February Edition
Feb 4th, 2022
Volume 3, Issue 5

Physiology Newsletter

COVID-19

HUB AT HOPKINS
JHU COVID RESOURCE CENTER
JHM COVID-19 INTERNAL RESOURCE PANEL
MARYLAND DEPT OF HEALTH
CENTERS FOR DISEASE CONTROL

CLICK HERE to read about Booster Shots: Hopkins encourages 3rd doses of COVID vaccines for all adults. Make an appointment for a booster through MyChart.

Johns Hopkins has moved to Phase 3 of reopening efforts, resuming higher-risk activities but still relying on distancing and mask-wearing in addition to providing online alternatives to in-person activities.

Universal masking; all personnel must wear masks in JHM facilities, regardless of vaccination status, unless alone in an office with the door closed.

Meetings and gatherings indoors and outdoors should not exceed 50 people. Food and drink should be individually wrapped in a "grab-and-go" fashion.

If you experience COVID-19 symptoms, call the Johns Hopkins COVID-19 Call Center at **443-287-8500** for evaluation and guidance.

Opportunities

The 2022 Lasker Essay Contest opens February 9th. The Lasker Essay Contest engages early career scientists and clinicians from the US and around the globe in a discussion about big questions in biology and medicine and the role of biomedical research in our society today.

JHU list of grad student funding sources
JHU list of postdoc funding sources

Welcome (back)!

Welcoming women awarded for their scientific wins in the world:

Hopkins hosts 2022 Kuggie Vallee Distinguished Lecture, includes Dr. Jen Pluznick on mentoring panel

Dr. Jen Pluznick
Physiology Faculty

On Tuesday, January 25, Johns Hopkins hosted the Kuggie Vallee Distinguished Lecturer, Dr. Eva Nogales. This lecture was sponsored by the Vallee Foundation to highlight women's major achievements in science and is named for Dr. Kuggie Vallee, who earned her EdD in 1952 and spent 27 years as a Professor at Lesley College, later serving as a Lecturer in Biology at Harvard University. Dr. Eva Nogales of the University of California at Berkeley gave a lecture entitled, "Structure, Dynamics, and Regulatory Interactions in Large Human Transcriptional Complexes" which showcased the power of single particle Cryo-EM to reveal molecular function. For example, she outlined work from the Nogales Lab which solved the structure of the human SAGA complex, an evolutionarily conserved complex which contributes to chromatin modification, gene regulation, and repair of DNA damage. By comparing the structure of SAGA in humans and in yeast, her group identified similarities between the human and yeast complex - and, surprisingly, large differences in geometry of functional elements between these two species.

In addition to the lecture, there were two Mentoring Panels featuring Dr. Eva Nogales along with women from the Johns Hopkins faculty, which included breakout sessions on topics such as Mentorship, Sustainability, and External Impact. One session was focused on navigating the junior faculty years, and the other was focused on navigating the postdoc experience and becoming a PI. Despite the fact that this event was necessarily held on zoom (where else?), Dr. Nogales' science certainly captured the imagination, and the discussions of career development were engaging and interactive. Fun fact: past awardees of this prestigious lectureship include Dr. Geraldine Seydoux of Johns Hopkins (2018)!

♫♪ Hello from the other side ♫♪ ...of CMP recruitment

Manuella Ribas Andrade
1st Year CMP Graduate Student

A year later, I am getting to experience in-person interview! But this time on the other side, helping plan and coordinate the events... As a first-year student, I remember very vividly the interview process, which I participated exactly a year ago from my bedroom. While I was warm and comfortable wearing slippers in my house in 60°F Florida, I missed the excitement of being in a different city that could soon become my reality. As we learn how to live with the restrictions of this new reality with COVID-19, I am so glad we got to have this year's interview weekend in person - one of the many perks from being a small program! It was definitely a different and unique experience of its own— from eating outside in 20°F weather (to follow Johns Hopkins requirements) to planning hybrid presentations and social events restricted to seven people. But I can confidently say we were able to successfully welcome eight people for in-person interviews in 2022!

The highlight of meeting the recruits in-person and learning about their research experiences was that it emphasized to me the great diversity and potential we have in this program. Even though it feels like I just arrived as a newby at Johns Hopkins, during recruitment weekend I was the one showing the campus and answering questions. It was a weird feeling, but it made me look back on what a great experience this first year has been— I got to meet many amazing, smart people, caring colleagues, and great mentors. I might not know how to get around using the tunnels yet, but I for sure learned how to get to the closer coffee shops around. At the end, it was very easy to sell them our program and show how to make science fun!

Members of each Physiology Department lab present short "flashtalks" of their lab's research to the prospective students.
-Photo courtesy of Manuella Ribas Andrade

Welcome back Dr. Shubhrajit Roy, Ph.D.

Shubhrajit obtained his B.S. and M.A. degree in Zoology from the University of Calcutta, India. He then pursued his Ph.D. in Neuroscience at the University of Calcutta under Prof. Jharna Ray and Prof. Kunal Ray, elucidating the molecular basis of Wilson disease, a copper metabolism disorder. Shubhrajit was selected for the Fulbright-Nehru Doctoral Research program (USIEF) in 2018, doing part of his thesis work under the supervision of Dr. Lutsenko.

He returned to the Lutsenko lab as a postdoc fellow in December 2021. Currently, Shubhrajit is trying to understand the molecular mechanism associated with the regulation of copper metabolism in the brain. He is also interested in identifying the potential involvement of copper transporters in the differentiation of intestinal stem cells.

During his free time, Shubhrajit enjoys painting, reading books, cooking, listening to music and travelling.

Calendar

February is: Black History Month

Starting with Gerald Ford, every U.S. president since 1976 has officially designated the month of February as Black History Month. The story of Black History Month begins in 1915, half a century after the 13th Amendment abolishing slavery in the U.S. That September, the Harvard-trained historian Carter G. Woodson and the prominent minister Jesse E. Moorland founded an organization dedicated to researching and promoting achievements by Black Americans and others of African descent, known today as the Association for the Study of African American Life and History (ASALH). The group sponsored a national "Negro History week" in 1926, choosing the second week of February to coincide with the birthdays of Abraham Lincoln and Frederick Douglass. The event inspired schools and communities nationwide to organize local celebrations, establish history clubs and host performances and lectures.

-From History.com

Department Events

Feb 11: Department Research Seminar at Noon
Yi (Henry) Cheng
"PAC regulates macrophage function in bacterial infection"
Kevin Chen
"Endosomal PAC in neurons regulates synaptic plasticity"
LOCATION: WEST LECTURE HALL, GROUND FLOOR PCTB OR ZOOM

Feb 25: Department Research Seminar at Noon
Allatah Mekile
Yingzhi Yi
LOCATION: WEST LECTURE HALL, GROUND FLOOR PCTB

March 4: Journal Club at Noon
N-PERSON IN THE PHYSIOLOGY LIBRARY
Jessica Hernandez, Kevin Chen

Other Events

Feb 1: Lunar New Year (2022 is the Year of the Tiger)
新 年 快 乐
Xīn nián kuài lè!

Feb 2: Groundhog Day (Punxsutawney Phil saw his shadow! 6 more weeks of winter)

Feb 14: Valentine's Day

March 1: Mardi Gras

Dr. Roger Reeves graduates from work!

Professor Reeves - now Professor Emeritus - successfully concluded his work at Johns Hopkins University, School of Medicine, on Dec. 31, 2021. Sort of.

Roger Reeves, PhD
Faculty

I actually plan to keep working, but only on the fun parts. I have made important contributions in many areas relevant to Down syndrome (DS) including cancer resistance; risk of congenital heart disease; neural crest contributions to craniofacial maldevelopment; genetic risk factors for multiple organ dysfunction syndrome; chromosome 21 gene function; and others. However, I am best known for work in DS, especially comparative mapping (identifying chromosomal positions of genes in different species) and the application of this to development and characterization of rodent models of DS.

I arrived as a postdoc with Dr. John Littlefield, then Chair of Pediatrics, later Chair of the Department of Physiology, in October 1983 to study the possibility that combinations of co-expressed oncogenes may be responsible for some forms of cancer. Obtaining normal human cell lines from individuals predisposed to any of several different kinds of cancer, I transfected cocktails of up to ½ a dozen cDNAs of known oncogenes into them and surveyed many hundreds of plates of cells. I secured a Damon-Runyan fellowship. My hypothesis was correct. However, the experiment didn't work.[1]

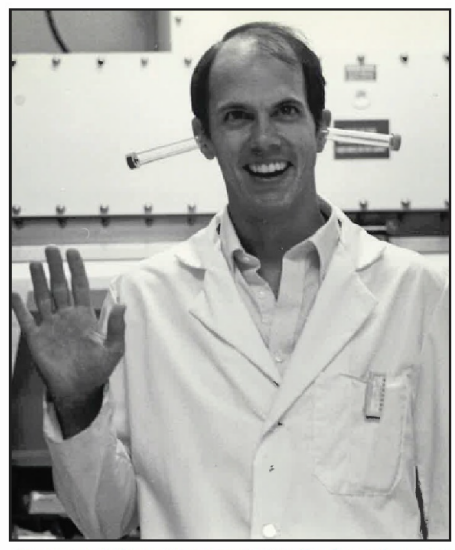
Fortunately, I simultaneously began working on the creation of a mouse model of Down syndrome with John Gearhart. That idea came about when my advisor, Steve O'Brien, a grad school friend of Gearhart's, pulled me out of the lab one evening and said "Come on, we're going to a ball game in Baltimore to see my buddy, John."

John was an interesting guy and talked about two things especially that struck a chord with me. First, he was one of maybe a dozen people in the country at the time who could make a transgenic mouse. Like DNA sequencing, in these dark ages of molecular biology it required more than a test tube of DNA, an established Core Facility and a credit card to make a mouse. Second, he was interested in a new model of Down syndrome, a mouse with three copies of chromosome 16 (MMU16). I had an additional data point relevant to Gearhart's comments. In the next corridor over from his at the National Cancer Institute in Frederick, MD facility was a guy named Ron Brown, who was one of two or three people in the world who could flow sort individual human chromosomes. I figured I would get Ron to sort a flask of HSA21's, go to Baltimore for a postdoc to have Gearhart show me how to make transgenic mice, and inject the mouse eggs to create the perfect mouse model of DS. Two or three years should then serve to figure out which HSA21 genes were important for DS and with that published, I thought he could probably find a job. This experiment also didn't work as planned. However, I did eventually publish the first non-mosaic mouse model of DS carrying HSA21 – in 2020.

In 1990, Muriel Davisson was carrying out a bold genetic screen for chromosome translocations that could produce a mouse with dosage imbalance (extra copies) of the mouse orthologs of HSA21 genes. From comparative mapping by the Reeves Lab and others, it was known that HSA21 orthologs were present on MMU16, so Davisson sent all of the mice that had a translocation involving this chromosome to Hopkins. Reeves' lab mapped the breakpoints relative to genes with molecular markers. Muriel's 65th mouse had an extra chromosome (like people with DS) that had the centromere of MMU17 attached to the distal end of MMU16 and they showed that these mice had several features analogous to those in people with trisomy 21, including midface skeletal retrusion (the main contributor to the characteristic facial appearance of people with DS), increased congenital heart disease, a disproportionately small cerebellum, and learning and memory deficits centered in hippocampal-based tasks – each of these has its own background stories.

Other models followed. Lisa Olson pioneered a genetic engineering approach to create a direct duplication of HSA21-orthologous regions in an experiment that disproved the existence of a so-called DS critical region. Apparently no one reads *Nature* as there are still papers every year claiming that there is such a region. Lisa's tour de force was followed closely by others and now more than 20 such duplication models cover all the orthologous regions to different degrees.

Muriel's vision was a major success as Ts65Dn provided a breakthrough for DS research and remained the leading model of DS for 25+ years. Lizzy Fisher succeeded in getting a somewhat rearranged chromosome 21 into mice in 2005. This was a major coup and brought more much-needed appreciation for DS research and the possibility of understanding one of the most complex genetic challenges in Homo sapiens. However, there was a serious issue with this mouse in that it was highly mosaic, that is, the HSA21 was lost from many cells in a random pattern at different stages of development. Although there were many publications based on this mice, the mosaicism was never properly acknowledged in their assessments.



As a postdoc, Reeves initially faced some challenges adjusting to Hopkins culture. -Photo courtesy of Roger Reeves

Mitsuo Oshimura and colleagues were also making a mouse model with HSA21. Their research took them far into the field of artificial chromosomes and in an amazingly arduous set of experiments, they succeeded in "cloning" the long arm of HSA21 (where nearly all of the genes are) as a mouse artificial chromosome, moved it into mouse embryonic stem cells, from there to mice and thence to the mouse germ line where, with state of the art reproductive technologies, it was moved into a background where it is efficiently transmitted. He contacted me about characterizing these "TcMAC21" mice, and Feng Gao in my lab took the lead on this, publishing this accomplishment at the height (we hope) of the pandemic in 2020. Mitsuo also mentioned that his group had succeeded in putting an HSA21 into rat. We also collaborated on that characterization and the manuscript describing it was finally accepted for publication on Dec 21, 2021, ten days before my retirement.

I stress that these models were all the products of intense and extremely productive collaborations within my lab and with many people in the small international DS research community. My contribution to animal models began with a focus on comparative mapping, and therefore I feel justified in saying that I have had a comparatively successful career.

---

[1]Several years later the experiment was completed by others essentially as I envisioned it, proving my hypothesis, but this required technological developments that did not exist when I attempted the experiment.

Awards and Accomplishments

Publications

Manuscripts

A collaborative work between the Rao and Claypool labs has been published recently, entitled Secretory pathway Ca^{2+}-ATPase SPCA2 regulates mitochondrial respiration and DNA damage response through store-independent calcium entry. Golgi/secretory pathway Ca^{2+}-ATPase isoform SPCA2 plays an unusual role in Ca^{2+} homeostasis. Separate from its ATPase-dependent pumping activity, SPCA2 interacts with Orai1 ion channels to elicit robust Ca^{2+} influx at the plasma membrane. This mechanism is termed store independent Ca^{2+} entry (SICE) and is distinct from the more widely known store dependent calcium entry (SOCE). In the study published in Redox Biology, Dr. Rao's lab discovered a novel role for SICE in maintaining genomic integrity, controlling ROS production and mitochondrial respiration. In the absence of SPCA2, or brief depletion of extracellular Ca^{2+} to block SICE, single and double stranded DNA breaks appeared, activating the ATM/ATR-p53 DNA damage response pathway. In collaboration with Dr. Claypool's lab, they uncover an unexpected link between SICE, mitochondrial Ca^{2+} entry and mitochondrial respiration that is critical for protection against ROS-mediated DNA damage. One therapeutic implication is that elevated levels of SPCA2 confer cancer cell resistance to DNA damaging agents in receptor positive breast cancer. The first author of this work, Dr. Makena mentioned that "we describe novel pump-independent functions of SPCA2 that have far reaching cellular consequences for mitochondrial function, redox homeostasis, and DNA damage response". He added, this study couldn't be possible without Dr. Rao's support during challenging times, and thanks to American Association of Cancer Research (AACR) and AstraZeneca for awarding the 2020 Breast Cancer Fellowship to carry out this project.

The work of Feng Gao is featured in a recent publication from the Reeves lab entitled A transchromosomic rat model with human chromosome 21 shows robust Down syndrome features. Progress in earlier

PDCO Calendar

Contact Us

Newsletter Team
Kelly Summers
Erica Avery
Monish Makena
Professor Rajini Rao

Physiology Department
Physiology Twitter @JHMIPhysiology
Physiology Slack Channel
Physiology Website

detection and clinical management has increased life expectancy and quality of life in people with Down syndrome (DS). However, no drug has been approved to help individuals with DS live independently and fully. Although rat models could support more robust physiological, behavioral, and toxicology analysis than mouse models during preclinical validation, no DS rat model is available due to technical challenges. Reeves group, by working with Kazuki lab (Tottori University) and other collaborators, characterized the first rat model of DS, TcHSA21rat, which contains a freely segregating and EGFP-labeled human chromosome 21 (HSA21) with >93% of its protein coding genes. TcHSA21rat exhibits learning and memory deficits and recapitulates well-characterized DS brain morphology, including smaller brain volume and reduced cerebellar size. In addition, the rat model shows reduced cerebellar foliation, which is not observed in DS mouse models. Moreover, TcHSA21rat exhibits anomalies in craniofacial morphology, heart development, husbandry, and stature. This work was published in the American Journal of Human Genetics. The co-first author of this work, Dr. Feng Gao mentioned that "TcHSA21rat is a robust DS animal model that can facilitate DS basic research and provide a unique tool for preclinical validation to accelerate DS drug development”.