CLEMSON UNIVERSITY
CENTER FOR HUMAN GENETICS

The Transcript

Newsletter of the Center for Human Genetics at Clemson University
Spring, 2023

From the Director

Many advances in genetics are dependent on the sustained dedicated work of experienced staff members. Dr. Richard Lyman is such an unsung hero who has worked in the Mackay laboratory for about 34 years and has directed the Drosophila Research Core facility at the Center for Human Genetics at Clemson University. Roberta Lyman has been the Mackay and Anholt lab manager and played an instrumental role in enabling the Center for Human Genetics. Always staying on the background, Richard has quietly made substantial contributions to the Drosophila research community, culminating in the Drosophila Genetic Reference Panel, which in a tour-de-force effort has recently been expanded to 1600 wild-derived inbred lines with complete DNA sequences. The characterization of this new resource is currently underway and will provide important new tools for comparative genomic studies. Richard and Roberta Lyman are retiring at the end of January, and we wish them an enjoyable and rewarding retirement. We will miss them. Dr. Nestor Nazario Yepiz will be the next director of the Drosophila core and Patrick Freymuth will take on lab management duties of the Mackay-Anholt laboratory.

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.

The Center for Human Genetics welcomes Dr. Sachin Rustgi as a new faculty member of the Center for Human Genetics along with his student, Zachary Jones. Dr. Rustgi is an Associate Professor of Molecular Breeding at the Department of Plant and Environmental Sciences, and Faculty Scholar at the Clemson University School of Health Research, as well as an Adjunct Associate Professor at the Department of Crop and Soil Sciences. His team uses conventional plant breeding in conjunction with genome editing strategies to develop novel dietary therapies to alleviate food allergies, including sensitivity to wheat and peanut proteins as well as therapies that can ameliorate celiac disease, an autoimmune disorder. Rustgi and his colleagues will add a new dimension to the Center, improving human nutrition through genomic technologies.

The spring semester promises to be filled with vibrant academic activities. The Distinguished Seminar series in Human Genetics will include Dr. David Threadgill from Texas A&M University who will discuss his latest findings on colorectal cancer in the mouse model and Dr. Adrian Bird from the University of Edinburgh, whose pioneering studies on DNA methylation on CpG islands made a seminal impact on understanding epigenetic mechanisms of gene regulation.

Dr. Michael Lynch will deliver the annual Darwin Lecture on Monday, February 13, in the auditorium of the Watt Family Innovation Center on the Clemson campus.

We are especially looking forward to the Science and Music event on March 9, which will feature Nobel laureate and former President of the Royal Society of London, Dr. Venki Ramakrishnan, along with cellist Raman Ramakrishnan and pianist Benjamin Hochman. Dr. Ramakrishan will discuss his book “Gene Machine” and his presentation will be augmented with performances from Bach, Fauré and Chopin. The event will be in the Brooks Center for the Performing Arts. Get your tickets now.

The Center for Human Genetics also sponsors a recital by Ramakrishnan and Hochman on March 10 in the Greenwood Arts Center with music by Beethoven, Britten and Brahms.

As always, we will continue our weekly Advances in Human Genetics discussion meetings and our monthly lunch-and-learn sessions. The annual summer symposium of the Center of Biomedical Research Excellence in Human Genetics is scheduled for May10 and will feature invited speakers and a poster session. Save the date.

I am looking forward to another productive and stimulating semester.

Transcriptional Enhancers and Their Phenotypic Effects

by Elizabeth Greif

On September 16, 2022, William Allan Award recipient Dr. Aravinda Chakravarti from the New York University Grossman School of Medicine presented a seminar in the Distinguished Lectures in Human Genetics series at Clemson University Center for Human Genetics titled "Transcriptional enhancers and their phenotypic effects."

In his lecture, Chakravarti highlighted the importance of sequence variation in the transcriptional trio when studying human genetics. The transcriptional trio refers to three sequences that cause phenotypic effects: (1) the sequence of transcription factors, (2) the sequence of enhancers, and (3) the sequence of the target gene. He emphasized that we should not only focus on sequence changes in coding regions, but also sequence changes in regulatory elements. He discussed two examples that stress the importance of studying all elements of the transcriptional trio for human genetics and disease.

First, Chakravarti described his early research on a variant of a regulatory element associated with Hirschsprung disease (HSCR). HSCR is an intestinal dysmotility disorder caused by the lack of nerve cells in the gut. The disease does not follow simple mendelian inheritance patterns, and environmental triggers have not been identified despite research efforts. Chakravarti initially advanced our understanding of HSCR by studying families with multiple affected members. His team identified a variant in a highly conserved noncoding region that segregated with HSCR. A single base pair change was identified within the sequence of an enhancer for the 'Rearranged during Transfection' (RET) tyrosine kinase receptor. RET plays important roles in cell proliferation, differentiation, and migration. The enhancer variant Chakravarti and his team identified leads to diminished activity of RET and explains the cause of HSCR: the absence of enteric nerve cells.

After his discovery of the first RET enhancer variant, his team and other groups discovered additional enhancers of RET with variants associated with HSCR. We now know there are different RET tyrosine kinase receptors with unique enhancers during different stages of development. The HSCR-associated variants are transcriptional enhancers that are independent of each other, which means that the number of enteric nerve cells can differ depending on the stage of an individual's development. Depending on the RET enhancer, effects may cause tissue-specific (gut) or non-specific changes in gene expression. Importantly, the regulatory variants associated with HSCR are not limited to effects in RET alone but can also overlap with regulatory variants of other signaling cascades.

For the second part of his lecture, Chakravarti showed how we can consider this transcriptional trio not only for a rare disease, but also for common conditions like high blood pressure. His group built a map of cardiac enhancers that defines where enhancers are found and predicts where enhancers should be even if they are not observed due to a

Dr. Aravinda Chakravarti

weak signal. The map overlaps with other cardiac-relevant DNA hypersensitive sites, and importantly, the map can identify the collection of transcription factors that best explains the signal across a group of enhancers. He emphasizes "signal." There is not an isolated target with a precise phenotypic effect, but instead there is a signaling outburst that affects more than one level in a cascade and leads to varying phenotypes.

Chakravarti tied his two examples together with his final message: extreme phenotypes like human disease are probably occurring because of a failure in multiple steps of a signaling cascade, particularly a cascade of homeostatic mechanisms. He further explains that partial failure of transcriptional enhancers can ultimately lead to changes in cellular function causing phenotypic variation. Chakravarti's team is continuing his work with the transcriptional trio by investigating the phenotypic effects of enhancers using a humanized mouse model.

Reflecting on his work, I feel encouraged as a genetics student to consider the transcriptional trio during my own investigations of complex disease. I am excited to see such progress in the field of genetics, where reinvention is certain in this emerging discipline!

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

An Enhancer RNA that Modifies Susceptibility to Alzheimer's Disease

by Allie Randazza

Dr. Vivian Cheung

On October 10, 2022, Dr. Vivian Cheung from the University of Michigan presented a lecture titled "An Enhancer RNA that Modifies Susceptibility to Alzheimer's Disease" as part of the Distinguished Lectures in Human Genetics series. After a quick reminder that over 150 RNA modifications are known to date, Dr. Cheung demonstrated the importance of these modifications and their roles in susceptibility to diseases such as Alzheimer's disease.

After earning her M.D. in Pediatrics from the University of Pennsylvania School of Medicine, Cheung joined the Life Sciences Institute at the University of Michigan. She currently is an Investigator of the Howard Hughes Medical Institute and Frederick G.L. Huetwell Professor in the Department of Pediatrics of the Division of Neurology at the University of Michigan. The goal of her research is to provide genetic tools and knowledge from basic science research to enable physicians to develop individualized treatments for their patients. human genetics and study gene regulation. She combines computational and experimental methods to study variation in human traits and the genetics of susceptibility to complex diseases. Cheung is particularly interested in regulators that affect transcription and RNA processing.

The function of RNA was previously limited to acting as a transient intermediate of protein synthesis. However, since the mid-1970s, the role of this seemingly simple macromolecule has become appreciated as being more complex and extensive. Specific types of RNAs have been discovered to catalyze reactions and to regulate gene expression via numerous mechanisms, most of which are still unknown. By studying regulation in normal cells, Cheung hopes to gain insights into how dysregulation can lead to diseases.

RNA sequences are not identical to their corresponding DNA sequences. Numerous processing events and nucleic acid modifications significantly impact the RNA's function and structure. One of these structures is R-loops: three-stranded nucleic acid structures with an RNA-DNA hybrid and a displaced single-stranded DNA. R-loops are prevalent in cells and are sites for RNA modifications. These modified bases are more likely to be cleaved by methylpurine glycosylase (MPG) resulting in abasic sites.

R-loops are stabilized by abasic sites and result in RNA Polymerase II (RNAPolII) pausing. This event occurs in AANCR, a non-coding, enhancer RNA transcribed upstream of *APOE.* If the stability of the R-loop is compromised, RNAPolII will pause less often and transcribe AANCR more efficiently. This enhancer RNA increases the expression of *APOE*, which is a modifier of Alzheimer's disease. In other words, specific alleles of *APOE*will later the risk of developing Alzheimer's disease

This example alone highlights the significant impact that RNA modifications can have on human health. Modifications are currently difficult to study since RNA sequences are obtained through reverse transcription of RNA to DNA leading to the loss of information about the modifications that were originally present. Cheung is one of the organizers of The RNome Project. This project aims to develop technologies that will enable the characterization of the modifications present in an RNA sequence. Knowledge of a RNA's complete sequence will allow for better study of RNAs, their influence on disease, and development of RNA-based treatments.

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

A Conversation with Jennifer Mason

Could you briefly describe your research program?

My lab focuses on how DNA damage is repaired during the process of replication. DNA must be copied in an accurate and precise way to maintain genomic integrity of cells and organisms. Inaccurate repair of damage leads to an increase in mutations and genomic rearrangements resulting in human disease including cancer. Current research projects in the lab aim to 1) understand the mechanism of DNA repair in response to different genotoxic stresses and 2) identify ways to exploit DNA repair defects in cancer as potential chemotherapeutic strategies.

Can you tell us what made you interested in this research area?

My love for the field of DNA repair and molecular genetics began in graduate school when I joined the lab of Dr. JoAnn Sekiguchi at the University of Michigan for my PhD work. I love the challenge of figuring out how a specific protein functions in the cell to respond to DNA damage. Every experimental result is a new piece of the puzzle and figuring out how the pieces fit together, and which pieces are still missing is both challenging and rewarding.

What made you interested in working at Clemson University?

The Department of Genetics and Biochemistry was a great fit for me and stood out. I really enjoyed the collaborative environment and the diverse research fields of the faculty. There were so many exciting things happening when I interviewed for the position including the establishment of the College of Science, Clemson receiving R1 status, the Eukaryotic Pathogens Innovation Center (EPIC) had just received a COBRE grant from the NIH, and the plan to open the Center for Human Genetics. It really felt this was an opportunity to be at the ground level of a growing research enterprise at Clemson University.

What has been the most rewarding part of your research?

My favorite part of my job is mentoring people in the lab. I love teaching others how to perform research and it is so much fun to watch individuals grow as independent scientists. I owe all my success to the hard work and dedication of the great members of my lab.

Outside of Research tell us who is Jennifer Mason?

When I am not working, I spend time with my partner. We enjoy playing mini golf, running, and watching British murder mysteries. After moving to South Carolina, we joined the Palmetto curling club in Greenville, South Carolina and fell in love with the sport. It allows me to completely step away from lab for a few hours a week and meet people outside of Clemson. We even won the league championship in 2020!

What is your advice to a young person starting their research journey?

Don't be afraid to fail. Science is hard and does not work a lot of the time. If you make a mistake, own up to it and learn from it. If you have an idea, speak up. On occasion, do the hard experiment with a high chance of failure. This is how you learn and grow and sometimes those impossible experiments work.

Jennifer Mason is an Assistant Professor in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University

Viewpoint: Reflections on the Umwelt

by Robert Anholt

The renowned twentieth century zoologist Baron Jakob von Uexküll who worked in Heidelberg and later at the Zoological Station in Naples is often considered the founder of ecology. In his studies on invertebrates, the Baron von Uexküll realized that different organisms perceive their surroundings differently in space and time so that animals that share the same environment in fact live contemporaneously in different perceptual worlds. He coined the term "Umwelt" to define this concept. Giorgio Agamben in his book "*The Open: Man and Animal"* quotes from Jakob von Uexküll and Georg Kriszat, "*Streifzüge durch die Umwelten von Tieren und Menschen. Ein Bilderbuch unsichtbarer Welten (1934; Hamburg: Rowohlt, 1956)"* observations about the Umwelt of the tick:

"This eyeless animal finds the way to her watch post with the help of only her skin's general sensitivity to light. The approach of her prey becomes apparent to this blind and deaf bandit only through her sense of smell. The odor of butyric acid, which emanates from the sebaceous follicles of all mammals, works on the tick as a signal that causes her to abandon her post and fall blindly downward toward her prey. If she is fortunate enough to fall on something warm (which she perceives by means of an organ sensible to a precise temperature) then she has attained her prey, the warm-blooded animal, and thereafter needs only the help of her sense of touch to find the least hairy spot possible and embed herself up to her head in the cutaneous tissue of her prey. She can now slowly suck up a stream of warm blood."

It is difficult to imagine that my cat lives in a different world than me even though we share the same environment. Whereas I see the world in polychrome, my cat does not have color vision and sees me and my surroundings in shades of black and white. Compared to her, my sense of smell is pitiful, and her auditory perceptions are superior to mine. Yet, our environments and lives intersect, and our different Umwelts can connect to form a common experience.

In the current snapshot of evolutionary time the Umwelt represents the endpoint of successful adaptive evolution. Color vision is unique to higher primates, while canines and cats, and for that matter most mammals, have a better developed sense of smell. Mice have about 1000 functional olfactory receptors, whereas in humans two-thirds of odorant receptor genes have become pseudogenes, retaining representatives of each major odor class, but with substantially less sensitivity and granularity of perception. The African naked mole rat has poor hearing and is insensitive to chemical and inflammatory pain but has exquisite sensitivity to touch and vibrations.

Whereas in the pre-genome era, phylogeneticists relied on physical characteristics, today evolutionary biologists explore the tree of life based on molecular changes in the DNA. It is comforting to note the extensive concordance between the two approaches.

It might be of interest to construct an evolutionary tree based on the evolution of Umwelts to gain insights into how environmental perceptions evolve between and within clades and to what extent current Umwelts are still evolvable. Have we reached the endpoint or will we in future geological time evolve into a primate species that has entirely lost its sense of smell but can sense magnetism, the rotation of the earth, and polarized light?

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

Seminars

On Friday, **January 27**, at 2:30pm **Dr. David Threadgill**, University Distinguished Professor, The Tom and Jean McMullin Chair of Genetics, and Director of the Texas A&M Institute for Genome Sciences and Society at Texas A&M, will present a seminar titled "The genetic complexity of the EGFR/ERBB signaling axis in colorectal cancer development and therapy".

On Friday, **February 10**, at 2:30pm, **Dr. Adrian Bird**, Buchanan Professor of Genetics at the University of Edinburgh, will present a seminar titled "Proteins that interpret genomic signals to stabilize cell identity".

On Monday, **February 13**, at 2:00 pm, **Dr. Michael Lynch**, Director of the Biodesign Center for Mechanisms of Evolution at Arizona State University in Tempe, AZ, will deliver the annual Darwin lecture, titled "Drift, mutation, and the origin of cellular features".

On Thursday, **March 9**, at 2:00 pm, the Center for Human Genetics presents a science and music event in the Brooks Center for the Performing Arts. Nobel laureate, **Dr. Venki Ramakrishnan** from the University of Cambridge, UK, will present a lecture titled "Gene Machine." **Cellist Raman Ramakrishnan and pianist Benjamin Hochman** will perform works by Bach, Fauré, and Chopin.

On Friday, **March 31**, at 2:30 pm, **Dr. Evan Eichler**, Professor of Genome Sciences at the University of Washington, will present a seminar titled "Complex structural variation in a complete human genome."

Publications

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

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Earle A, Bessonny M, Benito J, Huang K, Parker H, Tyler E, Crawford B, Khan N, Armstrong B, **Stamatikos A**, Garimella S and Clay-Gilmour A. 2022. Urinary exosomal microRNAs as biomarkers for obesity-associated chronic kidney disease. *J. Clin. Med.* **11:** 5271.

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Meher PK, Sahu TK, Gupta A, Kumar A and **Rustgi S**. 2022. ASRpro: A machine-learning computational model for identifying proteins associated with multiple abiotic stress in plants. *Plant Genome* **13:** e20259.

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https://scienceweb.clemson.edu/chg/

Gene Machine

A science and music lecture with Nobel laureate Venki Ramakrishnan

Working at the MRC Laboratory of Molecular Biology in Cambridge, Venki Ramakrishnan, Ph.D., received the Nobel Prize in chemistry for elucidating the structure of the ribosome, the organelle which translates genetic information into proteins.

He was knighted by Queen Elizabeth and has served as president of the Royal Society of London. His book, "Gene Machine," describes the history of the field — and the personalities involved — which led to the discovery of the mechanisms that translate our genetic blueprint into a functioning individual.

Venki Ramakrishnan's lecture will be preceded and followed by musical performances by his son, renowned cellist Raman Ramakrishnan, and concert pianist and conductor Benjamin Hochman.

"Classical music doesn't get better than this…"

— The New York Times, about Hochman

Raman Ramakrishnan

Benjamin Hochman

There will be an open reception with the speaker and artists immediately following the performance

General admission $25 | Free for students
2 p.m. March 9, 2023
Brooks Center for the Performing Arts
Clemson University

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Tickets can be ordered at

https://clemson.universitytickets.com/w/event.aspx?id=1645&r=bf49c84db1464751a254ca54b9d4f661

CHAMBER MUSIC *in the* Emerald City

The Clemson University Center for Human Genetics proudly presents cellist Raman Ramakrishnan and pianist Benjamin Hochman

Cellist Raman Ramakrishnan has performed around the world. He was a member of the Horszowski Trio and a founding member of the Daedalus Quartet. Ramakrishnan has given numerous solo recitals, performed as guest principal cellist with the Saint Paul Chamber Orchestra and was a guest member of Yo Yo Ma's Silk Road Ensemble. Ramakrishnan is currently an artist member of the Boston Chamber Music Society and a faculty member at Bard College.

Pianist Benjamin Hochman has enjoyed an international performing career ever since his Carnegie Hall debut as soloist with the Israel Philharmonic under Pinchas Zukerman, appearing as soloist with the New York, Los Angeles and Prague philharmonic orchestras, and the Chicago, Pittsburgh, San Francisco and Jerusalem symphony orchestras. He has conducted the English Chamber Orchestra, The Orchestra Now at Bard Music Festival and the Juilliard Orchestra, among others.

"Classical music doesn't get better than this..." — *The New York Times, about Hochman*

Admission $45 | 7:30 p.m. March 10, 2023

The Arts Center of Greenwood | 120 Main St., Greenwood

CLEMSON UNIVERSITY CENTER FOR HUMAN GENETICS

To order tickets: Mail a check made out to Dr. Robert Anholt to Clemson Center for Human Genetics, 114 Gregor Mendel Circle, Greenwood, SC 29646. Include your mailing address. For more information, email ranholt@clemson.edu.