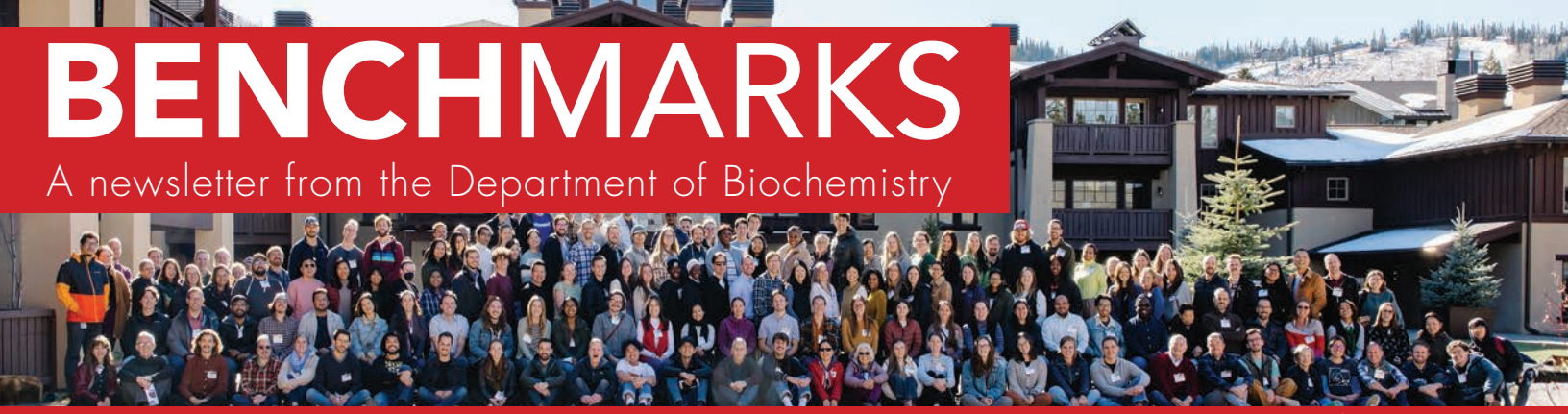
BENCHMARKS

A newsletter from the Department of Biochemistry



Spring 2025

THE DISCOVERY SCIENCE PIPELINE

Chair's Message from Wes Sundquist

That's the classic nature of people, though. We'll skip the basics and get pissed when the sexy stuff doesn't work.

- Martyn Rooney, European 400-meter dash champion

It will come as no surprise that I believe in the value of basic science. Honestly, though, I truly believe in the importance of every step along the entire biomedical research continuum, from bench to bedside to community. When the system works well, advances in understanding natural systems are translated effectively into products and real-world treatments that are distributed broadly and equitably to improve human health and living conditions. Advances at each stage of this natural pipeline amplify successes from the others, whereas bottlenecks impede the entire flow.

Fundamental discovery science is the critical first step in this pipeline. I'm far from the first to point out how often basic discoveries enable transformative medicines, yet I think this core concept still remains underappreciated, especially by the public and many policy makers. The impact of basic research can easily be confirmed by glancing through recent Nobel Prizes in Medicine or Chemistry, which honor discoveries that underpin many of the most powerful new medical treatments, including anti-cancer immunotherapies, mRNA vaccines, the cure for hepatitis C virus, de novo designed inhibitors, and gene therapy. In every case, the enabling discoveries were driven by scientists asking fundamental questions, such as: Why do T cells lose their ability to function effectively following prolonged antigen exposure?, How do cells sense foreign RNAs?, How do viruses replicate?, How can protein structures best be modeled?, and How do bacteria defend themselves against phages?. Time and again, fundamental biological insights have led to groundbreaking medicines and products, often in entirely unexpected ways. Make no mistake, discovery research is an essential feedstock for advancing human health.

I would also argue that trying to understand the natural world is inherently an elevating exercise. We are at our best when we're striving to unlock the secrets of the universe, be that through science, art, or philosophy. As any practicing scientist knows, the search for understanding is an imperfect exercise – it can be slow and humbling, and setbacks often impede our progress and wound our pride. But the overall success of the discovery research enterprise is beyond doubt. I am constantly amazed at how much more we know and can do than when I started here at the University of Utah 33 years ago.

On a smaller scale, my own recent experiences have further reinforced my belief in all of these core principles. It has been very satisfying to watch basic research on the HIV capsid performed in our lab, in the Hill and Pornillos labs, and in other labs, set the stage for development of a potent new HIV drug called lenacapavir (LEN) that targets the viral capsid. LEN was developed by Gilead Sciences, and it has the remarkable property that a single injection completely protects uninfected individuals against becoming infected by HIV for six months (an approach called Pre-Exposure Prophylaxis, or PrEP). 1.3 million people worldwide still get new HIV infections each year, so effective PrEP would fill a great unmet biomedical need. Last year, Gilead's large-scale clinical PrEP trials showed that LEN is nearly 100% effective in protecting all different types of at-risk individuals against new HIV infections. Based on this success, LEN was named Science Magazine's Breakthrough of the Year, and the drug is expected to be approved for PrEP applications and rolled out on a worldwide scale this summer. This experience has again reconfirmed for me three essential truths: 1) Basic Discovery Science Matters. LEN wouldn't exist without long-term, NIH-funded basic research showing that HIV replication was highly sensitive to even small perturbations in the viral capsid (implying that the capsid might be an unexpectedly good drug target), demonstrating that pure recombinant CA protein could self-assemble into capsid-like structures (forming the basis for Gilead's initial inhibitor screens), revealing the overall architecture of the conical capsid (thereby defining the drug target), and defining the atomic structures of the basic capsid building blocks (enabling Gilead's structure-based drug design program). We and our colleagues always knew that we were working on an important medical problem, but much of our work was driven by simple curiosity – What does the viral CA protein look like?, How does it make a conical capsid?, What does the capsid do for the virus?. 2) Translation Matters. Gilead Sciences deserves enormous credit for the epic accomplishment of developing lenacapavir. The quality and scale of the science performed by the Gilead Multidisciplinary Research and Development teams is inspiring. They initially identified promising lead compounds, then synthesized and evaluated more than 4,000 different derivatives, and then implemented world-class formulation, pharmacology, and clinical trials programs. No academic laboratory and very few other pharmaceutical companies could have accomplished what they did. 3) Population Health Science and Community Engagement Matter. Gilead simply could not have performed their impressive LEN PURPOSE PrEP trials without wonderful contributions from academic, non-profit, and community organizations like the South African Desmond Tutu HIV Centre and many other such organizations here and abroad. It was eye-opening for me to see the extensive trial design, clinical testing, treatment delivery, data analysis, population health science, and community outreach efforts required to test LEN rigorously in tens of thousands of at-risk individuals.

I chose this topic for the winter Chair's message because I am deeply concerned that several key nodes along the discovery, drug development, and treatment pipeline are currently in jeopardy, but also because I see great new opportunities. On the negative side, the proposed cuts in NIH and NSF funding, including reductions in institutional F&A rates, would cripple our ability to do foundational discovery science, as recently described by Bob Carter, our new Senior Vice President for Health Sciences. I find it painful that we would even consider making such cuts at a time when our country still leads the world in biomedical research, the tools for making fundamental discoveries are more powerful than ever, and our department is doing so well. As an employee at a public institution, I'm not allowed to speak for the University or recommend specific public policy actions, but if you're interested in learning more about actions that you might consider taking I'd refer you to the advocacy pages of our national society, the American Society of Biochemistry and Molecular Biology. I am also deeply concerned that the impending worldwide roll out of LEN will be hamstrung by failure to reauthorize George W. Bush's PEPFAR Program. The President's Emergency Plan

for AIDS Relief (PEPFAR) has been an enormously successful program that delivers HIV drugs and treatment to individuals in more than 50 developing countries. Since its inception in 2003, PEPFAR is estimated to have saved 26 million lives and prevented millions of new HIV infections. Gilead Sciences has also done their part. They have signed a non-exclusive, royalty-free voluntary licensing agreement that will allow six different pharmaceutical manufacturers to make and sell generic LEN in 120 high-incidence, resource-limited countries that are hardest hit by the HIV pandemic. That agreement will make LEN broadly accessible at greatly reduced cost. However, large-scale distribution of the drug to needy areas will still require PEPFAR funding, and the program is currently set to expire on March 25, 2025 unless it is reauthorized by Congress and allowed to proceed by the administration. A wonderful aspect of large-scale PrEP programs is that they would prevent, rather than simply treating, new HIV infections, and they could therefore save millions from misery while ultimately reducing the requirement for future PEPFAR-like programs. Relevant information on the outlook for PEPFAR and advocacy actions can be found at several public sites, such as the KFF Global Health Policy Research Center.

Despite these grave concerns, I'm also more bullish than ever about the opportunities for translating fundamental discoveries made in our department and in other research centers into products and medicines. We haven't always done this as well as we might have, but that's changing fast and if you're interested in learning more about our greatly increased departmental efforts in this space, then I'd refer you to the essay on this topic from Jared Rutter, our outstanding new Departmental Director of Commercialization and Industry Relations, in the Fall, 2024 Newsletter. The University of Utah and State of Utah have similarly created a number of ambitious new programs for supporting commercialization and innovation. It's a whole new world in terms of translational opportunities, and Biochemistry Department faculty and trainees are jumping in (e.g., we currently have 13 active invention disclosures that were submitted by department groups in the past two years alone).

We've reached an inflection point in biomedical research that feels like both the best of times and the worst of times. Biomedical research has never been more powerful, nor the opportunities for translational advances more accessible. We really do have the opportunity to understand and overcome major killers like TB, HIV, malaria, cancer, diabetes, heart disease, genetic diseases, and neurodegenerative diseases. It is my sincere hope that we are remembered as the generations of scientists who were able to do that.

THE 2024 POSTDOCTORAL RISING STARS SYMPOSIUM

Paul Sigala

The 2024 Postdoctoral Rising Stars Symposium was held on September 26-27 and featured 20 highly accomplished speakers in four half-day sessions in the areas of Cellular Metabolism, Chemical Biology, Molecular Neurobiology, and Cell Biology and Cancer. These sessions were collaboratively planned by the Department of Biochemistry with Oncological Sciences, Nutrition and Integrative Physiology, Medicinal Chemistry, and Neurobiology. This symposium featured an outstanding array of speakers from broad backgrounds and institutions across the country. As our department grows, it remains an important goal to attract and recruit outstanding faculty who can effectively mentor our diverse graduate students and postdoctoral fellows. We consider this year's event to have been a major success and to have substantially advanced our efforts to attract highly accomplished new faculty to the University of Utah Dept. of Biochemistry.

The McCloskey Endowed Lecture and keynote address for this year's symposium was given by Dr. Elizabeth Villa, who is a former speaker at this symposium in 2014 and is currently an HHMI Investigator and Associate Professor at the University of California San Diego (see accompanying article below). Funding for the event was provided by a grant from the Burroughs Wellcome Fund, the James and Kathleen McCloskey Endowed Lecture, the Senior Vice President for Health Sciences, and by the partnering departments. We look forward to another exciting Postdoctoral Rising Stars Symposium on Oct. 2-3, 2025!

Postdoctoral Rising Stars and Dr. Elizabeth Villa (far right).

ELIZABETH VILLA PRESENTS THE 2024 MCCLOSKEY BIOSCIENCE ENDOWED LECTURE

Julia Brasch

A pinnacle of our annual Postdoctoral Rising Stars Symposium in September 2024 was the McCloskey Bioscience Endowed Lecture presented by Dr. Elizabeth Villa. We have had wonderful McCloskey lectures over the years, but this year was particularly special, since Elizabeth herself was a rising star in one of our first Postdoctoral Rising Stars events in 2014 just as she was just about to start her own lab at University of California San Diego. The McCloskey Bioscience Endowed Lecture, which is held annually in the fall, is made possible by a generous endowment from the McCloskey family created by Kay McCloskey, who was a leader in making our Eccles Health Science Library the wonderful resource it is today. Kay created this endowment to honor her husband Dr. Jim McCloskey, a scientist and former professor at the University of Utah with an unwavering passion for science. Jim had a joint appointment between Medicinal Chemistry in the College of Pharmacy and Biochemistry in the School of Medicine, and through this shared endowment, Jim remains a bridge between our departments. Notably, this year's lecture marked another special occasion, as Darrell Davis, who was stepping down as the chair of Medicinal Chemistry, and Kerry McPhail, the new chair, were both present to continue tradition. Kay and her son Gus were in the audience listening to Elizabeth's captivating lecture describing how cryo-electron tomography (cryo-ET) helped to discover new jumbo phage biology. Jim would have enjoyed the keynote lecture by Elizabeth because he himself was fascinated by unusual organisms – as was demonstrated by him visiting the Yellowstone mudpots in pursuit of hyperthermophiles where he could discover exotic nucleic acid modifications. The stage was set for a truly wonderful evening.

Elizabeth Villa, who is a physicist, started her career at the Universidad de las Americas-Puebla in Mexico obtaining a BSc in Physics. During graduate school she trained in biophysics and bioinformatics

in the Schulten lab at the University of Illinois at Urbana-Champaign, followed by a postdoc funded by a Marie Curie postdoctoral fellowship in Wolfgang Baumeister's lab at the Max Planck Institute in Martinsried, Germany. There she learned cryo-ET while pushing the new frontier of *in situ* structural biology, using focused ion beam milling to open up vitrified cells for investigation by cryo-ET by creating thin lamellae that can be imaged without the requirement of staining.

At the McCloskey lecture, she shared how this method helped to understand an internal defense system of jumbo phages, which are large viruses infecting bacteria. Jumbo phages express a tiny protein that can assemble into square tiles through defined protein interactions between four subunits. These tiny squares, which represent a novel assembly mechanism, ultimately come together to guard the phage DNA against internal bacterial defense systems. Cryo-ET was used to obtain 3D information of jumbo phage-infected bacteria and allowed them to be reconstructed into 3D volumes. This revealed how individual squares assembled into a massive shield that protects the phage DNA from the bacterium. While cryo-ET defined the assembly, cryo-electron microscopy studies of purified proteins, in collaboration with Joe Pogliano's lab, defined how the squares associate with one another, since the particles formed a cube when purified. Using cryo-ET, the group was also able to observe how the tiles of the cubes can link together inside the infected bacterium to form a nucleus-like sheet that protects the phage DNA from bacterial immunity. Since this little protein created a protective barrier, they named it 'chimallin' arising from chimalli — a shield carried by ancient Aztec warriors. Working together with Janet Iwasa's Animation lab from the Biochemistry Department at the University of Utah

Elizabeth Villa presents the McCloskey Bioscience Endowed Lecture to a full house.

(a connection that was formed ten years ago!), Elizabeth integrated the molecular and cellular information to show the intricate assembly mechanism of chimallin, resolved by the different techniques, with each of the tiles organized into a fishnet-like shell to protect the replicating DNA as soon as the bacteria are infected. This novel and remarkable process revealed by Elizabeth Villa's group, inspired the next generation of trainees and faculty alike to use cryo-ET to visualize other complicated macromolecular processes in cells.

During the day, Elizabeth interacted with the rising stars and chatted about job applications, selecting research projects, and frontiers and caveats of cryo-ET, and she shared her own experiences, highlighting the multifaceted scientist she is. Elizabeth has become the world leader in visualizing macromolecular complexes in their native environment, and has been recognized by a number of very prestigious awards, including being named an NIH New Innovator, a Pew Scholar, a Keith Porter Fellow of the ASCB, and an HHMI investigator.

At the rising stars dinner, Gus McCloskey, who is an excellent ceramic artist, presented Elizabeth Villa and Darrell Davis with gorgeous, personalized art pieces as personal mementos for years to come. Both recipients were touched by Gus' kind gesture and it was the perfect close to the 2024 McCloskey lecture.

Gus McCloskey presents the beautiful cups he created to honor 2024 McCloskey Lecturer Elizabeth Villa

Biochemistry Trainee Childcare Support Fund

Biochemistry trainees often face challenges in balancing their academic and professional aspirations with their family responsibilities. Attending conferences and other forms of professional training are critical for career advancement, networking, and staying current in their fields. However, for students with children the cost of childcare can be a major barrier, preventing them from fully participating in these essential opportunities. Our new Biochemistry Trainee Childcare Support Fund is designed to bridge this gap, and will be the featured fund for the Biochemistry Department 2025 UGiving Day Event. The fund will provide financial assistance to trainees, helping to offset childcare or other necessary related expenses while they attend professional events. By alleviating this burden, the fund will empower trainees to advance their educations and careers without creating undue financial stress.

Please mark the April 8-9 dates, and consider donating to this worthy cause. Your generous support will directly impact the lives of trainees, fostering their success and ensuring they can fully engage in opportunities that enhance their future. Together, we can create an environment where all trainees can thrive, regardless of their care giving responsibilities.

April 8-9 2025

Please mark the date!

BIOCHEMISTRY HOSTS SUCCESSFUL ANNUAL RETREAT FOCUSED ON CAREER DEVELOPMENT & RESEARCH

Keren Hilgendorf

Wes addresses the department at the 2024 annual retreat. Photo by Julie Kirby.

The University of Utah's Biochemistry Department gathered once again for its highly anticipated annual retreat last November, marking a key event in the department's calendar. Nearly 200 researchers came together for two days of insightful presentations, scientific discussions, and career development activities. This year's retreat highlighted both cutting-edge research and provided invaluable resources for trainees to explore career paths beyond academia.

The first day of the retreat was dedicated to showcasing the research of the department's trainees. Nine presentations covered a broad range of topics, from hormone-mimetic compounds secreted by frog skin to the structural basis of ribosome reactivation. Department Chair, Dr. Wes Sundquist, delivered a "State of the Department" address, celebrating recent departmental achievements while also outlining ambitious research goals for the future. The day concluded with two dynamic poster sessions, where trainees presented their research to their peers.

Several awards were presented during the retreat. Amber Vogel (post-doctoral fellow, Dr. Chris Hill's lab) received the "Best Trainee Talk" award. Deirdre Mack (graduate student, Peter Shen's Lab), Talia Cahoon (graduate student, Matt Miller's Lab), Claudia Consalvo (former graduate student, Brenda Bass' Lab), and Meghan Curtin (graduate student, Keren Hilgendorf's Lab) were all honored with "Best Poster" awards, voted on by their fellow trainees and faculty.

As in previous years, the second day focused on introducing trainees to alternative career paths outside traditional academic research. This year, trainees expressed interest in learning more about science policy, science outreach, and science communication. Dr. Morgan Nelson, faculty member in the Biochemistry Department, delivered an inspiring talk about her journey into science education, communication, and outreach. A panel discussion followed, featuring experts in science policy, outreach, and communication. Drs. Andrew George (University of Utah, Vice President for Research), Morgan Nelson (University of Utah, Biochemistry), and Chris Pickett (NIH Office of Portfolio Analysis) shared valuable insights on the skills and experiences required for success in their fields, their day-to-day tasks, and their perspectives on future career trends.

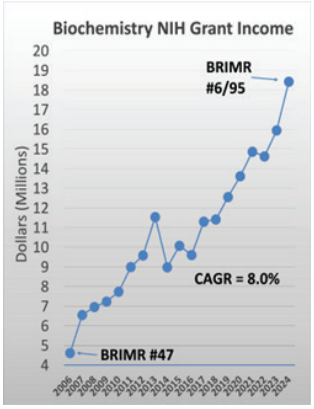
A networking lunch allowed trainees and faculty to engage with these experts in informal discussions, deepening their understanding of potential career pathways. The retreat concluded with a hands-on communication workshop led by Scot Singpiel, director of The Scope Radio team at the University of Utah, which specializes in creating audio content to engage and educate audiences within the health system.

Reflecting on the success of the retreat, Dr. Sundquist expressed enthusiasm for the department's continued growth and learning. "The retreat is an outstanding opportunity for trainees to gain exposure to a wide array of career options while also engaging deeply with the department's ongoing research. We look forward to next year's retreat, which will focus on industry careers, providing even more opportunities for career exploration."

The annual retreat is a key opportunity to celebrate the year's remarkable scientific discoveries and to strengthen our departmental community. As in past years, the 2024 retreat was a resounding success, and the department is already looking ahead and planning next year's event.

BIOCHEMISTRY NIH FUNDING ON THE RISE!

Every year, the Blue Ridge Institute for Medical Research ranks all US medical school academic departments in terms of total NIH funding. Last year, we rose from #9 to #6 of all 95 US Biochemistry Departments who received NIH funding, and we are significantly smaller than the five departments ranked above us. We have now risen from #47 (FY06) to #6 (FY24) since the start of the BRIMR rankings, with a compound annual growth rate of 8% over that period (graph). We're proud of that success, but no single metric perfectly measures our primary goals, which remain to perform impactful biochemistry that changes how we understand the natural world and ultimately improves human health, and to train the next generation of successful scientists, physicians, educators and policy makers.



WES SUNDQUIST WINS THE HORWITZ PRIZE

Dana Carroll

Last September we were delighted to learn that Wes Sundquist was awarded the Louisa Gross Horwitz Prize for his work on the ESCRT (Endosomal Sorting Complexes Required for Transport) pathway. Co-recipient Scott Emr, of Cornell University, was the first to identify this pathway in yeast and to describe its role in the trafficking of multivesicular bodies. Wes subsequently identified the human ESCRT pathway components, defined their role in multiple cellular processes, and determined the structures and mechanisms through which they mediate membrane budding events.

Wes was not expecting to find ESCRT components when he asked what cellular proteins participate in the budding of HIV from a host cell. Nonetheless, his group discovered that ESCRT proteins initially interact with the viral Gag protein, which then directs other pathway components to the plasma membrane. The fission process itself, that releases virus particles from the cell, is mediated specifically by ESCRT-III components and the VPS4 protein. This mechanism is now recognized as the most common way in which enveloped viruses escape the cell.

Wes's group was also among the first to show that ESCRT proteins are involved in the separation of daughter cells at cell division – a process called abscission. Pursuing the specific ESCRT members involved led them to identify additional proteins that participate in and regulate abscission.

In collaboration with Adam Frost, Wes determined the structures of ESCRT-III proteins that underlie the initial budding process in both viral exit and cell division. With Chris Hill, they elucidated the mechanism by which the VPS4 protein uses the energy of ATP hydrolysis to complete release of the bud. This hand-over-hand process is common to all of the many cellular AAA ATPases that work on polypeptides.

It is worth mentioning two other ESCRT-related advances. Using the

Scott Emr (left) and Wes Sundquist (right).

knowledge that the ESCRT pathway is required for viral budding, Wes collaborated with Neil King to devise synthetic virus-like protein nanocages that can bud from cells and carry novel cargoes. With Nels Elde, the Sundquist group identified a natural, truncated copy of one ESCRT-III protein in monkeys that interferes with HIV budding but not with cell division. This has the potential to lead to the development of a similar defense in human cells.

Wes's contributions to biochemistry and cell biology of the ESCRT pathway is wide-ranging and clearly deserving of recognition. We anticipate additional prizes will follow.

CELEBRATING THE SEASONS WITH SACNAS

Luis Cedeño-Rosario and Jessica Pita-Aquino

The goal of the University of Utah Society for Advancement of Chicanos/Hispanics & Native Americans in Science (SACNAS) chapter is to create an environment where everyone feels welcomed. Every year, we host our multicultural and holiday potlucks where faculty, staff, graduate students and postdocs can share their most delicious dish that represents their culture. These activities provide a sense of community and an opportunity to engage with people from different departments across the University of Utah. Last year, our multicultural potluck was put on in partnership with QUAFFS, A3, and the Center for Community and Cultural Engagement and everyone loved it! So, if you like delicious food, we hope to see you at our next potluck. Everyone is welcome!

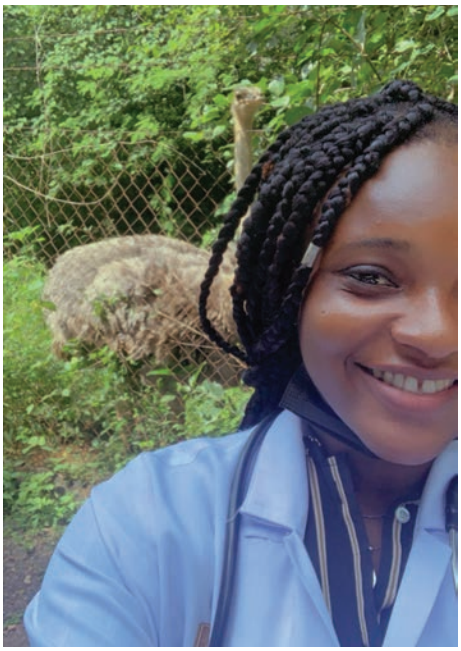
A photo from the 2024 SACNAS Holiday Potluck.

LISTENING TO THE STORIES THAT VIRUSES TELL

Annabel Anyang

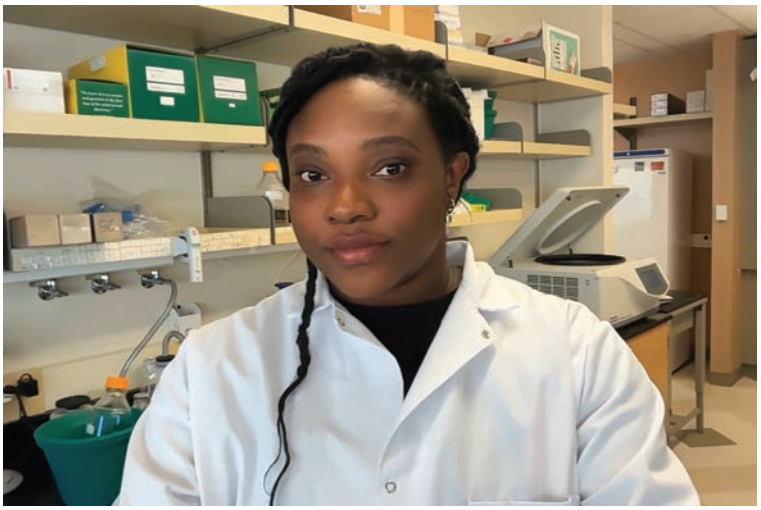
I've always been fascinated by stories—how they connect us, teach us, and reveal truths about ourselves and the world we live in. But the most compelling stories I've encountered aren't found in books, television shows, or movies. Instead, they're written in the molecular and biochemical mechanisms of viruses. These microscopic storytellers have shaped my journey from veterinary medicine to virology, taking me from the vibrant West African hub of Nigeria to the rugged Mountain West beauty of Utah. Back in veterinary school, zoonotic diseases shared between animals and humans like Lassa fever and rabies weren't just textbook cases or abstract lecture topics studied in class. They were tangible threats that could upend entire communities. Remembering poultry farms ravaged by avian influenza and rural communities haunted by stray rabid dogs, my experiences left an indelible mark. I was especially intrigued by the phenomenon of viral zoonoses, which describes how a virus could jump from infecting wild animals to infecting humans, defying the barriers between species. This sparked my desire to further understand viruses, spillover events, and our connection, as humans, to these phenomena through a One Health perspective, a framework that recognizes the interconnectedness of human, animal, and environmental health. Ultimately, this has led me to pursue a PhD investigating viral evolution where I can explore the mechanisms that allow zoonotic viruses to adapt and spread between species.

My background in veterinary medicine became the foundation of this journey. Working with animals taught me to think holistically about health and disease, not just at the individual level, but also at the population and ecosystem levels. The SARS-CoV-2 pandemic, which struck during the penultimate year of my veterinary training, further solidified my interests. As the world grappled with this unprecedented global health crisis, I saw the power of the One Health approach in action. I realized my next step after veterinary school would not be in the clinic or in the field, but in a research lab, where I could investigate pandemic-potential viruses that blur the lines between species and reveal the fragile connections uniting us all.



A selfie with an ostrich from Annabel's vet school days.

Today, my research in the Starr lab focuses on the evolution of viral proteins, with a particular emphasis on how zoonotic viruses adapt in intermediate host animals like minks. Outbreaks of SARS-CoV-2 on mink farms in Europe and North America prompted large-scale culling operations and raised concerns about minks serving as viral reservoirs, enabling spillback into human populations. Utah, home to some of the largest mink farming operations in the United States, was no exception. The urgency of understanding these dynamics became even clearer when wild mink near an infected Utah fur farm tested positive for SARS-CoV-2. Genetic sequencing revealed that the virus in the wild mink was identical to that found in infected farmed minks, underscoring the potential for viral transmission between farms and surrounding wildlife. More recently, detections of the highly pathogenic avian influenza (H5N1) and viruses related to the pathogenic human virus MERS-CoV in farmed minks have raised further alarms. Even more concerning, recent studies demonstrated that the same H5N1 strain from minks was capable of airborne transmission between ferrets, which are a close relative of minks. This is an alarming finding given the respiratory similarities between ferrets and humans that mark ferrets as a common lab model for influenza transmission. Mink susceptibility to various zoonotic viruses therefore positions them as potential "mixing vessels", capable of harboring and facilitating the evolution of viruses with severe pandemic potential.



Annabel in the Starr lab.

Each day in the lab, I am reminded of the farmers, animals, veterinarians, and communities I encountered back home. Their stories drive my work, pushing me to ask questions and gain training that could one day help prevent or prepare for future outbreaks, ensuring we are not caught off guard by the next pandemic. But my journey has not been confined to the lab. As an international student, I have the incredible opportunity to view cutting-edge science through a global lens. Moving to Salt Lake City for my PhD, an ocean away and over seven thousand miles from everything I had ever known, was both challenging and enriching. I remember my first days in grad school, feeling a mix of excitement and uncertainty, asking myself questions like: Would I be able to adapt to a new scientific culture? However, here in the Department of Biochemistry at the University of Utah, I found a new home and soon realized that my unique perspective was an asset. Viruses, after all, do not respect borders. The 2020 pandemic proved this reality beyond doubt. Science, too, should have no borders, and diversity is more than just a buzzword. It is a necessity for great innovation and progress, and ensuring that our research has maximal global impacts. My experiences and the amazing opportunity to be here have made me more aware of the disparities in access to scientific resources and education around the world. As a Black woman in science and an international student, I understand the barriers that many face in pursuing opportunities in research, which fuels my commitment to science communication and STEM advocacy. Through the science communication club and the STEM Ambassadors Program (STEMAP) at the U, I have been able to engage in impactful outreach initiatives making science accessible. I am not only a researcher but also a storyteller, with science as my tool to connect people, discovery, and ideas to inspire and drive a meaningful impact.

Looking back, my journey to this point has been anything but linear, anything but smooth sailing. But each step and each challenge has shaped my identity as a scientist, advocate, and communicator. Zoonotic viruses have been the common thread, weaving together my passions in veterinary medicine, One Health, science communication, and STEM advocacy. In a world where the threat of zoonotic outbreaks continues to remind us of our shared vulnerability, I am excited to be on a journey using science to illuminate our shared humanity, foster trust and understanding between society and scientists, and contribute to a scientific community that is not only more knowledgeable but also more inclusive and interconnected across boundaries.

Annabel Anyang is a 2nd-year graduate student in Tyler Starr's lab.

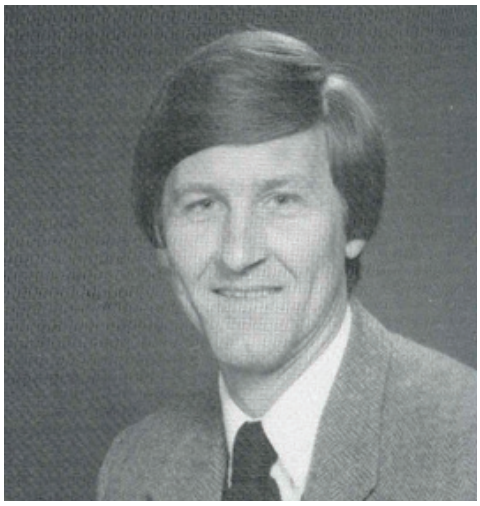
A HISTORY OF THE BIOCHEMISTRY DEPARTMENT: PART 4
THE RESURRECTION

Dana Carroll

In 1977 Sid Velick announced that he would leave the chairmanship of the Department the following year. Hans Rilling was installed as interim chair, and a search committee was formed to find Sid's replacement. In fact, five search committees worked toward this end for 8 years. External candidates of various calibers were considered, but none landed, at least partly because the recruitment package was rather meager. Hector DeLuca, discoverer of vitamin D and faculty member at the University of Wisconsin, said after his visit that he would need an entire new building to make the job attractive to him. Even more modest demands were unlikely to be satisfied with the resources available during much of that time.

Dana Carroll, 1985.

The fifth search committee, which included Steve Prescott and Costa Georgopoulos, was frustrated with the earlier failures, and ultimately suggested that Marty Rechsteiner – then in the Biology Department – and Dana Carroll – from Cellular, Viral and Molecular Biology* – be offered the position as equal co-chairs. There was a precedent for having co-chairs. When the Department of Human Genetics was formed earlier in 1985, it proved similarly difficult to recruit an eminent human geneticist from outside the University to head the department, so Ray Gesteland and Ray White were installed as co-chairs. In some quarters, they were dubbed the Rays of Hope – hope that was fulfilled, I should add.



Marty Rechsteiner, 1985.

Cecil Samuelson was the Medical School Dean at the time, and he acted on the search committee's recommendation. Marty and I had known each other ever since my arrival at the U in 1975 and had even taught a graduate seminar course on chromatin together. On a sunny September day in 1985, we met for lunch at the Market Street Broiler on 1300 East (in the old fire station now occupied by Rio Grande Restaurant). Each of us came with a list of goals for the department and found that our lists matched pretty much item for item.

Of prime importance was the recruitment of genuine biochemists. The existing departments of Biology, CVMB, Human Genetics and Pathology had cell and molecular biologists on their faculties, but there was a dearth of people working on biomolecular structure and mechanism. Another goal was to hire excellent scientists, using "people smarter than we are" as the standard. We also agreed not to rush the recruitment process but to insist on finding people who fit our vision for the department.

By this time the Medical School was experiencing a period of financial stability, and Dr. Samuelson was able to offer us a package that included 6 new faculty slots in addition to our own, funds for recruiting those people, and prime research space in the Wintrobe Building. This was enough for the co-chairs to sign on and begin the process of revitalizing the Biochemistry Department.

The first item of business was to recruit new, young faculty members. While that was getting started, we made some local additions by offering research track or adjunct appointments to biochemically-oriented faculty already on campus. This included Bill Gray and David Goldenberg from Biology, Dale Poulter from Chemistry, Steve Prescott and Tom McIntyre from Internal Medicine, and relying to a greater extent on Dennis Winge, who also had a primary appointment in Medicine. This made the Department's catalog entry appear more robust and got these people engaged in the rebuilding process. Ellie Ehrenfeld remained a productive member of and contributor to the department, but her lab and much of her effort was in CVMB.

During the initial search, Marty and I both read every application and gave each applicant an A, B, C . . . grade to winnow the list before presenting candidates to the larger search committee. Some years we saw well over 200 applications, but as with the case of the goals for the department, our scores matched for essentially every one of them. I think it is fair to say that the proportion of very promising applicants was lower and the proportion of disappointing ones much higher than our searches see these days. That was probably because our Biochemistry Department had a low profile at the time and the pool of available, well-trained candidates was smaller. Some years we interviewed 6 or 7 candidates without making an offer, thus maintaining our high standards.

A key to the recruiting process was to "hire the person, not the project." We either had very good taste or were extremely lucky in the choices we made. We were extremely fortunate to hire Tom Alber as our first addition to the faculty. Tom trained as a protein crystallographer with Greg Petsko at MIT and Brian Matthews at the University of Oregon. He had very broad scientific tastes and unique insights; he was also a delightful person. During his time here, he determined the first structure of a coiled coil, in collaboration with Erin O'Shea, who was at that time a graduate student in Peter Kim's lab at MIT. Tom stayed nearly 5 years then left for a position at UC Berkeley. Over the years the Department has lost a few faculty members to other institutions, but they always went to very highly rated places. Tragically, Tom died of ALS in 2014, shortly after his 60th birthday.

Next, in close succession, were Tim Formosa and Brenda Bass, both of whom trained with outstanding scientists. Tim got his Ph.D. with Bruce Alberts at UC San Francisco and did a postdoc with Lee Hartwell at the University of Washington. This combined background led to Tim's productive career using a combination of biochemistry and genetics to elucidate aspects of DNA replication in yeast. Tim's recruitment was assured when he and his wife Fran went cross-country skiing in a gentle snowfall on his second visit.

Brenda got her Ph.D. with Tom Cech at the University of Colorado during the period when catalytic RNA was discovered and characterized. As a postdoc with Hal Weintraub at the Fred Hutchinson Cancer Center in Seattle, she discovered the activity that was ultimately named ADAR (adenine deaminase that acts on RNA) and has formed the basis of her independent career. Brenda famously rejected our initial offer, but later had rejector's regret and ultimately agreed to join the Department.

*The Department of CVMB was initially called Microbiology but changed its name in 1979 to better reflect the interests of its faculty. It was renamed again in the 1990's as Oncological Sciences and became the academic home of basic scientists in the new Huntsman Cancer Center.

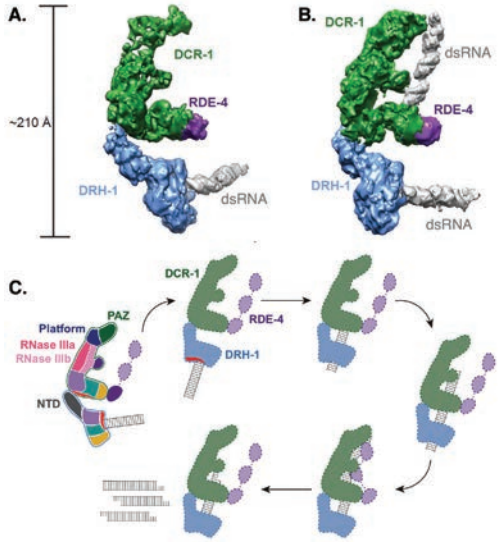
Dana Carroll is Distinguished Professor Emeritus of Biochemistry and is one year older than the Department.

2024 BIOCHEMISTRY RESEARCH ADVANCES

Caenorhabditis elegans Dicer acts with the RIG-I-like helicase DRH-1 and RDE-4 to cleave dsRNA

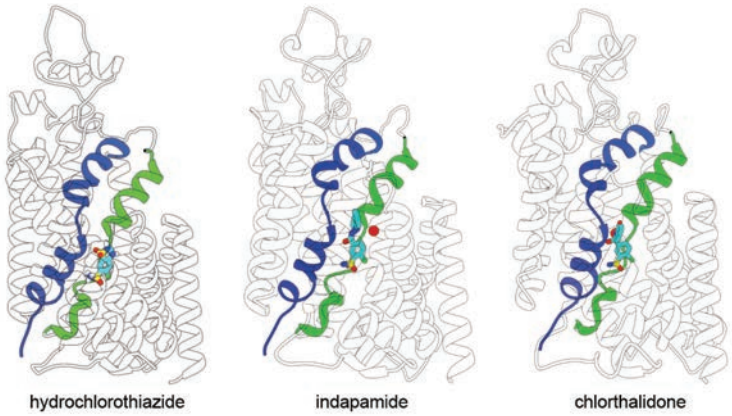
All organisms have pathways to fight viruses. Vertebrates, including humans, use proteins called RIG-I-like receptors to detect viral double-stranded RNA (dsRNA) and induce an interferon immune response. Invertebrates do not have interferon pathways and instead use RNA interference (RNAi), which involves cleavage of viral dsRNA by an enzyme called Dicer. Studies in the invertebrate worm C. elegans led to the Nobel prize-winning discovery of RNAi, yet, more than two decades after this discovery, C. elegans Dicer remained biochemically uncharacterized. In this paper we overcome challenges to purification of C. elegans Dicer by co-expression with its protein partners, a dsRNA binding protein called RDE-4, and surprisingly, a protein that looks just like the RIG-I like receptor used in human antiviral defense. Using biochemical assays, as well as cryo-electron microscopy to reveal three-dimensional shape, we determined that the C. elegans antiviral complex exhibits properties found in other antiviral Dicers, but has parsed the activities often intrinsic to Dicer, to other proteins in the antiviral complex. Most notably, it is DRH-1 that is primarily responsible for ATP hydrolysis and threading of dsRNA, rather than Dicer.

Caenorhabditis elegans Dicer acts with the RIG-I-like helicase DRH-1 and RDE-4 to cleave dsRNA. Consalvo CD, Aderounmu AM, Donelick HM, Aruscavage PJ, Eckert DM, Shen PS, and Bass BL. eLife, 2024. 13:RP93979.



Two cryo-EM structures (A and B) of the C. elegans antiviral complex are shown with proteins and dsRNA labeled. The structures likely represent intermediates rather than cleavage-competent structures, and reveal important interactions, such as that between the N-terminal domain of DRH-1 and Dicer (DCR-1), and two different dsRNA binding sites. A model (C) invoking a conformational change that allows the dsRNA to thread through DRH-1 to DCR-1's RNase III dsRNA cleavage sites, and the Platform-PAZ domains, suggests how the complex cleaves viral dsRNA.

Structural basis for blood pressure drug function



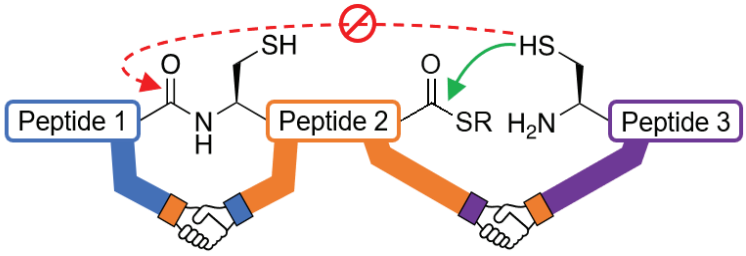
Hydrochlorothiazide, indapamide, and chlorthalidone are the top three most prescribed thiazide drugs in the United States and they all inhibit salt and water retention by the kidneys by binding and occluding the NCC ion translocation path.

Thiazide (e.g., hydrochlorothiazide) and thiazide-like diuretic drugs have been essential medications for lowering blood pressure and for treating fluid retention since the 1950s. They do so by acting on and preventing the Na+-Cl- ion co-transporter (NCC) from absorbing salt (and water) in the kidneys. Our NCC structures caught hydrochlorothiazide, chlorthalidone, and indapamide in the acts of inhibiting NCC from transporting ions. 'Seeing' how these drugs work in atomic detail paves the way for future medicinal chemistry efforts to further improve the potency and specificity of this important class of diuretic drugs. Aberrant activation of NCC by kinases, enzymes that add phosphate groups to a key motif of the transporter, cause hypertension. Our kinase-activated NCC structures now show how these enzymes change NCC structure and accelerate ion translocation rates. Our structures imply that small molecule compounds that interfere with this kinase activation process could serve as leads for the development of novel diuretic drugs.

Structural bases for Na+-Cl- cotransporter inhibition by thiazide diuretic drugs and activation by kinases. Zhao Y, Schubert H, Blakely A, Forbush B, Smith MD, Rinehart J, Cao E. Structural Bases for Na+-Cl- Cotransporter Inhibition by Thiazide Diuretic Drugs and Activation by Kinases. Nat Commun. 2024 Aug 14;15(1):7006.

Using templating to accelerate chemical protein synthesis

Chemical protein synthesis (CPS) is an emerging technology that enables precise atomic control of a protein's composition, enabling the production of custom proteins with non-natural amino acids and complex modifications that are not accessible using standard recombinant techniques. To make a synthetic protein, it is divided into ~50 amino acid segments (produced using standard peptide chemistry), which are then ligated together one-at-a-time to slowly assemble a full-length protein. These ligation reactions are complex and inefficient, requiring many reaction steps and purifications that often result in unusable yields. In this work, we describe a templated ligation technique that allows us to ligate three peptides in a single step with no intermediate purifications to facilitate small protein production. "Templating" is a process that brings each peptide into close proximity with its neighbor, speeding the ligation reaction and improving overall yields. This technology, called CAPTN - Controlled Activation of Peptides for Templated Native Chemical Ligations

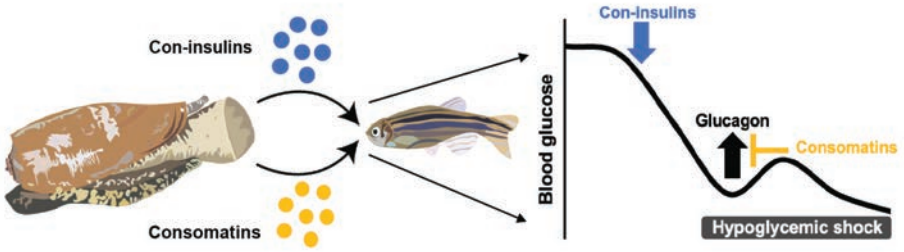


Schematic showing how CAPTN enables the ligation of three peptides in a single reaction.

– greatly accelerates the production of synthetic proteins while minimizing side-reactions, with wide applications in drug discovery, mechanistic studies, and structural biology. Future research will focus on extending this technology to a larger number of peptide segments to enable rapid production of larger proteins, especially valuable for production of mirror-image proteins (composed of D-amino acids) used in mirror-image drug discovery.

Selective Activation of Peptide-Thioester Precursors for Templated Native Chemical Ligations. Spaltenstein P, Giesler RJ, Scherer SR, Erickson PW, Kay MS. Angew Chem Int Ed Engl. 2025 Jan 2;64(1):e202413644. Epub 2024 Oct 25.

Fish-hunting cone snails use hormone mimics to disrupt blood glucose in their prey



The venom contains toxin mimics of insulin (Con-insulins) and somatostatin (Consomatins) that together induce dangerous blood glucose in fish prey.

Venomous animals have evolved diverse molecular mechanisms to incapacitate prey and defend against predators. Most venom components disrupt nervous, locomotor, and cardiovascular systems or cause tissue damage. The previous discovery that certain fish-hunting cone snails use weaponized insulins to induce hypoglycemic shock in prey highlighted a unique example of toxins targeting glucose homeostasis. In a new study, Yeung, Safavi-Hemami and colleagues show that, in addition to insulins, the deadly fish hunter, Conus geographus, uses a selective somatostatin receptor 2 (SSTR2) agonist that blocks the release of the insulin-counteracting hormone glucagon, thereby exacerbating insulin-induced hypoglycemia in prey. The native toxin, Consomatin nG1, contains a minimized vertebrate somatostatin-like core motif connected to a heavily glycosylated N-terminal tail. Remarkably, the toxin's N-terminal tail closely mimics a somatostatin isoform that is specifically found in fish pancreas. Collectively, this study provides a stunning example of chemical mimicry in nature, highlights the combinatorial nature of venom components, and establishes glucose homeostasis as an effective target for prey capture.

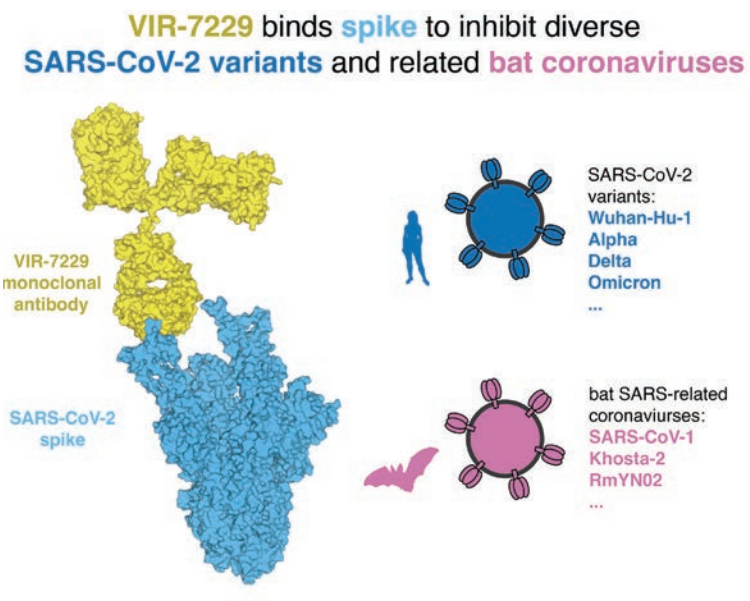
Fish-hunting cone snail disrupts prey's glucose homeostasis with weaponized mimetics of somatostatin and insulin. Yeung HY, Ramiro IBL, Andersen DB, Koch TL, Hamilton A, Bjørn-Yoshimoto WE, Espino S, Vakhrushev SY, Pedersen KB, de Haan N, Hipgrave Ederveen AL, Olivera BM, Knudsen JG, Bräuner-Osborne H, Schjoldager KT, Holst JJ, Safavi-Hemami H. Nat Commun. 2024 Aug 20;15(1):6408.

Also highlighted in ScienMag Morning News, Genetic Engineering and Biotechnology News, Cosmos Magazine, and Science Daily.

A promising broad-acting SARS-CoV-2 monoclonal antibody

Monoclonal antibodies (mAb) have proven effective and versatile tools for the treatment and prevention of viral infections, including COVID-19. Five mAb therapeutics against SARS-CoV-2 were authorized for clinical use in the first several years of the pandemic and saw widespread utility, but each lost activity soon after authorization due to the evolution of resistance mutations in successive viral "variants of concern." We therefore lack effective mAb treatments and preventatives against currently circulating strains, which is particularly important for those who cannot receive or mount a protective immune response to the COVID-19 vaccines. In this study, we collaborated with scientists at Vir Biotechnology and the University of Washington to isolate and characterize a promising mAb, VIR-7229, which we found can neutralize not only past and current SARS-CoV-2 variants, but also a broader range of related bat coronaviruses that could potentially spill over into humans in the future. The Starr lab used high-throughput binding assays to characterize the breadth of binding of VIR-7229 against SARS-CoV-2 mutants and a complete panel of SARS-related coronaviruses, the broader lineage of bat viruses from which SARS-CoV-1 and SARS-CoV-2 emerged. We found that VIR-7229 shows a unique ability to resist escape mutations and bind broadly across SARS-related coronaviruses compared to other mAbs in late-stage clinical development. These results support VIR-7229 as a promising clinical candidate for the prevention of infection by SARS-CoV-2 or future zoonotic coronaviruses.

A potent pan-sarbecovirus neutralizing antibody resilient to epitope diversification. Rosen LE, Tortorici MA, De Marco A, Pinto D, Foreman WB, Taylor AL, Park YJ, Bohan D, Rietz T, Errico JM, Hauser K, Dang HV, Chartron JW, Giurdanella M, Cusumano G, Saliba C, Zatta F, Sprouse KR, Addetia A, Zepeda SK, Brown J, Lee J, Dellota E Jr, Rajesh A, Noack J, Tao Q, DaCosta Y, Tsu B, Acosta R, Subramanian S, de Melo GD, Kergoat L, Zhang I, Liu Z, Guarino B, Schmid MA, Schnell G, Miller JL, Lempp FA, Czudnochowski N, Cameroni E, Whelan SPJ, Bourhy H, Purcell LA, Benigni F, di Iulio J, Pizzuto MS, Lanzavecchia A, Telenti A, Snell G, Corti D, Veesler D, Starr TN. Cell. 2024 Dec 12;187(25):7196-7213.e26.



Molecular structure of the VIR-7229 monoclonal antibody (yellow) bound to the SARS-CoV-2 spike protein (blue). Despite binding an evolutionarily variable site on the viral spike, VIR-7229 binds broadly across SARS-CoV-2 variants and related bat coronaviruses by accommodating sequence variation in its binding site.

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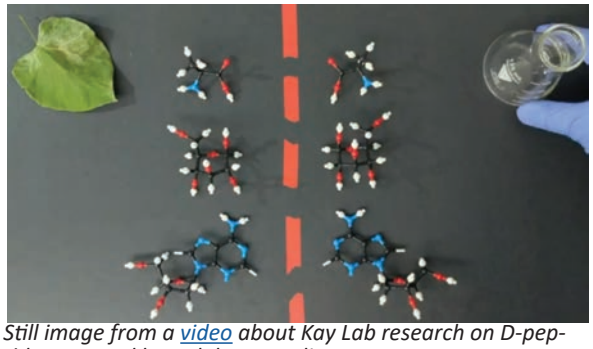
ASKING THE MAN IN THE MIRROR TO CHANGE HIS WAYS

Michael Kay

Look in the mirror – what do you see? Someone that looks a lot like you, but isn't exactly you. All your features are there down to every freckle, but something is a bit different – their 3-D arrangement. This property, called chirality or "handedness," is best exemplified by comparing your left and right hands. They are structurally the same but cannot be superimposed on each other. They also differ in how they interact with other chiral objects – you cannot put a right-handed glove onto your left hand. This property also exists at the molecular level in complex biomolecules like peptides and proteins, nucleic acids, and sugars. For reasons that remain mysterious, all life on Earth standardized exclusively on only left-handed (or L-) peptides and proteins. In theory, mirror-image life could exist that is composed of right-handed or D-proteins (along with mirrored versions of DNA, RNA, sugars, lipids, etc.).



Still image from a video about Kay Lab research on D-peptides, created by Judah Evangelista.

Our Work with Mirror Molecules

The Kay lab develops mirror-image D-peptide therapeutics, primarily targeting viral and bacterial pathogens. D-peptides are a very promising emerging class of therapeutics because they are highly resistant to proteolytic degradation in the body and therefore are long-lived and poorly recognized by the immune system. However, D-peptides cannot be made recombinantly and must be made by chemical synthesis. A major focus of the lab has been improving chemical synthesis methods to enable efficient production of larger D-proteins, both as drug targets and therapeutics. While smaller D-peptides are already straightforward to make at pharmaceutical scale and quality, simply making D-proteins, let alone in significant quantities, remains very challenging, though we and other peptide chemistry groups have made great strides in recent years.

The Mirror Life Question

As part of our work, we wondered: what if we could make an entire mirror-image cell - aka "*D. coli*" - to serve as a bacterial factory to recombinantly produce D-proteins? Such a synthetic cell would need to be made from scratch using mirror-image components. Likely the most challenging aspect of this engineering project of unprecedented complexity would be synthesizing the thousands of proteins needed to construct a cell, in addition to making all the DNA, RNA, lipids, and sugars. This idea is reminiscent of a Star Trek episode on mirror universes, but recent advances in chemical protein synthesis (by us and many other peptide chemistry groups) and synthetic biology (such as the engineering of minimal cells) are bringing this possibility into the visible horizon. To be clear, making a fully synthetic cell would be a very daunting challenge, requiring additional technological advances, tremendous resources, and pooled expertise from across the world, akin to the Human Genome Project. However, it now seems feasible that such a cell could be constructed in the coming decades.

Assessing the Risks

Long before any concerted effort to make a mirror cell gets underway, it is important to consider *D. coli*'s potential biosafety implications. This past summer, I participated in a mirror life working group to evaluate these potential risks and make an initial set of recommendations. This diverse group consisted of 38 international experts from a variety of relevant fields (including synthetic biology, chemistry, ecology, immunology, biosecurity, and policymaking). The two initial outputs of this group were a Science Policy Forum commentary and an accompanying 300-page technical report.

My colleagues and I investigated the potential risks that mirror bacteria could present to life on Earth. Such a cell would be unlike anything that nature has ever encountered – how would it interact with natural life? Of particular concern, would *D. coli* have any natural predators? Bacterial populations are controlled by bacteriophages (viruses that attack bacteria) or other organisms. Most of what we currently know about natural control mechanisms suggests that they are largely dependent on chiral interactions – and so are likely to be much less effective against a mirror organism. Mirror bacteria probably wouldn't be at a loss for nutrition either: although we initially speculated that *D. coli* would starve to death, recent evidence shows that bacteria can grow robustly on available achiral nutrients. There are also abundant racemases in nature that can flip the chirality of amino acids and sugars, and these might evolve rapidly in *D. coli*. As a result, mirror bacteria could very possibly establish a foothold within a wide variety of ecosystems that could displace natural organisms.

Similarly, our immune system heavily relies on chiral interactions to recognize and combat invaders, so mirror bacteria could become very challenging pathogens. Even with defects in small parts of their immune system, immunodeficient patients are at much higher risk of serious infections. With mirror life, many of these components could fail. Other "chemical warfare" tactics, like antibiotics, would very likely be insufficient against evasive immune bacteria. Plus, they'd have to be produced at a massive scale for what would likely be the entire lifecycles of many species—a practical challenge that we've never encountered before.

The upshot of this first systematic evaluation of the risk of mirror life is that despite many unknowns that warrant additional research, based on what we know today: mirror life should not be created. The unique and severe risks of a mirror organism - that could grow relentlessly and would likely be impossible to control once created - appear to greatly outweigh any potential modestly beneficial uses. This report and its recommendations are not intended to be the final word, but to catalyze an international discussion with all stakeholders to better understand the risks and ultimately develop policies to mitigate these risks. Importantly, we must ensure that efforts to halt the creation of self-replicating mirror cells do not stifle the tremendous promise of mirror therapeutics (chemically produced and non-replicating) and synthetic biology more generally. To start addressing these challenging questions and to hear differing arguments, the non-profit Mirror Biology Dialogues Fund has been created to sponsor a series of conferences around the world and keep this important discussion moving forward.

STAFF HIGHLIGHT: MEET KATE WILLDEN

Raised on the Western Slope of Colorado near Grand Junction, Kate Willden grew up in a small-town environment where each high school class had only about 100 students. Her parents worked as bankers, and she spent much of her childhood immersed in books, loving language arts and history but not particularly drawn to math or science. Although her family was very outdoorsy—camping, hiking, and skiing—she didn't always appreciate it as a child, and always brought along a book.

Kate stayed in Grand Junction for college, earning an associate's degree in liberal arts from Mesa University (formerly Mesa State). After college, she moved to Colorado Springs, drawn by the opportunity to experience a bigger city and live near her sister. She took a job as a front desk administrator at a hospital. It was there that she met her first husband, who was in the Army. Their life changed quickly when he was stationed in Hawaii, prompting a move to Honolulu with their young son.

While in Hawaii, Kate completed her degree in administrative sciences, balancing her studies with life as a stay-at-home mom. The

transition to living in Hawaii was challenging for Kate. With her husband frequently away for military duties, she found herself frequently alone but made the most of island life by going to the beach, biking, and exploring the rich food culture. She developed a love for local dishes like spam musubi, teriyaki with rice, and fresh seafood. After nearly three years, her husband was stationed in Texas, and they relocated to Fredericksburg, where her parents had also settled.

After a year in Texas, Kate decided to move to Utah, where her sister had recently moved, and began searching for secretarial positions. After working at a clinic specializing in prosthetics, she transitioned to insurance sales with AAA — a job that she didn't enjoy, but happily led her to meet her current husband, Joshua, who was also working there.

Kate then landed a role as an executive assistant at a real estate company, with Joshua joining as a real estate agent a little while later. She learned a great deal about the industry, and while the booming housing market initially made their careers exciting, the pandemic brought financial uncertainty. When the company eventually went under, Kate had to pivot again.

Kate is happy in her current role as an executive assistant to the Chair of Biochemistry, where she has been working for nearly two years. She manages Wes's meetings, tracks expenses and reimbursements, and coordinates events, including CHEETAH-related functions. She finds fulfillment in being a valuable support system, especially during high-stress moments when she can step in and make a difference. Her biggest challenge? Keeping Wes' calendar, which she says is always incredibly full.

Outside of work, Kate is an outdoorsy mom who organizes frequent camping trips. Her family makes an effort to visit national parks in Wyoming and Colorado, camping at least twice a month during the spring and summer. She and her husband Joshua have two ten-year-olds— a son and a daughter who are best friends and love spending time outdoors.

Kate with her kids and husband, Joshua.

In her personal time, Kate remains an avid reader, finishing about two books a week across fiction and nonfiction. She enjoys discovering new and interesting reads and highly recommends Clan of the Cave Bear, an 18-book series that she found particularly gripping.

A dedicated vegan, Kate enjoys cooking at home, particularly Indian cuisine. She and her husband share their passion for plant-based eating, frequently preparing meals together and indulging in their favorite local vegan sandwich spot, Buds.

FACULTY HIGHLIGHT: MEET RILEY GIESLER

Growing up in Lincoln, Nebraska, a mid-sized city in the heart of the country, Riley Giesler was part of a large, close-knit family. He attended Catholic school from kindergarten through high school and spent his summers and winter breaks working for his parents' wholesale lumber distribution company. There, he helped with various projects including cabinet and door assembly.

Although he enjoyed contributing to the family business, Riley's true interests always leaned toward the medical field. With a father who had been a pharmacist before transitioning into lumber and other relatives in healthcare, he found himself drawn to chemistry and biochemistry. During his junior year at the University of Nebraska, he had the opportunity to work with David Berkowitz, a highly regarded chemist who later became a Director of the Chemistry Division at the National Science Foundation. That experience shaped his approach to science, as Berkowitz pushed him to embrace discomfort and constantly challenge himself, both personally and professionally.

Under Berkowitz, Riley gained experience in organic chemistry, enzymology, and biochemistry, working with enzymes to synthesize small molecule intermediates. His research was intense—he spent every day in the lab while also taking graduate-level enzymology courses. Inspired by this work, he applied to graduate programs at the University of Utah, the University of Washington, and the University of Nebraska and ended up choosing the U for its high standard of living and strong research environment.

Riley started at the U in the Chemistry Department but soon found a home in the Kay Lab, where he focused on peptide research. An interest in method development and peptide synthesis drove his work in Michael's lab, where he worked on streamlining peptide production through the development of the "Helping Hands" tool and also contributed to drug discovery projects.

From the beginning, he had his sights set on the pharmaceutical industry, specifically working on peptides. However, when Riley graduated in 2021, job opportunities in Utah were limited due to the lingering effects of COVID-19. He decided to join Entrada Therapeutics in Boston as an industrial postdoc, where he specialized in intracellular drug delivery, focusing on cell-penetrating peptides. After eight months, he transitioned to a full-time scientist role and spent two years refining drug targeting strategies, particularly for localized delivery systems like those crossing the blood-brain barrier.

Riley with his 1-year old daughter, Ellie.

Life in Boston was exciting—he and his wife lived near Fenway Park and enjoyed the city's energy. However, when they learned they were expecting their first child, the high cost of living and lack of nearby family made them consider moving back west. A conversation with Michael led to an opportunity to return to Utah as a research faculty member in the Kay Lab. Excited for the opportunity to contribute to academic research while learning lab management and grant writing, he made the move in September 2023.

That transition coincided with the birth of their daughter, Eliza (Ellie), in January 2024. The first few months were a blur while Riley balanced fatherhood and reentering the lab, but now, with a toddler who is starting to talk, life is slowly settling into a new rhythm. His role in the Kay Lab has evolved beyond benchwork—he now focuses on project planning, mentoring students, grant writing, and learning the intricacies of running a successful lab.

Riley with Taylor and daughter Ellie.

Outside of work, Riley and his wife, Taylor, are rediscovering their hobbies. An avid outdoorsman, he enjoys hiking, skiing, and spending time with their black lab, Poe. Recently, he and Taylor have taken up golf, influenced by Taylor's family, who live in Heber, Utah. They also purchased a home and have embraced home improvement projects; he recently installed new kitchen windows with materials from his family's company and is in the process of finishing the basement, transforming it into a family room and play area.

ALUMNUS HIGHLIGHT: MEET QUINN DEVEREAUX

Raised in American Fork, Utah—often referred to as "Happy Valley"—Quinn Deveraux grew up immersed in the outdoors. Hunting, fishing, and working hard were ingrained in him from an early age. While academics weren't his strong suit, sports were his passion. He played football, baseball and basketball, traveling frequently for games, and often found himself prioritizing athletics over the classroom. Unfortunately, Quinn didn't leave high school with a diploma, which made pursuing higher education a challenge.

After high school, he found work at a lumber yard before deciding to continue his education at Utah Valley Community College (now Utah Valley University). With day and night classes, Quinn worked his way through an Associate's degree in mathematics. Unlike some other academic subjects, Quinn appreciated that math had definitive answers, and he thrived in that structured logic.

With an Associate's degree, Quinn was able to transfer to the University of Utah. There he pursued further studies in mathematics before discovering an interest in biochemistry and molecular biology. He was inspired by a molecular biology lab course taught by Dr. Theodore (Ted) Gurney, where he first learned about the intricacies of genes and operons through a mathematical lens. Unfortunately, financial constraints threatened to derail his education. With no money for textbooks and living off Pell grants, Quinn stumbled upon an ad posted in the library for an open position in Dr. Martin Rechsteiner's lab. During his interview with Marty, he candidly admitted his lack of biochemistry experience but promised to outwork anyone in the lab. Marty took a chance on him, giving him six months to prove himself. Quinn not only stayed in the lab - he excelled.

Quinn's work led to a first author publication as an undergraduate, which helped facilitate his acceptance to the Biochemistry and Molecular Biology program where he joined Marty's lab as a graduate student. There, his work on the ubiquitin-proteasome pathway led to a significant discovery: the first known ubiquitin-binding subunit of the proteasome, which helped explain the mechanism proposed by Avram Hershko. Quinn's research earned him widespread recognition, including an invitation to visit Hershko in Israel to present his work at a ubiquitin and proteasome pathway conference. This was an eye-opening experience that expanded his perspective on the global scientific community. After completing his Ph.D., Quinn found himself at a crossroad, as he was excited to graduate, but uncertain about the next step.

Quinn enjoys returning to Utah to fly fish in the Provo River.

Quinn's fascination with proteases regulating processes like cell growth and death led him to San Diego, where he joined Dr. John Reed's lab at the Burnham Institute as a Leukemia and Lymphoma Foundation Fellow, focusing on caspases and apoptosis inhibitors. His work on IAPs (Inhibitor of Apoptosis Proteins) led to groundbreaking discoveries and numerous highly cited publications. Opportunities flooded in, including an offer to stay at the Burnham Institute. However, a chance encounter with Dr. Peter Schultz shifted his trajectory toward translation of basic research into drug discovery at the Genomics Institute of the Novartis Research Foundation (GNF). Quinn became one of the first discovery scientists, working on high-throughput screening for small molecules, antibodies, genome-wide cDNA and siRNA libraries targeting cell death pathways.

Despite his success, Quinn grew frustrated with interactions with big pharma bureaucracy, which he says consisted of too many meetings and not enough action. In response, he co-founded the biotechnology company Inhibrx with his post-docs Brendan Eckelman and Mark Lappe. Employing protein-engineering expertise, they developed a proprietary single-domain antibody platform. What started in a makeshift lab in a garage quickly grew into a thriving biotech company. Within two years, they secured a major deal with Celgene, providing funding and stability, and the development of laboratories on Torrey Pines overlooking the Pacific Ocean. By 2020, Inhibrx went public with 4 clinical programs. The first program, INBX 101, for alpha-1 deficiency was recently acquired by Sanofi, while the remaining oncology assets continue through various phases of clinical development through Inhibrx.

When his spouse of 32 years, Kristin, retired from UCSD in 2021, they

established the Deveraux Family Fund, which focuses on supporting education, medical research, and community support initiatives. Together with their children, Chase and Erin, they support a variety of non-profit organizations. Some notable projects have included psychedelic medicine research for PTSD and depression, supporting end-of-life care initiatives, and helping underserved students and faculty in Southern California through Bridge Labs. In addition, Quinn serves as an advisor, board member, and works with several biotech start-ups in San Diego.

Despite his high-intensity career, Quinn has always maintained an active lifestyle, staying grounded through rugby while in graduate school, and later jiu-jitsu, mountain biking, and fly fishing in Utah's Provo River. He cherishes time outdoors and values staying physically engaged and maximizing his time with family. His journey—from struggling student to scientist, entrepreneur, and philanthropist—serves as a testament to the importance of perseverance, adaptability, and surrounding oneself with the right people. He encourages young scientists to cast a wide net, embrace challenges, and always look for ways to differentiate themselves in their field. Quinn is eternally grateful to Marty Rechsteiner and the many mentors in the Biochemistry and Molecular Biology programs at the University of Utah.

HONORS, GRADUATIONS, AND TRANSITIONS

MAJOR FACULTY AWARDS & RECOGNITIONS

Minna Roh-Johnson was selected for the 2025 Outstanding Educator Award for the University of Utah Health Sciences Graduate Students.

Yang Liu and his lab won a new Neon NxT electroporation instrument from ThermoFisher.

Congratulations to the Biochemistry Department HIV Center researchers for their foundational research on the HIV-1 capsid and support for the development by Gilead Sciences of the HIV prophylactic, Lenacapavir, which was selected as 2024 Breakthrough of the Year by Science Magazine.

Minna Roh-Johnson received a large NCI Administrative Grant Supplement to Recognize Excellence in Diversity, Equity, Inclusion, and Accessibility (DEIA) Mentorship that recognizes "scientists who have demonstrated compelling commitments and contributions to enhancing diversity, equity, inclusion, and accessibility (DEIA) in the biomedical sciences."

Keren Hilgendorf's research project, Harnessing Lean Fat Cells to Kill Breast Cancer, was selected for funding through the Philanthropic Partners Group, and thanks to UU HSC Advancement for creating this group.

Helena Safavi-Hemami's work on cone snail toxins was featured in a cover story of the Sunday Times print magazine on November 17th entitled: "What We Can Learn from Venoms".

Peter Shen, David Belnap, Barbie Ganser-Pornillos, and others organized a very successful and well attended university-wide symposium on cryo EM.

Justin English was selected as the UU "Innovator on the Rise" as part of the UU Innovation Awards Program.

Minna Roh-Johnson, Kevin Hicks, and Jared Rutter had their research advances on macrophage transfer of mitochondria to promote cancer cell proliferation (Minna) and MIDAS (Kevin and Jared) included in Discovery and Innovation at University of Utah Health, which highlights top recent research advances made by today's U of U Health scientists. The digital archive and accompanying publicity campaign, called Pioneering the Future, celebrates impactful research with a goal of reaching the U community and leadership, legislators and potential donors, and the general public. New discoveries are highlighted on an annual basis through a vetted process.

Wes Sundquist was awarded the Horwitz Prize from Columbia University, together with Scott Emr, for their work on the cellular ESCRT pathway.

MAJOR GRADUATE STUDENT & POSTDOC AWARDS

Graduate student **Meghan Curtin** (Hilgendorf lab) was invited to participate in the Moffitt Cancer Center Innovators of Tomorrow Symposium for promising predoctoral students.

Taylor Stevens, a postbac scholar in the Roh-Johnson lab, was awarded a diversity supplement from the NCI.

Kade Loverdige and **Radeck Omelianczyk** (Sigala lab) were awarded a Best Talk and Poster Honorable Mention, respectively, at the 2024 Molecular Parasitology Meeting.

Queren Alcantara (Rutter Lab) received a 2024 ASCB Cell Bio travel award, and got selected to give a talk at the Metabolism and Biosynthesis scientific symposia at the 2025 ASBMB national conference.

Luis Cedeño-Rosario (Rutter lab) was selected to give a talk and chair a session at the 2024 NDiSTEM SACNAS conference. He was also selected to give a talk at the 2024 ASCB Organelles and Extracellular Vesicles Microsymposium. Luis also received a 2024 ASBMB Molecular Motifs Bioart Competition Award (image featured in the 2025 ASBMB calendar) and was selected to give a talk at the 2025 ASBMB national conference.

Juan Cantres-Vélez and Katrarina Heyden (Rutter Lab) were awarded positions on the PITCH Chemical Biology T32 Training Grant. Juan also received a 2024 Twist Bioscience Gene-ius Grant runner-up award. **Tarun Yadav** (Rutter Lab) was awarded an AHA Predoc Fellowship.

Grant Schlauderaff (Liu lab) was awarded a position on the Genetics T32 training grant.

Nathan Krah (Rutter Lab) was awarded an F32 Kirschstein-NRSA postdoctoral fellowship.

GRADUATIONS & TRANSITIONS

Steven Draper (Kay lab) moved to the Mayo Clinic as a Peptide Chemist.

Zach Wilson (Hughes lab) started a new position as an Assistant Professor of Biology at Pitzer and Scripps College.

Adedji (Deji) Aderounmu (Bass lab) started a postdoc fellowship in Kathy Collins' lab at UC Berkeley.

Kristina Magee (Rutter lab) started a position as an Associate Director of Lab Operations at Teiko Bio.

The following students completed their degrees since the last publication of the newsletter in Fall 2024: Emily Pitsch (Hughes lab), Michael Stewart (Shen lab), Mitchell Wopat (Hughes lab), and Kyle Dunlap (Ducker lab).

KUDOS AND THANKS

Thanks to the Bill Rutter Foundation! They provided our department with a very generous gift that fund the purchase of an Oroboros instrument for measuring oxygen consumption, which will be made available to all metabolism researchers at the University of Utah.

Thanks to Brian Allen and Rachel Merrill! Our New England Biolabs Recharge Center, which helps us to offset administrative staff costs, did 17% of all NEB business at the University of Utah in FY24. NEB also praised the ordering system that Rachel put in place.

Thanks to Brian Kelly (UU Biochemistry PhD)! His generous financial gift forms the anchoring gift for our Biochemistry Trainee Childcare Support Fund, which will be the focus of our 2025 UGiving Day Event.

Thanks to Dana Carroll! His generous financial gift, coupled with a gift from the Firuza Foundation that was facilitated by Peter Bower and Chris Hill, enabled us to upgrade the Carroll Endowed Professorship in Biochemistry. Adam Hughes will continue in this position, which is now an endowed Full Professorship.

Thanks to Matt Miller, Helena Safavi-Hemami, Keren Hilgendorf, Julie Kirby, and Megan Hendrickson! The fall, 2024 Biochemistry Department Retreat was also a smashing success.

Thanks to Paul Sigala and the other organizers! The fall, 2024 Postdoc Rising Stars and McCloskey Lecture Event was better than ever.

Thanks to Peter Shen, David Belnap, Barbie Ganser-Pornillos, and others! They organized a very successful fall, 2024 EM symposium.

Thanks to Quinn Devereaux (UU Biochemistry PhD)! His generous financial gift to the Biochemistry Development Fund will provide critical support for our teaching and research missions, postdoctoral and graduate training opportunities, state-of-the-art equipment and emerging technology, and initiation of new programs.

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

HEALTH
UNIVERSITY OF UTAH

Lenacapavir is Science Magazine's 2024 Breakthrough of the Year

Annually, Science magazine chooses scientific advances that have occurred in the prior 12 months and identifies one as the Breakthrough of the Year. For 2024 the journal chose the development of the novel HIV drug lenacapavir by Gilead Sciences. This remarkable molecule binds to the HIV capsid and interferes with multiple steps in the infectious cycle.

The design of lenacapavir is based on structures of the viral capsid determined in the Sundquist, Hill, and Pornillos labs, who also set the stage for lenacapavir in other ways. In two large phase 3 clinical trials, lenacapavir was demonstrated to be almost 100% effective in preventing HIV infection in populations at risk in Africa and elsewhere. Protection lasts at least 6 months after a single dose and is more effective than current drug regimens for pre-exposure prophylaxis (PrEP).

An associated video released by Science has a further discussion of lenacapavir and its implications, including comments from Wes himself.

https://www.science.org/content/article/breakthrough-2024#section_video