BPA-exposed mothers exhibited increased food intake and metabolic issues, suggesting a direct correlation between maternal BPA exposure and the propensity for obesity and metabolic syndrome in progeny. These alterations were found to persist for multiple generations, indicating that the effects of environmental exposures can transcend immediate offspring and impact subsequent generations.

Corces' research emphasizes the complex mechanisms by which epigenetic information is maintained and transmitted through the germline. Contrary to the traditional view that the sperm nucleus merely delivers highly condensed paternal DNA, Corces' findings reveal that sperm DNA is intricately associated with nucleosomes containing various histone modifications. These nucleosomes are not randomly distributed but are strategically positioned, suggesting a regulatory role in transmitting epigenetic information. Specifically, sperm DNA is bound by CTCF, cohesin, and other transcription factors, which organize the chromatin into compartmental domains and loops. These structures are crucial for maintaining the epigenetic landscape from the germline to the embryo. Corces' data show that certain chromatin features, such as nucleosomes containing H3.3 and H2A.Z, are conserved in both sperm and oocytes and persist through early embryogenesis, up to the blastocyst stage.

Corces' findings have broad implications, revealing how environmental factors shape the epigenome and contribute to complex diseases. For instance, obesity and metabolic

Dr. Victor Corces

disorders prevalent today may stem not only from lifestyle but also from inherited epigenetic changes due to ancestral exposures. Studies like the Dutch Hunger Winter Families Study and the Overkalix cohort in Sweden showed that parental diet and stress can affect metabolic health across generations. The Dutch Hunger Winter Families Study showed that children of women pregnant during the 1944-45 famine had higher rates of obesity, diabetes, and cardiovascular diseases. The Overkalix cohort found that the nutritional status of paternal grandparents affected the health and longevity of their grandchildren. These findings align with Corces' research in animals, highlighting the critical role of epigenetic inheritance in disease susceptibility.

Corces' research explores how stress and trauma can induce heritable epigenetic changes. Maternal stress during pregnancy links to depressive-like behaviors in offspring for up to two generations, while paternal trauma affects the next generation's behavior and neuroanatomy. This underscores how environmental factors impact both physical and mental health across generations. His laboratory investigates the molecular mechanisms, focusing on interactions between transcription factors and DNA methylation in germline differentiation and early embryogenesis. Studying proteins like CTCF and cohesin, which shape 3D genome structure and gene expression, aims to develop strategies mitigating adverse health effects from environmental exposures.

Certain chromatin features persist from the germline to the embryo, suggesting their crucial role in maintaining epigenetic information across generations. For instance, nucleosomes with H3.3 and H2A.Z are conserved in sperm and oocytes, lasting through early embryogenesis. These histone modifications likely protect genomic regions from re-methylation during post-fertilization reprogramming.

Corces' pioneering research advances our understanding of transgenerational epigenetic inheritance mechanisms, offering new avenues for research and potential therapeutic interventions against environment-influenced complex diseases.

Bhoomi Mirani is a doctoral student in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

Unraveling the Myth: Rosalind Franklin and the Double Helix

by Hui Ma and Rebecca H. Bishop

In the captivating realm of science, where discoveries can become legendary tales, few stories compare to the debated account of Rosalind Franklin and the Double Helix. Recently, Clemson had the privilege of hosting a seminar by Dr. Nathaniel Comfort from Johns Hopkins University as part of the Distinguished Lectures in Human Genetics and the Discover Science Lectures series, titled "Reflections on Gender, Science, and Myth: Rosalind Franklin and the Double Helix." His seminar shared insights into the profound impact of Franklin's work and the controversies surrounding her role in one of science's greatest discoveries.

Rosalind Franklin, born in London in 1920, emerged as a pioneering figure in physical chemistry and crystallography. Her groundbreaking research on the structure of coal and carbon laid the foundation for her pivotal contribution to the discovery of the DNA double helix. However, it was her work with X-ray diffraction, particularly the iconic "Photo 51," that captured the essence of her scientific impact.

In a world where scientific achievements often overshadow the individuals behind them, it is essential to acknowledge the human stories embedded in the process of discovery. Rosalind Franklin's journey from London to the forefront of molecular biology is not just a story of scientific breakthroughs but also a testament to her strength and determination in overcoming challenges.

The seminar explored the intricate interplay between historical facts, imagination, speculation, and aspiration in shaping scientific narratives. Franklin's role in the discovery of the DNA structure, immortalized by James Watson's infamous reaction to Photo 51, underscored the complexity of her legacy. Despite her instrumental contribution, Franklin's portrayal as "Rosy" and the challenges she faced within the scientific community revealed the pervasive gender biases of her time.

Comfort elucidated the evolving narrative surrounding Franklin, emphasizing her depiction as a feminist icon for reasons both right and wrong. The seminar dissected the dynamics of the MRC biophysics group at King's College London, where Franklin's collaboration with Maurice Wilkins and others intersected with the ambitious pursuits of Linus Pauling and Francis Crick. The details of Franklin's interactions with others and how Watson described her in "The Double Helix" revealed the biases present in scientific discussions.

The seminar delved into alternative myths surrounding Franklin's contribution and her subsequent projects, shedding light on her enduring impact beyond the Double Helix. Comfort highlighted instances where Watson actually advocated for Franklin and her research endeavors, challenging prevailing narratives of animosity and competition.

Franklin's exploration of the structure of the Tobacco Mosaic Virus (TMV) exemplified her enduring commitment to scientific inquiry. Her contributions to understanding protein structures and helical formations paved the way for future advancements in molecular biology.

It is important to note Franklin's enduring impact on science education and mentorship. Despite the challenges she faced during her career, Franklin remained dedicated to nurturing the next generation of scientists. Her commitment to fostering intellectual curiosity and scientific inquiry continues to inspire aspiring researchers worldwide. Beyond her contributions to molecular biology, Franklin's legacy lives on through the countless individuals she inspired to pursue careers in STEM fields.

Franklin's posthumous recognition has grown over the years, as the scientific community acknowledges her indispensable role in shaping our understanding of DNA structure. Institutions and initiatives dedicated to promoting women in science often cite Franklin as a pioneering figure and advocate for gender equality in academia and research.

"Reflections on Gender, Science, and Myth: Rosalind Franklin and the Double Helix" offered a profound exploration of Franklin's enduring legacy and the complexities of scientific storytelling. Through her groundbreaking research and strong commitment, Franklin overcame gender biases to make a lasting impact on scientific history. Rosalind Franklin's legacy serves as a poignant reminder of the challenges faced by women in science and the imperative of recognizing their invaluable contributions.

Hui Ma and Rebecca H. Bishop are doctoral students in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

A Conversation with Aaron Masino

Could you briefly describe your research program and what triggered your passion for AI?

The primary focus of my research is the development and application of novel artificial intelligence (AI) methods motivated by challenges related to the diagnosis and treatment of rare diseases and clinical decision support in continuous monitoring settings such as intensive care units. These seemingly disparate domains share characteristics such as small study cohorts, clinical heterogeneity, and longitudinal progression that present significant challenges to AI system performance. Simultaneously, the increasing digitization of health data including structured electronic health records, imaging, physiological monitoring, and multiomic data often requires advanced AI methods that currently lack explainability. I first encountered machine learning, a subfield of AI, in 2011 when I transitioned from optics to biomedical research. The idea that machines could not only model real world phenomena but learn how with just data fascinated me. From there on, I was hooked and started learning everything I could about the larger field of AI.

Why did you decide to leave industry and return to academia?

I missed the autonomy that one has as an academic researcher. While I found my industry research experience interesting, I missed having the ability to decide what research problems to pursue and with whom I collaborate. I also missed working with students on research projects. They bring many fresh ideas and enthusiasm to research that was lacking in my industry environment.

What is the significance of developments in AI for human genetics and the study and treatment of diseases?

Well, this is a very far-reaching question! AI, specifically machine learning, has a long history in facilitating human genetics research such as the development of bioinformatics and phenotyping tools. That trend will certainly continue as deep learning and explainable AI tools are developed to support in-silico prediction of pathogenic non-coding variants and polygenic risk, improve design of candidate therapeutics, and streamline clinical trials, just to name a few. However, my hope is that multifaceted AI systems that include not only machine learning inference models, but also elements of deductive reasoning and multimodal human-computer interfaces will emerge that can interact with scientists and clinicians in much the same way that human-human interactions occur to develop and conduct new research and manage personalized treatments.

How important are collaborations to your research program and what criteria do you use when choosing your collaborators?

Collaborations are critical to both my methodological and applied research interests. For an AI system to have significant applied impact, one needs to work with domain experts to accurately identify their challenges, develop innovative concepts to address them, and understand the ecosystem in which they will operate. My methodological research interests are motivated by identifying AI or other advancements that are necessary to realize these innovative

concepts. None of this is possible without interdisciplinary collaboration. I find that most collaborations form organically rather than through specific criteria, though it is important that collaborators bring complimentary knowledge and share similar values with respect to research conduct.

What is the most rewarding part of your research?

Although there is nothing quite like the thrill of getting positive experimental results after months (or years) of effort, the most rewarding aspect of my research is the relationships that are formed with collaborators and students. In my opinion, it's these "in the trenches" relationships that provide a great deal of the day-to-day support needed to persevere in research.

What activities do you enjoy outside your academic activities?

Most importantly, I enjoy spending time with my amazing spouse regardless of the activity! Otherwise, I am an avid surfer and enjoy traveling, preferably combining the two as in this past June when I, my wife, and several friends surfed in Costa Rica. I also enjoy reading history, particularly works on the American Revolution and World War II, and landscape photography.

What is your advice for young investigators?

I think the main thing is not to get discouraged. I've yet to meet someone for whom research is easy. Research success is largely about grit (see Angela Duckworth's work). You also need to put your work out into the world early and often. It will get critiqued and at times that will be painful. However, it will also make your work better and help you grow as a researcher. Finally, have fun. Remember, very few people can pursue their passion as a career, so enjoy it.

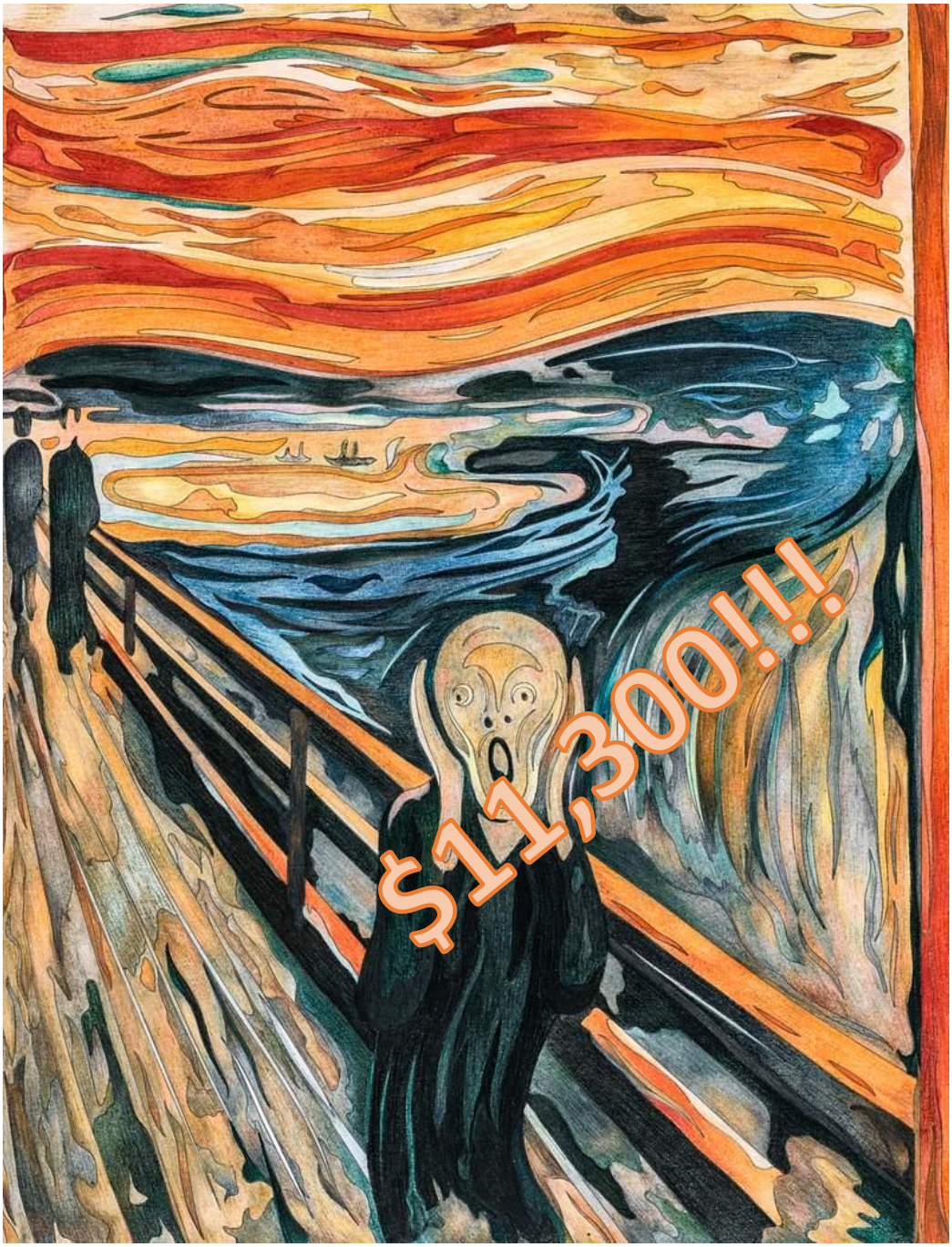
Dr. Masino is an Associate Professor in the School of Computing at Clemson University and holds the Clemson University Center for Human Genetics Dr. Gary Spitzer Endowed Distinguished Professorship in Genomics.

Viewpoint

Cheap Labor – Big Profits

by Robert R. H. Anholt

You got your paper accepted in Nature and are in a celebratory mood……..until you find out that the Open Access charge is a whopping $11,300. The Open Access fee in Neuron is $8,900, excluding taxes. To make us feel better, the large publishing houses, like Springer and Elsevier, use the term Article Processing Fee. And there is the problem. Maintaining the quality of elite journals requires peer review by the best experts in their respective fields. Some consider it an honor to be asked to review manuscripts from elite journals, others feel compelled to review articles that are in their area of expertise driven by professional ethics. Thus, the major publishing houses exploit the scientific community to rake in huge profits without compensating the reviewers.



Providing expert consultation that requires considerable time investment *pro bono* is unthinkable in any field other than science. Large independent publishing houses, such as Elsevier and Springer, should appropriately compensate reviewers and associate editors for their services, which are essential for their journals' viability, and with more than a T-shirt or a coffee mug. Respecting reviewers' expertise and contributions to peer review through appropriate remuneration will also make it easier to recruit and motivate reviewers. Such expenses can readily be accommodated within their huge article processing fees while still allowing a substantial profit.

Don't take me wrong. There is a difference between journals published by the large independent publishing houses and professional societies, including the American Association for the Advancement of Science. As a member of the Genetics Society of America, I consider reviewing for Genetics or G3 or serving on their editorial boards a community obligation and I would never expect a consultation fee for services that benefit the society.

The AAAS and professional scientific societies return benefits to their memberships and to the scientific community. Income from their journals sustains these organizations and enables them to support education and advocacy for science. Profits from their journals are returned as benefits for the scientific community. This is not the case for the large independent publishers. They prey on the scientific community for profit. It is time for them to start paying their dues.

Robert Anholt is Provost Distinguished Professor and Director of Faculty Excellence in the College of Science at Clemson University. The opinions expressed in this article are his own.

Grants

Renée Cottle received a one-year $565,787 grant (R56) and a subsequent four-year $2,463,454 (R01) grant from the National Heart Lung and Blood Institute of the National Institutes of Health to study nonviral delivery of CRISPR-Cas9 into hepatocytes combined with APAP selection for treatment of familial hypercholesterolemia.

Zhana Duren received a two-year $419,375 grant (R21) from the National Institute on Drug Abuse to study statistical methods for gene regulatory analysis of substance use disorder.

Trudy Mackay and **Robert Anholt** received a two-year $170,000 grant from the Cure Sanfilippo Foundation to study genetic modifiers of Sanfilippo A and B.

Prakrit Subba received a Biological Sciences Interdisciplinary Fellowship to explore the transcriptional mechanisms by which prenatal acoustic communication in zebra finches modifies social and cognitive phenotypes in offspring at single-cell resolution.

Seminars

On Friday, **September 13**, at 2:30 pm, **Dr. Rasmus Nielsen**, Trevor J. McMinn Endowed Professor of Integrative biology at the University of California at Berkeley, will present a seminar titled “Human evolutionary adaptation - as revealed by our genomes.” The seminar will be via Zoom. https://clemson.zoom.us/j/94485784719?pwd=R0hrOWJ0eFBGdlgrQy9lWTZpanFVQT09

On Friday, **September 27**, at 2:30 pm, **Dr. Rodolphe Barrangou**, Todd R. Klaenhammer Distinguished Professor in Probiotics Research in the Department of Food, Bioprocessing and Nutrition Sciences at North Carolina State University, will present a seminar titled “Applications and implications of genome editing technologies.” The seminar is also part of the Provost’s Distinguished Lecture series and will be held at 174 Poole Agricultural Center.

On Friday, **October 25**, from 9:00 am - 5:00 pm, the Center for Human Genetics will hold its **annual COBRE retreat** at the Greenwood Genetic Center.

On Monday, **October 28**, at 2;00 pm, **Dr. Jonathan Pritchard**, Professor of Genetics and Biology at Stanford University, will present a seminar titled “How GWAS and functional genomics provide insight into molecular pathways of human trait biology”. The seminar will be via Zoom, https://clemson.zoom.us/j/9326606783.

On Thursday, **November 7**, from 4:00 pm - 5:30 pm, **Dr. Holden Thorp**, Rita Levi-Montalcini Distinguished University Professorship of Chemistry and Medicine at Washington University and Editor-in-Chief of *Science* will present a seminar titled “The role of graduate education in science and its impact on society.” The seminar will be held in the Self Auditorium at the Strom Thurmond Institute.

Publications

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

Ates I, Stuart C, Rathbone T, Barzi M, He G, Major AM, **Shankar V**, **Lyman RA**, **Angner SS**, **Mackay TFC**, Srinivasan S, Farris AB, Bissig, K-D and **Cottle RN**. 2024. Ex vivo gene editing and cell therapy for hereditary tyrosinemia type 1. *Hepatol Commun* **8:** e0424.

Bai X, **Duren Z**, Wan L and Xia LC. 2024. Joint inference of clonal structure using single-cell genome and transcriptome sequencing data. *NAR Genom Bioinform* **6:** lqae017.

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Feliciano DM. 2023. Modeling somatic mosaicism in the mammalian cerebral cortex. *Front. Mamm. Sci. Sec. Nervous System and Cognate Behaviors* **2:**1-26.

Feliciano DM. 2024. Do neural stem cell extracellular vesicles help evade depression? *Neuroscience* 538: 93-94.

Forenzo C and **Larsen J**. 2024. Bridging clinical radiotherapy and space radiation therapeutics through reactive oxygen species (ROS)-triggered delivery. *Free Radic Biol Med* **219:** 88-103.

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Hogan MP, Holding ML, Nystrom GS, Colston TJ, Bartlett DA, Mason AJ, Ellsworth SA, Rautsaw RM, Lawrence KC, Strickland JL, He B, Fraser P, Margres MJ, Gilbert DM, Gibbs HL, **Parkinson CL** and Rokyta DR. 2024. The genetic regulatory architecture and epigenomic basis for age-related changes in rattlesnake venom. *Proc Natl Acad Sci U S A* **121:** e2313440121.

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Jan S, **Rustgi S**, Barmukh R, Shikari AB, Leske B, Bekuma A, Sharma D, Ma W, Kumar U, Kumar U, Bohra A, Varshney RK and Mir RR. 2024. Advances and opportunities in unraveling cold-tolerance mechanisms in the world's primary staple food crops. *Plant Genome* 17: e20402.

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Konkel MK and Casanova EL. 2024. A mobile DNA sequence could explain tail loss in humans and apes. *Nature* **626:** 958-959.

Kraft FH, Crino OL, Adeniran-Obey SO, Moraney RA, Clayton DF, **George JM** and Buchanan KL. 2024. Parental developmental experience affects vocal learning in offspring. *Sci Rep* **14:**13787.

Lee JJ, Wang T, Wiggins K, Lu PN, Underwood C, Ochenkowska K, Samarut E, Pollard LM, **Flanagan-Steet H** and **Steet R**. 2024. Dysregulated lysosomal exocytosis drives protease-mediated cartilage pathogenesis in multiple lysosomal disorders. *iScience* **27:**109293.

Li X, Freeman N and Wang L. 2023. Q-learning based methods for dynamic treatment regimes. In: *Y Zhao and D Chen (Eds) Precision Medicine: Methods and Applications*, Springer.

Li X, Yu S, Wang Y, Wang G, Wang L and Lai M-J. 2024. Nonparametric regression for 3D point cloud learning. *JMLR* **25:**1-56.

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Meher PK, Sahu TK, Gupta A, Kumar A and **Rustgi S**. 2024. ASRpro: A machine-learning computational model for identifying proteins associated with multiple abiotic stress in plants. *Plant Genome* **17:** e20259.

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Wang Z, Rowe DB, **Li X** and Brown DA. 2024. A fully Bayesian approach for comprehensive mapping of magnitude and phase brain activation in complex-valued fMRI data. *Magn Reson Imaging* **109:** 271-285.

Williams L and **Larsen J**. 2024. Nanoparticle-mediated delivery of non-viral gene editing technology to the brain. *Prog Neurobiol* **232:**102547.

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Yamamoto A, Huang W, **Anholt RRH** and **Mackay TFC**. 2024. The genetic basis of variation in *Drosophila melanogaster* mating behavior. *iScience* **27:**109837.

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Out and About

Robert Anholt was a keynote speaker at the Genomics Education Partnership symposium, Carolinas Regional Node at Clemson University. He was a panel moderator of a discussion panel on Genomics and Informatics in Mental Health Research: Ethical practices and Considerations, TIDE (Tigers for Inclusion, Diversity and Ethics) Conference. He also served on an NIGMS COBRE Phase 1 reviews Special Emphasis Panel.

Robert Anholt and **Trudy Mackay** attended the biannual meeting of the American Philosophical Society in Philadelphia.

Robert Anholt, **Trudy Mackay** and **Anurag Chaturvedi** attended the European Commission sponsored Precision Toxicology meeting in Brussels, Belgium. **Robert Anholt** gave a presentation and **Anurag Chaturvedi** presented a poster, titled “Sodium arsenite-induced neurotoxicity at single cell resolution in the Drosophila brain.” A poster by **Katelynne Collins**, **Elisa Howansky**, **Maria Adonay** and **Vijay Shankar** was also presented.

Gavin Arno has been appointed Co-Lead of the Genomics England Genotype-Phenotype Association research community. He also attended the annual Association for Research in Vision and Ophthalmology (ARVO) meeting and was elected to the ARVO planning committee, Biochemistry/Molecular Biology section. He also acquired leadership roles of ClinGen as co-chair of the Retina Gene Curation Expert Panel and member of the Ocular Genomics working group, *ABCA4* variant curation expert panel. He received a significant contributor award from the organization.

Anurag Chaturvedi attended the Allied Genetics Conference (TAGC) 2024 in Washington, DC, organized by the Genetics Society of America and gave a talk at the workshop on “Emerging roles for model organisms in precision toxicology” titled “Invertebrate models for toxicogenomics: Lessons from *Drosophila* and *Daphnia.*

Zhana Duren gave invited presentations on gene regulatory network analysis from single cell multiome data at the International Conference on Intelligent Systems for Molecular Biology (SMB) in Montreal, Canada, and the 7th International Conference on Econometrics and Statistics (EcoSta 2024) in Beijing, China.

Brianna Dyer and **Christopher Farrell** presented a poster at the annual American Association for Cancer Research (AACR) meeting in San Diego, CA, titled "Induction of the p-glycoprotein with atorvastatin using colorectal cancer cells".

David Feliciano served as the 2023 Chairperson for the US Department of Defense CDMRP National Review Panel. He also served as Special Collection Editor for Molecular Autism Scientific Reports.

Shyamalika Gopalan attended the annual meeting of the Society for Molecular Biology and Evolution in Puerto Vallarta, Mexico and presented a poster on evolutionary simulations. Her student, Gillian Meeks, gave a talk on epigenetic aging in diverse human populations.

Jeffrey “Spencer” Hatfield gave a presentation at the Genetics and Epigenetics Cross-Cutting Research conference of the National Institute on Drug Abuse in Bethesda, MD. **Robert Anholt**, **Olivia Rose Hamilton**, **Trudy Mackay** and **Alp Ummet** also attended the conference.

Miriam Konkel gave a presentation at the Human Genome Structural Variation Consortium meeting in Berlin, Germany. She also served on the ‘Genetic Variation and Evolution’ Study section of the NIH and has been appointed guest editor of the transposable element collection of Genome Biology.

Jessica Larsen attended the 2024 Annual Meeting and Exposition of the Controlled Release Society in Bologna, Italy.

Lela Lackey, **Austin Herbert**, **Alexandra Randazza** and **Debarati Majumdar** attended the RNA Society 2024 Conference in Edinburgh, UK. **Debarati Majumdar** received the RNA Society Travel Fellowship and presented a poster titled “Exploring splicing and APA isoforms of DNMT3A: Stability, localization and function”. **Alexandra Randazza** presented a poster titled “High throughput workflow to study the impact of mutations on RNA structure in the adenine riboswitch”. **Austin Herbert** presented a poster titled "Precursor RNA structural patterns at SF3B1-mutant sensitive 3’ splice junctions”.

Trudy Mackay has been elected a Laureate Distinguished Fellow of the International Engineering and Technology Institute.

Madeline Santana did an interview for Clemson Blogs https://blogs.clemson.edu/genbiochem/2024/06/07/genetics-and-biochemistry-hosts-fulbright-scholar/

Vijay Shankar received the inaugural Award of Excellence from the Clemson University Center for Human Genetics.

Vijay Shankar, **Maria Adonay** and **John Poole** organized the annual Clemson University RNA-seq retreat in collaboration with the Clemson University Genomics and Bioinformatics Facility (CUGBF). This three-day instructional workshop had an enrollment of 31 participants and provided an in-depth overview of transcriptomics, from experimental design to analysis and interpretation.

Alp Ummet gave a presentation at the National Institute of Drug Abuse Animal Genomics Conference in Bethesda, MD. **Robert Anholt** and **Trudy Mackay** also attended the conference.

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