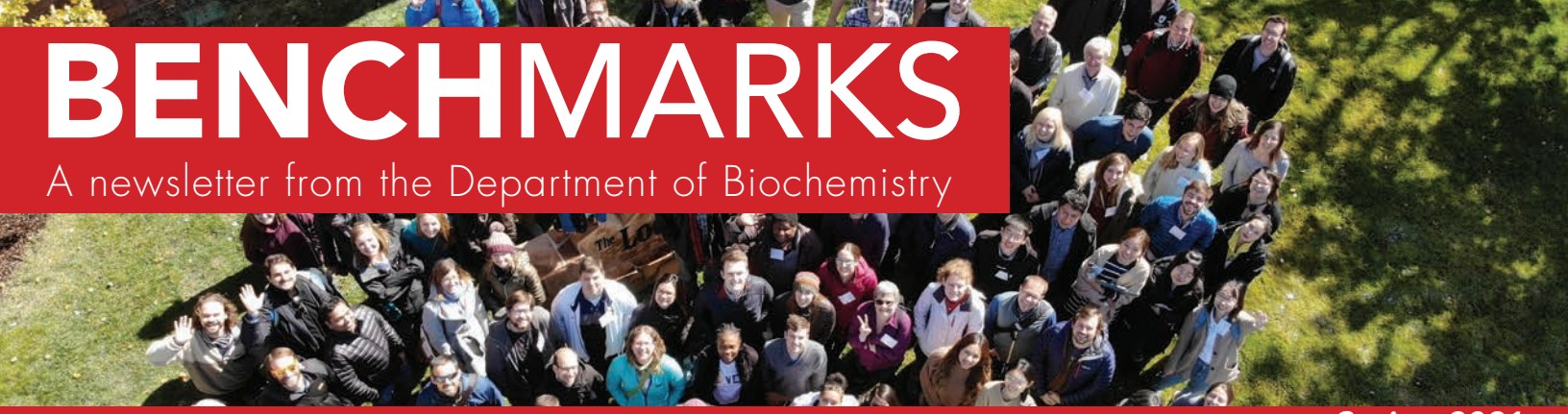
BENCHMARKS

A newsletter from the Department of Biochemistry



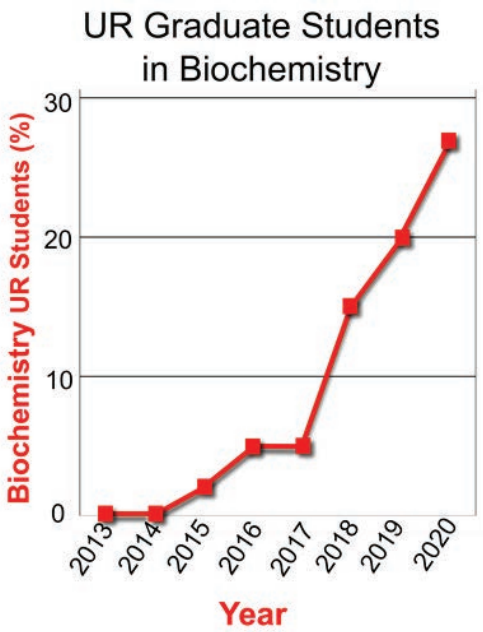
Spring 2021

CELEBRATING DIVERSITY, BUILDING INCLUSION

Chair's Message from Wes Sundquist

As I noted last fall, it has been a challenging past year and a half, headlined by the COVID-19 pandemic, George Floyd's murder, a rancorous national election and a series of natural disasters. It strikes me, though, that as we emerge from the pandemic that defined 2020, the defining cause of 2021 may well turn out to be the push for racial justice. Most of us breathed an enormous sigh of relief and felt a sense of satisfaction when the jury returned a just verdict in the Floyd case, even as we know that their decision will not bring back George Floyd and that there is much, much more work to be done for us to become a truly equitable society. As Minnesota's Attorney General Keith Ellison noted in his comments following the verdict, we "continue the journey to transformation and justice." In that vein, we are determined to do our part in moving forward together to create a more equitable future for BIPOC scientists in biochemistry and in our department. Equity, diversity and inclusion (EDI) is a theme of this edition of Benchmarks, and I would draw your attention to the very interesting essays on our new departmental EDI Interest Group (by Julio Fierro Morales) and on Race in Medicine (by Tim Formosa).

One area where we are achieving success is in increasing the diversity of our departmental graduate student community. Graduate students represent our legacy and the future of biochemistry, and it is a privilege to collaborate with them on their training. Until quite recently, however, our department lacked significant numbers of students from underrepresented (UR) populations. Thanks to the very hard and effective work of a number of people, this situation is improving dramatically, as illustrated by the graph on the right showing the increasing percentage of NIH-defined UR students in our department. Our diversity is further enriched by ~20 talented international students from around the world (even though they are not included in the NIH UR definitions). It has been truly exciting and invigorating to witness this transformation, and our department is a much better place for it.



Space limitations preclude me from describing all of the wonderful efforts behind these improvements, but several people merit special mention. Claudio Villanueva (now at UCLA), was hired as a faculty member in our department in 2012, and he led the charge to reinvigorate the dormant UU chapter of SACNAS (Society for the Advancement of Chicanos/Hispanics and Native Americans in Science), a national STEM organization that supports diversity and fosters the success of scientists from UR backgrounds. We are proud of the fact that many of our trainees have held leadership roles in the UU SACNAS chapter, including Jordan Berg, Faith Bowman, TK Coody, Zach Cruz, Maria Disotuar, Vanja Panic, Judi Simcox, and Jesse Velasco. Two Biochemistry Department faculty members, Minna Roh-Johnson and Paul Sigala, currently serve as Faculty Co-Advisors for SACNAS. Jeanette Ducut-Sigala, whose work was supported through Biochemistry at its inception, has been a tireless champion for diversity and inclusion, and has been a transformative presence in her roles in interdepartmental UR graduate recruiting and support, Diversity & Inclusion Manager for our Combined Graduate Bioscience Programs and in SACNAS. Janet Iwasa has been active in outreach efforts and is a master communicator, including on Twitter and on these pages of Benchmarks. Paul Sigala has done an amazing job in UR recruiting and support, particularly in his role as Co-Chair of the Recruiting Committee for our Combined Graduate Bioscience Programs. Finally, Peter Shen is continuing Paul's efforts in graduate student recruiting, and Minna Roh-Johnson is spearheading our efforts to enhance postdoc diversity, which currently lags behind that of our graduate program. It takes a village, but the village has to have leaders and we're all grateful to all of them (and others) for their spectacular efforts.

It is critical that we are not only diverse, but also that we create an inclusive community that ensures and celebrates the success of all of our students. Toward that end, our departmental retreat featured a special session that profiled two outstanding trainees from diverse backgrounds. We have also enhanced the Trainee pages on our departmental website, and our Diversity Working Group has designed new Diversity pages. We have also added a series of educational, funding and celebratory activities that include "Summer Camps" focused on anti-racism topics, an EDI interest group, endowed student travel fellowships with priority given to UR Biochemistry students (funded by a very generous gift from the estate of Sherman R. and Deborah Ann Dickman), co-sponsored "Rising Stars" symposia in Cell Biology and Cancer and Metabolism that feature world-leading postdocs from underrepresented groups, improved the equity of our faculty search protocols, and submitted a series of successful and pending NIH and private foundation grant applications aimed at funding UR-focused educational efforts.

As Keith Ellison noted, the quest for universal inclusion is a challenging journey, but the principles are actually rather simple. Enhancing diversity, inclusion and equity is morally right, it drives greater innovation, and it makes us a stronger department.

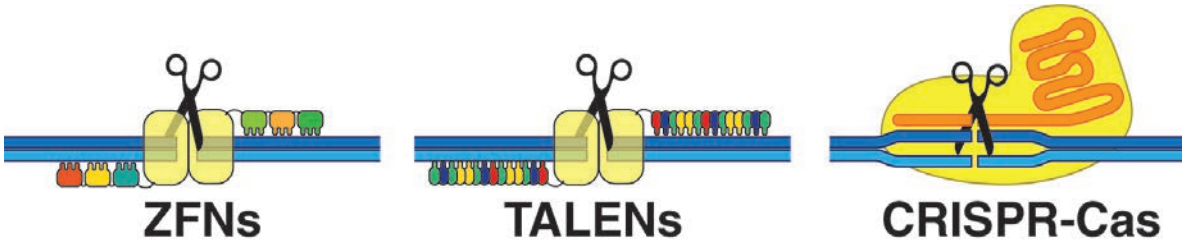
GENETIC THERAPIES

Dana Carroll

We resemble our parents. This comes as no surprise since we know how chromosomal inheritance works. Of course, people had observed traits being passed through generations for millenia, but a quantitative understanding was only gained with Mendel's work in the mid-nineteenth century and its rediscovery in 1900. The first human disease to be declared Mendelian was alkaptonuria (manifested as dark urine), which Garrod showed, in 1902, segregated in families as a recessive trait. Since that time, thousands of diseases with simple or complex inheritance patterns have been described, but typically without providing any approach to treatment.

The situation began to change in the 1970's when methods for manipulating and characterizing DNA emerged. Once the exact defect in DNA sequence was identified and a good version of the affected gene could be isolated, people began thinking about treatments based on restoring a functioning copy. Among the first successes were gene therapies for X-chromosome-linked immunodeficiency, or "bubble boy disease."

One difficulty with this approach is that the therapeutic gene does not go to its normal location in the genome, but may integrate at random in any chromosome. This caused adverse effects in early clinical trials for the immunodeficiency called SCID-X1. Although 19 of 20 treated patients had their immune system largely restored, five developed an unusual T-cell leukemia due to the integration of the viral vector carrying the therapeutic gene in a position where it apparently activated an oncogene.



Since that time, viral vectors and delivery methods have improved significantly, and the SCID therapies have continued with good outcomes. A gene addition therapy for spinal muscular atrophy (SMA) is being used in our University Hospital, and promising examples are being tested for sickle cell disease, beta-thalassemia, muscular dystrophy, an eye disease called Leber Congenital Amaurosis, and several others.

Beginning about 20 years ago, another approach to therapeutic genetic manipulation began to emerge. Rather than supplying a good gene to restore function, tools were developed that allowed the direct alteration of the DNA sequence that causes the disease at its normal chromosomal location. The technology is now called genome editing.

The key to making targeted genome modifications is the development of enzymes that can be programmed to recognize a unique DNA sequence and then make a break at that site. One class of genome editors is CRISPR-Cas, but that technology was preceded by two others, called zinc-finger nucleases (ZFNs) and TALENs. The key to these technologies is the linkage of a DNA-cutting module to a DNA-recognition module, where the latter can be programmed to bind pretty much any specific DNA sequence in the genome.

Making a break in DNA sounds like a bad idea, but cells have mechanisms to quickly repair such damage. One process allows copying of a homologous template provided by the experimenter to introduce desired new sequences – restoration of a normal sequence at the site of a disease mutation, for example. Another leads to errors upon rejoining the broken ends and can be used to knock out the function of a gene or of a regulatory sequence. Neither process is completely controllable, but they can be quite efficient in favorable circumstances. In addition, recent advances have avoided inducing a DNA break, while still catalyzing targeted sequence changes.

Each of the editing platforms in turn provided amazing capabilities to researchers for making specified genetic changes in model organisms to study gene function, and each has been turned to clinical uses. The first clinical trial based on genome editing began in 2009 and involved the use of ZFNs to modify T cells to make them resistant to most strains of HIV-1. By now a few trials based on TALENs and several with CRISPR are underway for some of the same conditions that are targets of gene addition therapy.

Why are the same few diseases getting this much attention? First, to be a candidate for a genetic therapy, the disease must have a clear, simple genetic cause – i.e., be the result of variation in a single gene. Second, there must be an available mechanism to deliver the therapeutic materials – be they a gene or the editing reagents – to the correct tissues and cells. This is a stumbling block for many conditions.

Most accessible are diseases for which delivery to cells can be accomplished ex vivo – that is, outside the body. This is possible for blood cells because hematopoietic stem cells, that are the source of continuous production of both red and white cells, can be recovered from a patient's circulation or bone marrow. After modification in the laboratory and thorough characterization, they can be returned to the same patient, now carrying a therapeutic correction. Some individuals are already enjoying relief from sickle cell disease and beta-thalassemia due to a CRISPR-based treatment.

In vivo delivery directly to a living person is more challenging, but is the subject of intensive research. The therapeutic materials can be encapsulated in a modified virus particle and injected, either systemically or into a particular tissue. This is the approach that is being taken for diseases of the eye and for muscular dystrophy. Non-viral delivery via nanoparticles is also being explored. I haven't seen any results from in vivo delivery trials as yet.

A key issue with any of these therapies is cost. It is very expensive to prepare a patient for what is essentially a hematopoietic stem cell transplant. Production of the materials, particularly in the case of viral delivery, is complex and costly. Laboratory manipulation of stem cells requires specialized facilities and materials. Even with in vivo delivery, production of sufficient viral vector and preparation and monitoring of the patient are expensive. And companies marketing the therapies seek to recover development costs. The currently available gene therapies are priced between $1 million and $2 million for a single treatment.

Who will cover these costs? Insurance companies have stepped up for the small numbers of patients treated so far. If they balk, will the therapies be available only to those people who can afford them? What about patients in poorer countries, where diseases like sickle cell are more common and more often fatal in children? It would be tragic if the wonderful advances in treatments served only to exacerbate health care disparities at home and around the world.

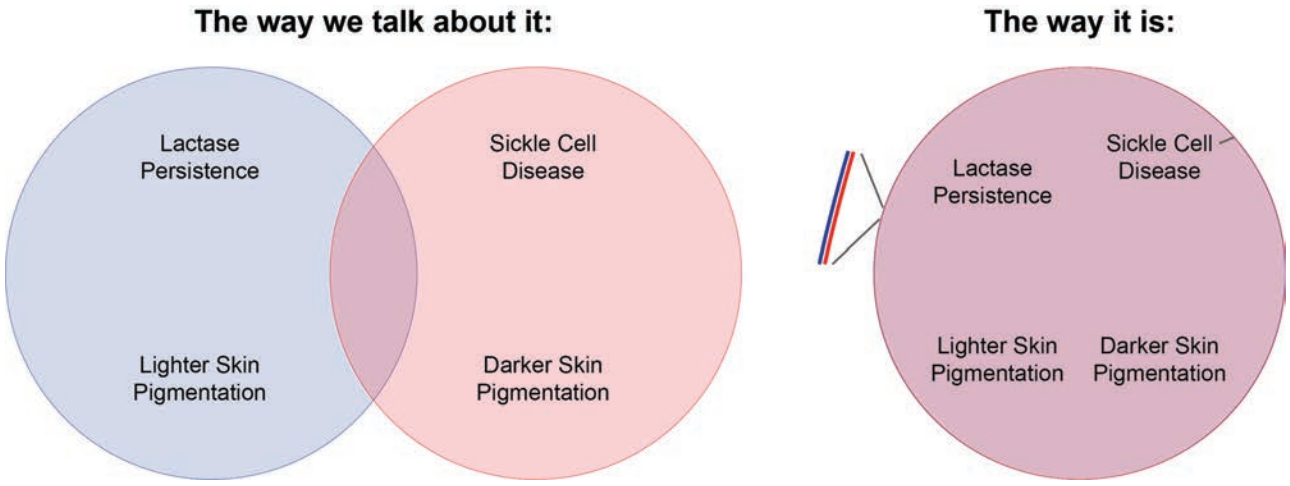
(I have not had space here to address the prospects and problems for heritable or germline genome editing. This is a big topic that needs broad discussion. In the meantime, I can recommend the National Academies/Royal Society report on the subject, available for free at: https://www.nap.edu/read/25665/chapter/1).

Dana Carroll is a Distinguished Professor in the Department of Biochemistry. His lab pioneered the development of zinc-finger nucleases as gene targeting tools and has also investigated gene editing by TALENs and CRISPR-Cas9. Dana is broadly interested in the complex ethical and societal issues surrounding genome editing.

RACE IN MEDICINE

Tim Formosa

I participate in a course for first-year medical students that includes teaching basic concepts in hematology. One of the questions we use routinely on exams leads to responses that are puzzling to me, at best. In the question, a young woman presents to a clinic with clear symptoms of anemia and the students are asked to choose the most likely cause. Without additional identifying information, the students correctly choose "iron deficiency" at a high frequency. However, if the woman is identified as being Black or having African ancestry, about a third of the students pick "Sickle Cell Disease" (SCD) as the most likely cause. Iron deficiency anemia is very common, affecting about 20% of women worldwide according to UpToDate, and about 4% of women in the US in the age group mentioned in the question. It is even more common among Black women in the US, by roughly two-fold, so adding this to the description makes iron deficiency more likely, not less. In contrast, SCD is quite uncommon, at about 0.1% worldwide, and 0.3% among African-Americans. This raises several questions. The one we asked first was "why do so many of our students consider the patient's ancestry to be more important than her sex?" That is, how does providing a partially relevant but ultimately insignificant feature like a woman's ancestry cue students away from the obvious (young women tend to be iron deficient because of blood loss from normal menstruation) and towards the obscure (she might have an undiagnosed genetic variant)? However, perhaps it is more important to ask, "how are we as educators contributing to this bias and the resulting systemic racism?" And finally, "what can Molecular Biologists contribute to discussions of race and social inequity in medicine?"



I think the answer to the first two questions is "because we stress the differences among people of different ancestries and reward students for recognizing the cues we embed in our questions that amplify these differences." The answer to the third question is "stop doing that, and instead represent genetic variation among humans accurately." Because, fortunately, at the level of our genes, racism is based on a set of fallacies that are easily debunked, so we can contribute by just teaching the facts. Which is kind of what we were supposed to be doing anyway!

Medical students have to absorb an enormous body of facts in a short amount of time to perform well on their licensing exams, which leads us as educators to take some shortcuts to provide a framework for rapid pattern recognition. If we are asking a question about the effects of genetic hemoglobin variants, we make the patient a member of an ethnic group where the variant is more common as a shorthand way to cue the student to include that variant among the possible explanations for the rest of the clinical presentation. A patient with SCD is Black, a patient with G6PD deficiency is of "Mediterranean ancestry," one with thalassemia is "Southeast Asian." There are two problems with this: it isn't accurate, and it tends to reinforce the opposite conclusion, that Black people have SCD, people from the Mediterranean have G6PD deficiencies, and Southeast Asians have thalassemias.

It isn't accurate because human ancestry is not so easily deconvolved: a 2019 study from Michigan found that while 80% of the babies born with one allele of the gene associated with SCD (a benign condition called "Sickle Cell Trait" in which a person has one "variant" and one "normal" copy of the gene) were identified as "Black," but the second most common description was 7% who were identified as "White." Worldwide, Sickle Cell Trait is most common in Sub-Saharan Africa, but even in these populations it describes only about a third of people. Estimates for other regions of the world are as high as 13% in India, about 6% in Greece and Latin America, and as much as 27% in some regions of the Middle East. The genetic mutation leading to G6PD deficiency is more common, and has a similar geographical distribution. The numbers confirm that genetic variants are more common in some populations, but these variants are still less common than the "normal" variant. As in the left side of the diagram, we talk about genetic variants as if they have a 1:1 association with ethnic groups, reinforcing the idea that humans are genetically distinct and can be put into bins easily labeled "us" and "the others." The truth is much more complicated (and interesting).

In fact, humans are 99.9% identical to one another at the level of DNA sequence, and there is more variance within any given population (for example, one identified by a feature like skin pigmentation or geographical region) than there is between populations. The actual overlap of two theoretical populations is represented more accurately in the right side of the diagram, although this is admittedly somewhat of an exaggeration: when overlapped to 99.9% the circles had no visible gap between them so I decreased the overlap to create a space for illustration purposes. Human populations are actually more related to one another than shown! So why is it so easy to get (and give) the impression that we are so different? And why do I keep putting "normal" in quotation marks?

Skin pigmentation is an easily observed trait that is clearly heritable. As the "largest organ" and the most visible one, our skin has an outsized role in our impression of a person. But pigmentation is the result of variation at many genes, and we actually don't know what most of those genes are or how they interact to produce the overall pigment level. That is, while sequencing someone's genome allows us to use a pattern of genetic variance to guess their ancestral roots by knowing which groups usually have similar patterns of variants, we can't use the sequence itself to say what color that person's skin is. In a very real genetic sense, "race" is a cultural construct, not a genetic one.

In my course, we are trying to correct these misimpressions by stressing two principles: first, genetic variation among humans is small and affects traits that are unimportant for being human, and second, the concept of "normal" varies with local conditions.

Variation is small: see the figure. We are all the same species, we share 99.9% identity at the level of DNA sequence, and the things that can vary are by definition not important. Things that are important for being human, like the sequences of our histone genes or our DNA polymerases, or the thousands of DNA-binding proteins that regulate the transcriptional programs that govern our development display little or no variation.

Normal is relative: evolution works by taking the variation that occurs randomly and asking if the new variant is better or worse than the original. The reason variation is small is that most new variants are worse than the original, and therefore are selected against. However,

selective pressures change with local conditions, so what is disadvantageous in one environment may be advantageous in another. For example, the variant of hemoglobin that leads to SCD and the variant of G6PD that leads to hemolytic anemias both occur in regions of the world where malaria has been endemic over a significant portion of human evolution. The parasite that causes this disease reproduces partially in red blood cells, and these genetic variants appear to reduce the reproductive capacity of that organism. In these environments, then, it is advantageous to have a genetic condition that would otherwise be selected against. Similarly, darker skin pigmentation is more protective against damage from ultraviolet light, but some of this light is needed to activate vitamin D, so the selection for pigmentation varies with latitude. Which pigmentation level is "normal?" That depends on the intensity of the sunlight, which varies with geography. The case of lactase production is particularly informative, as this selection is cultural. Mammals feed their young with milk, whose primary carbohydrate is the sugar lactose. Adults in the ancestral human populations, like other mammals, stop producing lactase, presumably to restrict consumption of milk to children during development. Mutations that allow lactase expression to persist into adulthood have occurred several times in different human populations over the last ~20,000 years, always associated with adoption of using milk from goats, sheep, or cows as a cultural practice. This created a strong new selective pressure, with some Northern European populations essentially fixing a mutation that occurred within the last 10,000 years in over 90% of the members; literally a "new normal" driven by a cultural practice. I wonder what texting with our thumbs will do to the shape of our hands?

As educators, our goal then becomes simple: teach the concepts accurately and the role of ancestry in human medicine will take on its appropriate, minor role. Stress the sameness of humans and variation becomes a response to local conditions, not a distinction that defines our humanness. Common gene variants are only common in the environment in which they produce a significant selective advantage, and even then they make up 0.1% of our genomes. In short, seeing race as a cultural construct and ancestry as a minor component of a person's medical history is not a capitulation to political correctness, it is a biologically accurate conclusion. We strive to put these principles at the core of an uncompromising molecular biology curriculum that respects but does not overemphasize our diversity.

Oh, and if it says anemia? Pick iron deficiency. It's always iron deficiency.

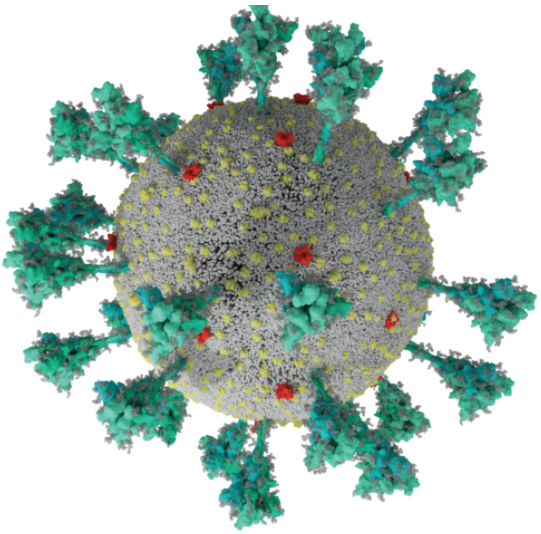
Tim Formosa is a Professor in the Department of Biochemistry. His lab studies how DNA is packaged to ensure appropriate expression of genes and accurate copying of genomes. Tim is also actively involved in the Medical School curriculum.

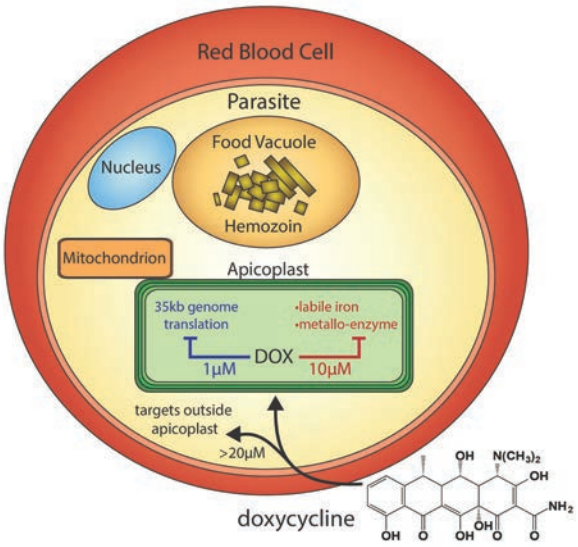
DEPARTMENTAL ADVANCES IN THE BIOCHEMISTRY OF INFECTIOUS DISEASE

Visualizing the SARS-CoV-2 Life Cycle

This past year, many biological researchers have redirected their focus to understanding SARS-CoV-2. As a result, we have rapidly gained mechanistic insights into how the virus gains access and hijacks human cells. Iwasa and colleagues are using these data to create detailed molecular animations of different stages of the SARS-CoV-2 life cycle that will be released to the research community and the public (. The animations will be embedded within a custom web-based user interface that allows users to interact with the animation in order to view annotations (https://animationlab.utah.edu/cova) such as protein names and citations) and to ask questions or make comments. This annotation functionality, being developed in collaboration with Miriah Meyer (SCI), is critical for describing the data used to create the visualization, and also to discuss aspects of the life cycle that are not yet well understood. Based on community feedback, Iwasa and colleagues will iteratively revise the animations to reflect the most current understanding of the viral life cycle.

Segments of the SARS-CoV-2 entry animation have been featured by the "It's Okay to be Smart" series by PBS Digital Studios and in the InsideCorona.net website.





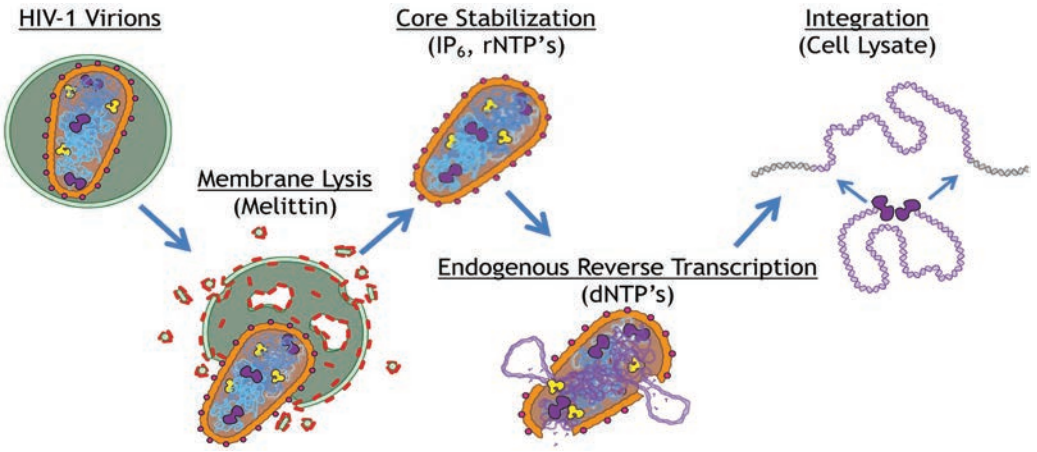
Faster Antimalarial Activity of Doxycycline

Malaria is a pressing global health challenge, and drug resistance by P. falciparum parasites is a major barrier to treatment efforts. Although new drugs are in development, these medicines will take many years to clear safety hurdles. Doxycycline (DOX) is a key antimalarial drug that is largely limited to prophylaxis due to delayed parasite clearance at current clinical dosage. This slow activity has been thought to be a fundamental limitation of DOX and other drugs that target the essential apicoplast organelle of Plasmodium. Sigala and colleagues discovered, however, that DOX can kill P. falciparum on a faster time-scale via a novel apicoplast-specific mechanism of action at slightly higher drug concentrations than are normally used. These doses can be clinically achieved and are well tolerated. These results expand our understanding of the fundamental antiparasitic mechanisms of DOX and suggest repurposing DOX as a faster-acting antimalarial at higher dosing, where the multiple mechanisms of action are also expected to limit parasite resistance.

Doxycycline has distinct apicoplast-specific mechanisms of antimalarial activity. Okada M et al. Elife. 2020 Nov 2;9:e60246.

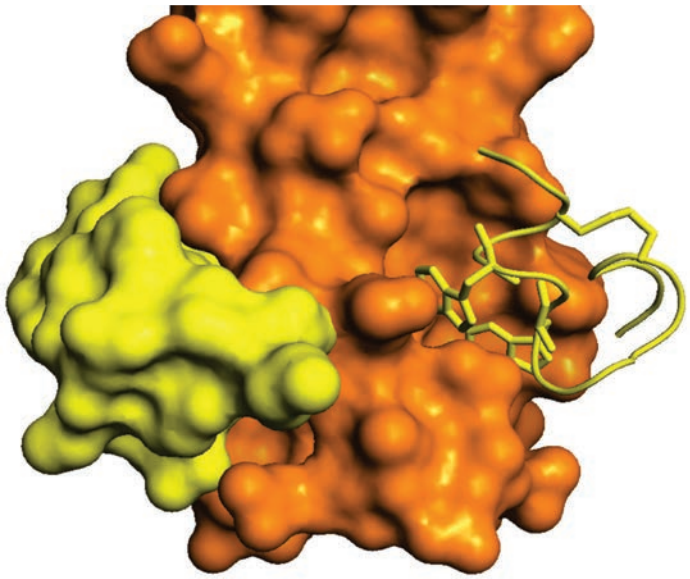
Reconstituting HIV Replication in vitro

Reverse transcription and integration are the signature events of retrovirus replication and are also targets of successful anti-HIV therapies. Reverse transcription creates a double-stranded DNA copy of the positive-sense viral RNA genome, and integration archives that copy within the genome of the infected cell. However, mechanistic studies of these processes remain challenging because they are performed by viral core particles deep within the infected cell cytoplasm and nucleus. To address this limitation, Sundquist and colleagues reconstituted efficient HIV reverse transcription and integration in a cell-free system, and showed that the system responds appropriated to antiviral compounds. They further found that the viral capsid plays an active role in supporting efficient reverse transcription. Thus, the entire core particle, including the outer capsid shell, is the true viral "replication complex". This cell-free system should enable systematic analyses of viral replication and integration and thereby help elucidate the first half of the viral life cycle.



Reconstitution and visualization of HIV-1 capsid-dependent replication and integration in vitro. Christensen et al. Science. 2020 Oct;370(6513):eabc8420.

And highlighted in scientific and public outlets, including: UHealth, ScienceAlert, MSN Entertainment, Medical News, Science Daily, Science News Net, EurekAlert.



HIV Inhibitor Development

Our NIH P50 CHEETAH Center supports basic research in HIV structural biology and molecular virology, with the long-term goal of identifying effective new strategies for therapies, vaccines and cures. Such medicines are needed to reduce treatment frequencies, treat drug-resistant patients, prevent new infections, and cure individuals who are already infected. Fundamental studies of HIV capsid structure and function performed by Sundquist, Hill and colleagues formed the basis for Gilead's development of highly potent, and remarkably long-lasting HIV capsid inhibitors that support quarterly dosing and have just completed very successful Phase I clinical trials. Similarly, Kay and colleagues have pioneered the development of a platform for creating an entirely new and general class of therapeutic inhibitors, called D-peptides. This year, D-peptide inhibitors were shown to protect macaques very effectively against infection in a primate model of HIV.

A highly potent long-acting small-molecule HIV-1 capsid inhibitor with efficacy in a humanized mouse model. Yant et al. Nature Medicine. 2019 Sep;25(9):1377-84.

Clinical validation of targeting HIV capsid with a small molecule long-acting inhibitor. Link J. et al. Nature. 2020 Aug;584(7822):614-618.

Prevention and treatment of SHIVAD8 infection in rhesus macaques by a potent d-peptide HIV entry inhibitor. Nishimura et al. Proc Natl Acad Sci U S A. 2020 Sep;117(36):22436-22442.

And highlighted in scientific and public outlets, including: Biospace, POZ Newsletter, Fierce Biotech, Bloomberg Business.

BILL RUTTER AWARDED HONORARY SCIENCE DEGREE

One of the distinguished alumni of our department, Dr. Bill Rutter, was awarded an honorary Doctor of Science Degree at this year's University of Utah Commencement.

Bill is famous as "the father of biotechnology", and is even more famous as the "uncle of Jared" (our own distinguished faculty member Jared Rutter!).

You can watch a video celebrating his accomplishments and honorary degree in this commencement video on YouTube:

https://www.youtube.com/watch?v=xwv0ed3zz8M&t=2233s

And you can read more about Bill and other 2021 honorary degree recipients here:

https://commencement.utah.edu/commencement/honorary_degree.php

THE BIOCHEMISTRY EQUALITY, DIVERSITY, AND INCLUSION INTEREST GROUP

Julio Fierro Morales

This spring, Sangeetha Balasubramaniam and Julio Fierro Morales, two second-year graduate students in the Biochemistry department, helped introduce an Equality, Diversity and Inclusion (EDI) Interest Group within the department aimed at challenging preconceived notions and biases within the scientific community both at large and at the personal level. The goal of these seminars is to provoke thoughtful discourse on looming EDI issues, educate community members on how these issues may affect our community and the way we approach science, and provide a platform to identify action items at multiple levels to combat barriers to successful EDI. Working alongside an incredible in-house committee – comprised of Paul Sigala, Janet Lindsley, Chelsea Kidwell and Kristen Davenport – Sangeetha and Julio hope providing a safe space to discuss pertinent DEI issues will fuel the discourse and rhetoric necessary for changes to occur at both a personal and institutional level.

Meetings thus far have focused on the history of a Eurocentric bias in science and a frank discussion on personal identities and imposter syndrome. Community involvement is at the core of the success of this initiative, with Biochemistry members sharing their unique narratives and even leading meetings on passion topics, such as TK Coody spearheading the identities discussion.

By emphasizing community involvement and opportunities to lead meetings, the EDI interest group hopes to drive a diverse interchange of narratives and perspectives mirroring the unique makeup of our department on a variety of levels. Doing so will espouse a diverse range of voices and narratives that may otherwise be forgotten. At a time when challenging pre-existing norms and championing EDI is at the forefront, the EDI interest group hopes to provide the discourse and opportunities required to plant the seeds necessary for EDI to start to become a reality and not just a goal.

THE 2020 MARJORIE RICHES GUNN AWARD FOR GRADUATE STUDENT EXCELLENCE

Adam Hughes

The fifth annual Marjorie Riches Gunn Award for Graduate Student Excellence was awarded this past year to Lara Rheinemann, a Ph.D. student in the Sundquist lab. The Gunn Award is given annually in honor of long-time Department friend Marge Gunn, to the Biochemistry Ph.D. candidate(s) judged by the faculty to most exemplify our values of scientific excellence. Lara originally hails from Germany, and prior to coming to Utah in 2015, she completed a combined BS/MS program in Molecular Medicine at the Albert-Ludwigs-Universitat in Frieberg, Germany. It was during her time as a master's student that Lara became fascinated with virology, and her interest in this area ultimately led her to pursue her Ph.D. studies in the lab of Dr. Wes Sundquist studying host-virus interactions. During her time in Wes's lab, Lara's work focused on understanding how viruses hijack the endosomal sorting complexes required for transport (ESCRT) machinery within cells to promote viral budding, and identifying cellular defense strategies to combat this viral hijacking. Working in close collaboration with the lab of Dr. Nels Elde here at Utah, Dr. Rheinemann made the breakthrough discovery that mammalian cells are equipped with a special copy of one of the ESCRT proteins, called retroCHMP3, that has evolved to inhibit the ability of viruses to take over the ESCRT machinery. Remarkably, retroCHMP3 arose independently through duplication and truncation events in both New World Monkeys and mice, and expression of this protein in human cells prevents release of several types of viruses from cells, including HIV and Ebola. This discovery, which will be published in the very near future, has greatly enhanced our understanding of how cells combat viral hijacking, and has the potential to open up new antiviral therapeutic strategies. In recognition of her excellent work, Lara had the opportunity to present her findings at the American Society for Virology this past year. In addition to her scientific excellence, Lara is widely lauded by her peers as a phenomenal colleague, mentor, and friend who is always willing to go out of her way to help others around her. Lara is also described by colleagues as a "truly exceptional graduate student who is destined for a stellar scientific career".

Outside of the lab, Lara is an avid outdoor enthusiast and runner. Not surprisingly, she also excels in those pursuits as well, twice finishing second in the Salt Lake City marathon! In the next few months, Lara will be headed back to Germany to conduct postdoctoral studies in the lab of Dr. Andreas Pichlmair, where she will continue to tackle important questions at the host-pathogen interface. Congratulations to Lara again for her success as a graduate student and receiving this very well-deserved honor!

THE 2020 EVELINE BRUNGER AWARD FOR POSTDOCTORAL EXCELLENCE

Minna Roh-Johnson

The Eveline Bruenger award for Postdoctoral Excellence was established in 2018. Eveline was a dear friend of the Biochemistry Department, a distinguished scientist, a gifted artist, an avid hiker, and a life-long learner. When Eveline passed away in April 2018, the Department sought to continue her legacy with a Departmental Postdoctoral Award that bears her name. In honor of her scientific excellence, her love of learning, and her commitment to supporting the community, we were very pleased to present the 2020 award to Sara Nowinski, a postdoctoral fellow in Jared Rutter's lab.

Sara played a critical role in the surprising discovery that the mitochondrial system of fatty acid synthesis regulates mitochondrial biogenesis and activity. Sara first made a significant contribution to the original discovery of this important phenomenon in yeast, and then discovered that this regulatory network functions in mammalian cells. The sole function of the mitochondria fatty acid synthesis pathway was originally thought to be for the production of lipoic acid, a key co-factor for several mitochondrial enzymes. However, Sara and colleagues found that the mitochondrial fatty acid synthesis pathway plays a critical role in the direct regulation of mitochondrial activity, functioning as a nutrient-sensitive pathway to tightly coordinate nutrient status and metabolism.

In addition to her scientific excellence, Sara was instrumental in creating the University of Utah Postdocs Curricular design And Teaching (UP-CAT) program, an innovative program aimed to provide hands-on experience with curriculum developmental and delivery. The seeds of the UP-CAT program were primarily developed by Sara, two other postdoctoral fellows, and under the mentorship of faculty member, Janet Lindsley. The program has been wildly successful, and has grown to become available to all postdocs in the School of Medicine.

We were very excited to learn that Sara has accepted a tenure-track faculty position at the Van Andel Institute in Michigan, and will begin her independent position in July of 2021. While Sara will be leaving Utah this summer, she will leave a lasting influence in the Department through her superb mentorship of researchers in the Rutter lab and the UP-CAT program that she helped to develop. Congratulations to Sara on all fronts.

STAFF HIGHLIGHT: MEET JARED KIRBY

Jared Kirby has been with the Department of Biochemistry for almost seven years and has worked at the University of Utah for ten. In his current role as Administrative Manager, Jared oversees all of the administrative functions of the department and supervises the other front office staff. When asked about what he enjoys most about his position, he says, "I really enjoy working with such great people who take seriously and are passionate about making a difference in the world of medical research."

Jared is a native of Utah, and like many Utahns, he enjoys the outdoors. Specifically, he enjoys cycling and has been able to see much of the state on two wheels. He has found that riding his bike allows him to think about problems in all areas of his life in a way that he hadn't previously appreciated. Jared has been actively involved in racing for the past six years as part of a road cycling group called the Bountiful Mazda Master Cycling Team. His hardest event so far has been the Baker City Cycling Classic, a stage race that takes place over four days. In 2019, he placed 8th overall in his category - a huge accomplishment!

When he's not working or biking, Jared's time is consumed by his wife and three beautiful daughters, Olivia (17), Evelyn (15), and Lillian (11). The family enjoys being outside together and traveling as much as possible. Although the pandemic has been rough, it has allowed Jared to organize his previously cluttered garage and spend more time with his kids.

STAFF HIGHLIGHT: MEET AMITY MOWER

Amity Mower joined the Biochemistry Department in September of 2019 and has been with the U since 2015. As the administrative program coordinator, Amity manages the logistics of the graduate student program, including onboarding new students, coordinating their stipends and health insurance, and helping to walk them through graduation requirements. She also manages the HR side of faculty employment, a role that includes posting new faculty positions, hiring and onboarding, and managing annual career-line reappointments. She also manages the faculty grant mentorship program and assists with faculty tenure/promotion/retention actions alongside Tim Formosa.

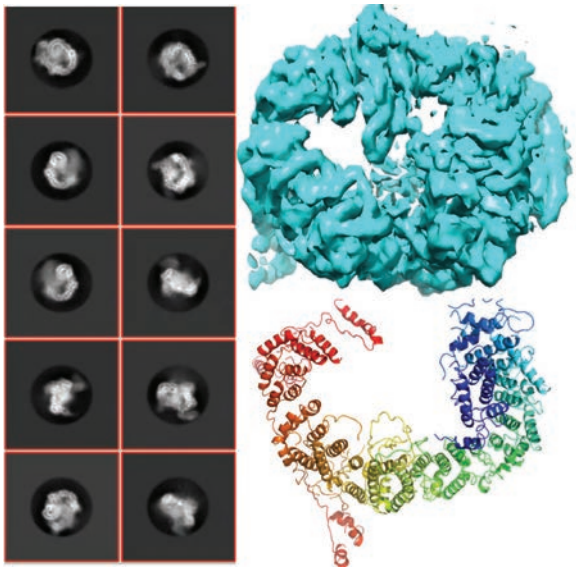
She enjoys the unpredictability of her current position; it keeps her engaged and provides her with new challenges every day. Her favorite part of the job is working with the graduate students. She finds it incredibly rewarding to see them succeed in the program.

Amity grew up in Utah, and has lived in the state for most of her life. She says that one of her favorite aspects of Utah is that Utahns enjoy all four seasons, "sometimes all in the same day!" Some of her favorite hobbies, like traveling and scuba diving, have been impossible in the last year, but she has managed to stay busy during the pandemic by working on a master's degree in economics, painting, reading, and playing videogames with friends.

FACULTY HIGHLIGHT: MEET HEIDI SCHUBERT

Heidi Schubert is a structural biologist trained in X-ray crystallography during her PhD at the University of Michigan. She joined the University of Utah in late 1999 after a 3-year post doc at the University of York, England. Heidi is currently a Research Associate Professor and works closely with Chris Hill's lab.

As part of the long-term collaboration between the Hill and Sundquist labs, Heidi has contributed to the understanding of several structure-function relationships between human proteins that facilitate HIV infection and the HIV proteins with which they interact. One example is the ESCRT system, which is co-opted by HIV as it buds from the cell membrane. Heidi characterized the TSG101-Ubq interaction and the structures of CHMP3 and IST1. Heidi also worked on solving the structure of a human membrane-bound extracellular protein called Tetherin after work by the Sundquist lab showed that the protein could catch budding viruses and hold them close to the cell surface, restricting their maturation. More recently, interest in the labs has turned towards the understanding of transcriptional silencing that is required for latent HIV infection - the situation where an infected cell has the HIV genome embedded in its DNA but is not actively producing viral proteins which would make it a target for current anti-viral drugs. This is a major road block in developing a cure for HIV.



Another of Heidi's projects has focused on transcriptional regulation, a long-term interest of the Hill and Formosa labs. Recently, Heidi has solved the structure of Tom1 – a large HECT E3 ubiquitin ligase involved in a phosphorylation-dependent interaction with the yeast transcription factor Spt6.

In her free time, Heidi enjoys cross-country skiing, hiking and mountain biking all over Utah.

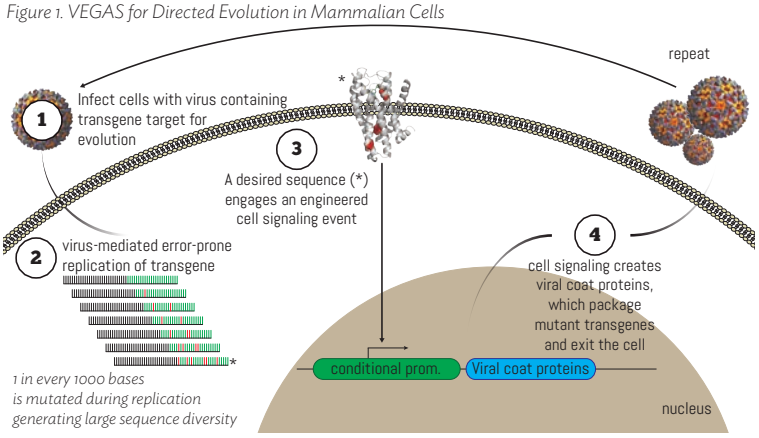
FACULTY HIGHLIGHT: MEET JUSTIN ENGLISH

Justin grew up in Chittenango, NY -- a small rural farming town in the "upstate" portion of New York State. He spent most of his childhood hiking, biking, horseback riding, creek swimming, and fencing; all activities he still enjoys today. He met his wife Michelle in Chittenango, they were middle school sweethearts. He also developed an early love for nature and biology during his mostly outdoors childhood, spurring him to earn his bachelor's in biology & genetics from the Cornell University College of Agriculture and Life Sciences in 2007.

Justin's undergraduate research work in yeast genetics during his time at Cornell led him towards a career in science research. The year following his graduation from Cornell he worked as a post-baccalaureate researcher at the NCI in Bethesda, Maryland before pursuing a PhD at the University of North Carolina at Chapel Hill. Justin joined the Department of Pharmacology at UNC, and earned his PhD in yeast cell signaling research with Dr. Henrik Dohlman. During his PhD he developed a scientific appreciation for the work of Dr. Bryan Roth in the same department and chose to pursue his postdoctoral training in the Roth lab in 2014. Justin used his postdoc to develop a method for the directed evolution of proteins in mammalian cells in an effort to acquire control over the cell signaling systems he had labored to understand during his PhD work. The result of that work is the platform Justin has now based his lab on here in the Department of Biochemistry at the University of Utah.

On a personal note, Justin and Michelle have one son, Maceo (6), and two hound dogs named Pete (0.5) and Sally (7). Justin makes it a point to cook from a new culture each year and learn the nuances of regional cuisine from different countries. Justin and his family are enjoying living in Utah and the adventure of exploring a whole new part of the United States.

Figure 1. VEGAS for Directed Evolution in Mammalian Cells



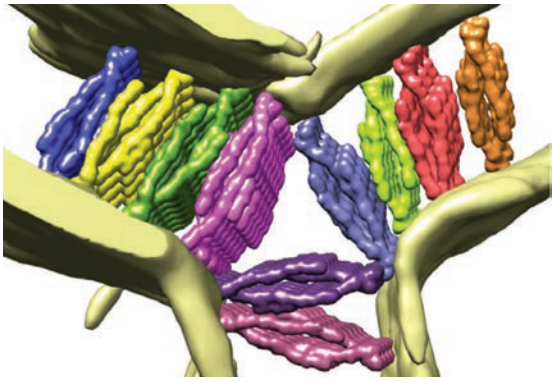
FACULTY HIGHLIGHT: MEET JULIA BRASCH

Julia Brasch joined the Biochemistry department as an Assistant Professor in February 2020 after completing postdoctoral work at Columbia University and the New York Structural Biology Center, where she worked with Lawrence Shapiro, Barry Honig, Bridget Carragher and Clint Potter to structurally characterize cell-cell adhesion molecules including cadherins and protocadherins.

The Brasch Lab continues this important work, and will be applying a variety of techniques, including cryo-ET, cryo-EM, and X-ray crystallography to address how proteins on cell surfaces arrange themselves into functional superstructures. One specific line of research is focused on synapses, highly specialized junctions in the brain connecting neurons to form complex neural circuits. To establish how synapses work, the Brasch lab will focus on the molecular logic that underlies the formation, establishment and properties of each of these synapses, likely driven by synaptic cell adhesion molecules. The lab aims to understand the protein complexes formed at these junctions and how they assemble and arrange in respect to each other in the synaptic cleft with the overall aim to understand the extracellular

architecture of the synapse, which will allow for understanding of one of the most complex junctions in the body.

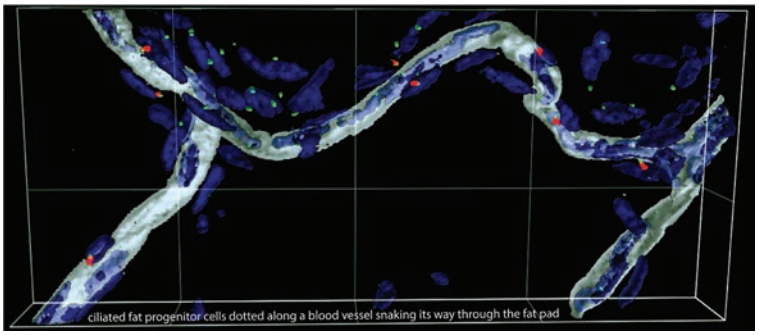
When not in the lab, Julia spends time with her kids, Finja (2) and Robin (2.5 months). She also has a green thumb; during her post-doc years, she rescued and raised upwards of 40 plants in the lab (including a ficus cutting that grew to be 9 feet tall!). She looks forward to eventually transforming her lab and office into a mini arboretum.



FACULTY HIGHLIGHT: MEET KEREN HILGENDORF

Dr. Keren Hilgendorf joined the Department of Biochemistry as an Assistant Professor in September 2020, and her lab studies how signaling pathways activate fat stem cells during obesity. She earned her PhD in Biology at MIT, where she was awarded an NSF graduate fellowship and worked in the lab of Dr. Jacqueline Lees to study molecular mechanisms driving tumorigenesis. Keren then pursued her postdoctoral training at Stanford University with Dr. Peter Jackson, where she was awarded a Damon Runyon Cancer Research Foundation Postdoctoral Fellowship to study signaling pathways regulating adult stem cell differentiation to enable the maintenance, expansion, and repair of tissues.

Her work on how a specific type of fatty acid, called omega-3 fatty acids, triggers fat differentiation has significant health implications, showing that the composition of our diet can regulate how fat tissue



expands: “Good” fatty acids promote a healthy expansion of fat tissue allowing for proper storage of excess nutrients, while “bad” fatty acids can lead to unhealthy nutrient storage and diabetes. At Utah, Keren will continue to explore molecular mechanisms regulating stem cell differentiation, and how dysfunctions in signaling pathways contribute to various diseases.

When she is not in the lab, she enjoys traveling and spending time with her family, exploring the many great hikes, parks, and museums that Utah has to offer.

HONORS, GRADUATIONS, AND TRANSITIONS

MAJOR FACULTY AWARDS & RECOGNITIONS

2020 Work from the Rutter, Bass, Shen, Iwasa, Chou, Kay, Hill, Sundquist, Cao, Cazalla, Carroll, and Safavi labs are featured in the digital collection of Discovery and Innovation by the Eccles Health Sciences Library.
2020 Brenda Bass is awarded the NIH Transformative Research Award with Nels Elde (Genetics), Jane Jackman, and Dan Stetson. Brenda's work is later featured in the NIH Director's Blog.
2020 The work of Michael Kay, Chris Hill, and Wes Sundquist are featured in the U of U's "Pioneering the Future: From Basic Discovery to Bedside."
2021 Minna Roh-Johnson and Wes Sundquist are awarded NIH MERIT awards.
2021 Work from Adam Hughes' lab is nominated as one the best innovations in biomedicine as part of "STAT Madness."
2021 Wes Sundquist is selected as a member of the first class of Fellows of the ASBMB.

MAJOR GRADUATE STUDENT & POSTDOC AWARDS

2020 Jake Winter (Rutter lab) is awarded a F30 fellowship from the NIH.
2020 James Carrington, an undergrad in the Roh-Johnson lab, receives the 2020 Outstanding Undergraduate Research Award for the SOM.
2020 Casey Hughes (Hughes lab) is selected for the 2020-2021 University Graduate Fellowship
2020 Qinzhe Wang (Cao lab) is awarded a Research Fellowship from the American Society of Nephrology.
2020 Jesse Velasco (Ducker lab) is awarded a NIH Diversity Supplement for his work on glycine metabolism in cancer.
2020 Onyeka Obidi (Brasch lab) and Seyi Falekun (Sigala lab) are accepted into the African American Doctoral Scholars Initiative.
2020 Elliott Paine (Sundquist lab) and Ian Cooney (Shen lab) are awarded Ruth L. Kirschstein Predoctoral Individual National Research Service Awards.
2020 Jordan Berg (Rutter lab) is awarded the NCI Predoctoral to Postdoctoral Fellow transition award (F99/K00).
2020 Kristen Davenport (Sundquist lab) is awarded a NIH K01 Career Development award.
2021 Joey Casalini (Roh-Johnson lab) is awarded a F31 Fellowship from the NCI.
2021 Lara Rheinemann (Sundquist lab) is awarded the von Schwedler Prize for Retrovirology.
2021 Tianyao Xiao (Hughes/Shaw lab) is awarded the University Graduate Fellowship for 2021-2022.

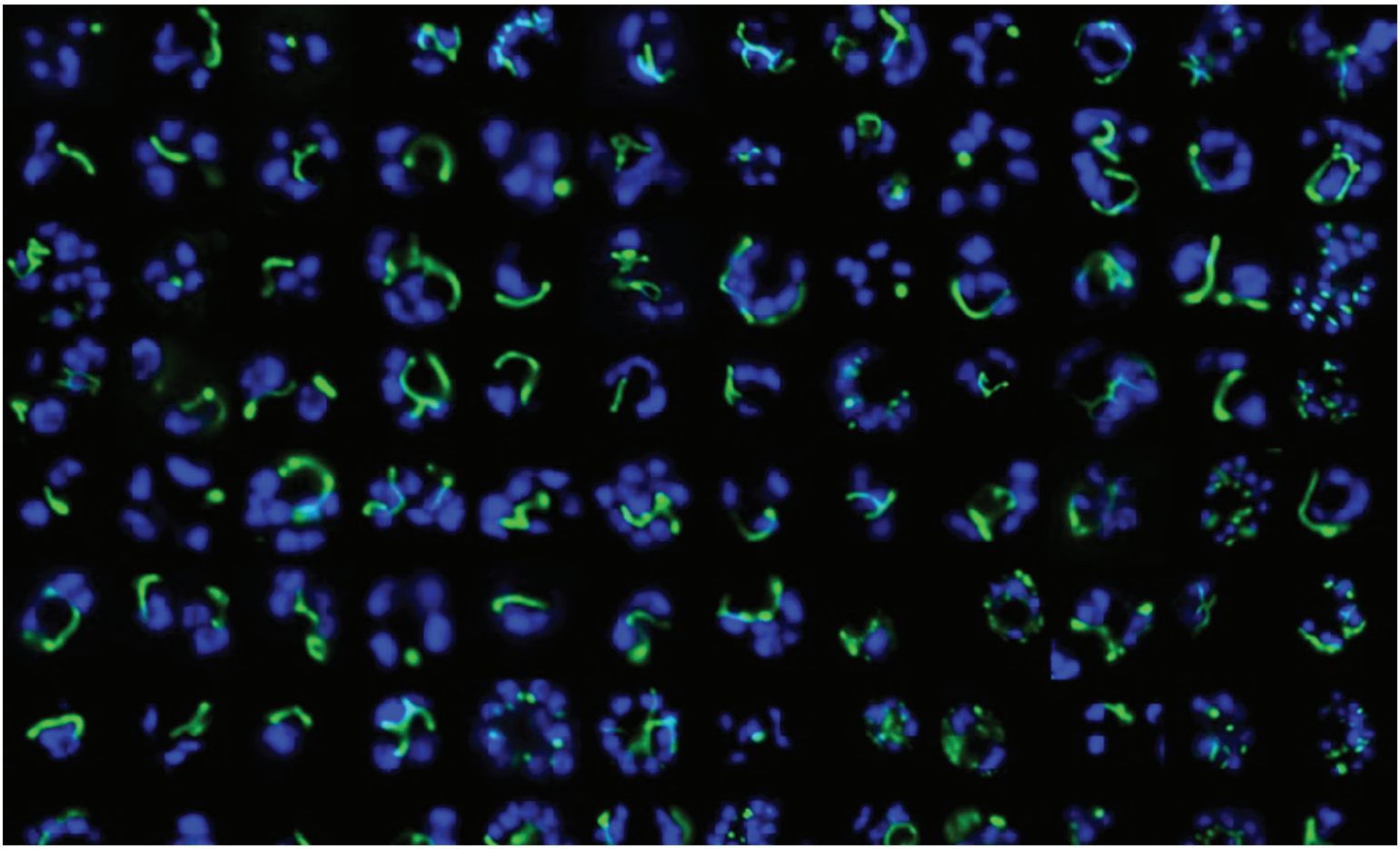
GRADUATIONS & TRANSITIONS

The following students completed their degrees since the last publication of the newsletter in Fall 2020: Sarah Apple (Kay lab, Ph.D. 2020), Jaime Sepulveda (Sigala lab, M.S. 2020), Lara Rheinemann (Sundquist lab, Ph.D., 2021), and Max Schuler (Hughes lab, Ph.D., 2021).

We said farewell to the following postdocs: Esther Nuebel (Rutter lab), Manidip Shasmal (Shen lab), and Han Han (Hill lab).

Department of Biochemistry
University of Utah
15 N Medical Drive East, Rm 4100
Salt Lake City, UT 84105

HEALTH
UNIVERSITY OF UTAH



Live fluorescent microscopy of *Plasmodium falciparum* showing nuclei (blue) and apicoplast (green). Images taken by Megan Okada (Sigala lab).