10-YEAR REPORT
2013-2023

Building a foundation to propel innovation

Reflecting on the first decade of Sarafan ChEM-H

Sarafan ChEM-H
Stanford University

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Message from Carolyn Bertozzi, Baker Family Director

An institute built for the future of academic research

When Chaitan Khosla, the founding director of Sarafan ChEM-H, came to me 10 years ago to describe the institute he was building at Stanford, I was thrilled. He envisioned a hub of diverse, interdisciplinary research that brings together chemists, biologists, engineers, and clinicians who embrace collaboration and foster scientific creativity. Our name embodies our ethos: by breaking down disciplinary boundaries between **ch**emistry, **e**ngineering, and **m**edicine we could tackle more problems in **h**uman health than any of us could address alone. I am grateful that he—and all of you—entrusted me with the responsibility of leading this institute into its next phase.

The beauty of building for the future is that we are never done, and I am proud of what we have accomplished in our quest to construct an institute that invites misfit molecular scientists to tackle some of the most challenging problems in human health.

We have hired 17 exceptional faculty members researching ground-breaking next-generation therapies, antibiotic resistance, and cellular engineering. Over the last 10 years, these amazing scientists have won numerous prestigious awards, like the Eli Lilly Award in Biological Chemistry and the Ono Pharma Breakthrough Science Initiative Award; been elected to the National Academy of Sciences; and been awarded distinguished grants, among many other honors. As we look to welcome three more Institute Scholars, starting with David Cox in 2025, I am filled with optimism and excitement.

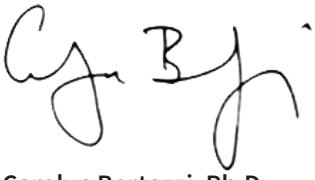
We have also established the Knowledge Centers, first of their kind collaborative labs staffed by professional scientists who bring sophisticated tools and expertise in medical chemistry, metabolomics, structural biology, protein engineering and high-throughput screening to Stanford labs.

In addition, we have stood up two major initiatives, the Stanford Innovative Medicines Accelerator (IMA) and the Stanford Microbiome Therapies Initiative (MITI), which are poised to translate discoveries made in our labs into entirely new kinds of therapeutics.

I am perhaps the proudest, though, of our investment in our undergraduates, graduate students, postbaccalaureate researchers, and postdoctoral scholars, who are the heart of academic research. Preparing them to be the scientific leaders of tomorrow, and creating a more diverse, equitable, and supportive academic environment is our priority. Through programs like the Chemistry/Biology Interface (CBI) Predoctoral Training Program, we are creating new models for cross-interdisciplinary education that both diversify the pipeline and establish supportive structures to improve retention.

I hope you will join me in celebrating a decade of interdisciplinary innovation and community. More than that, I hope you will join me in celebrating what is to come at Sarafan ChEM-H, an institute built for the future of scientific research.

Sincerely,



Carolyn Bertozzi, Ph.D.

Baker Family Director, Sarafan ChEM-H

Anne T. and Robert M. Bass Professor in the School of Humanities and Sciences

Professor of Chemistry and Professor (by courtesy) of Chemical and Systems Biology

Investigator, Howard Hughes Medical Institute

Photo credit: Christopher Michel.

A new name for our institute

In honor of a foundational gift from university trustee Lily Sarafan, BS ’03, MS ’03, Stanford ChEM-H changed its name to Sarafan ChEM-H. The investment will expand research in complex fields such as cancer, vaccines, immunology, the microbiome, and the molecular mechanisms of aging; help fund student training programs; attract new faculty; and fortify the Knowledge Centers at Sarafan ChEM-H.

Sarafan ChEM-H
Stanford University

“From the beginning, it was clear that this institute would be unlike any other in the world. Lily’s generosity will help ChEM-H continue to shift the culture of academic research at the university and advance scientific knowledge for the benefit of humankind.”

Carolyn Bertozzi, Baker Family Director of Sarafan ChEM-H

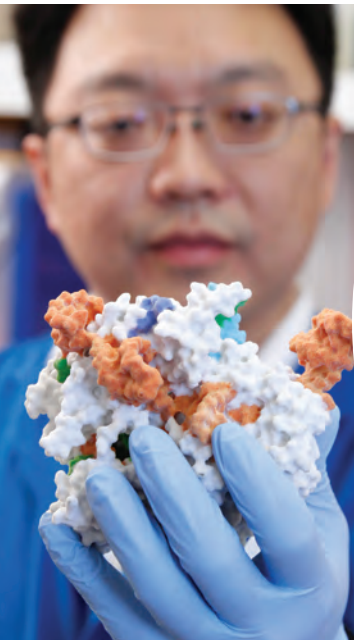
“This gift is playing a pivotal role in Stanford’s vision for the future. A decade from now, there will be stories about scientific advances launched at Sarafan ChEM-H that are impacting human health in a very real way.”

Chaitan Khosla, founding director of Sarafan ChEM-H, Director of the Stanford Innovative Medicines Accelerator

“ChEM-H represents a new kind of flexible research model—one that successfully bridges theory and practice to speed up the translation of basic science into applied discoveries. As a passionate supporter of the life sciences and a longtime admirer of Carolyn, I’m inspired by the way ChEM-H emphasizes diversity of all forms to recruit and train a new generation of entrepreneurial researchers. It will take a broad range of disciplines, experiences, and people to maximize the impact of world-class science on human health.”

Lily Sarafan, BS ’03, MS ’03

Photo credit: Andrew Brodhead.



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Meet the Sarafan ChEM-H Institute Scholars

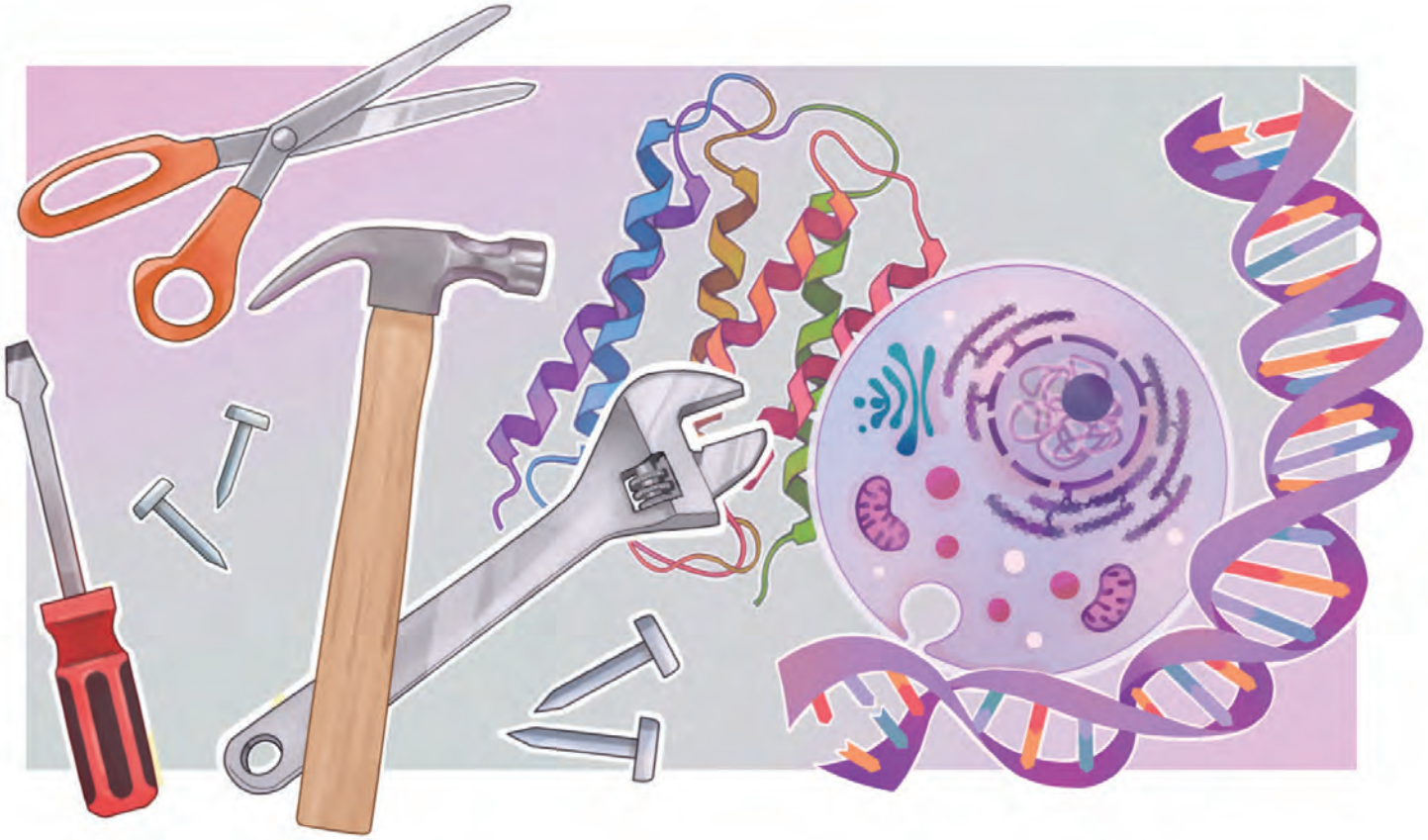
Scientific misfits tackling interdisciplinary problems

In collaboration with departments in the Schools of Engineering, Medicine, and Humanities and Sciences, Sarafan ChEM-H has recruited and hired 17 faculty members, known as Institute Scholars. When viewed through a traditional academic lens, these Institute Scholars have little in common.

In this diverse group are **Nicole Martinez**, who is unraveling how small changes to the chemical structure of RNA affect which genes are expressed in our cells and when; **Michael Fischbach**, who is developing new ways to build complex microbial communities from the ground up; and **Lingyin Li**, who is uncovering and ultimately undermining the ways cancer cells evade detection by the immune system. But at their heart, these scholars are all scientific misfits who refuse to limit themselves to research questions, tools, and approaches of a single discipline. These pioneers are tackling problems and inventing solutions in a variety of areas. They are the tool builders, cancer drug hunters, molecular trackers, emerging disease fighters, and immune system wranglers who are shaping the future of science and medicine.

Michael Fischbach
Bioengineering & Microbiology and Immunology

Lingyin Li
Biochemistry



Tool builders

Molecular and cellular engineering and biophysics

Cells are complex and highly specialized machines, capable of performing and coordinating all the small tasks that together allow organisms to live and grow. To unravel and manipulate those pathways, Sarafan ChEM-H researchers are developing tools that precisely manipulate individual cells or specific contents within them, creating new platforms to better understand how cells work and what exactly goes wrong in diseases.

Polly Fordyce
Bioengineering & Genetics

Proteins are the molecular machines of the cell. Each protein is made of a linear chain of amino acid building blocks that folds into the right 3D shape to generate a functional machine capable of performing a variety of cellular tasks. Understanding how the amino acid sequence of a protein encodes its function would be transformative across medicine and engineering, from improving our ability to predict the health consequences of mutations to designing new enzymes for green chemistry and environmental remediation. Generating more data linking sequence to function is critical to gain this understanding, and **Polly Fordyce** is on a mission to do just that.

Her lab designs and fabricates microfluidic devices that contain channels the diameter of a human hair. Similar to how integrated circuits in electronics can precisely direct current to control electronic calculations, these devices can precisely manipulate tiny volumes of liquids to control biological reactions. The methods her lab has developed dramatically reduce the volumes of precious biomolecule reagents that are required for biological

Illustration credit: Cindy Lin.

experiments and speed the pace of discovery by making it possible to perform thousands of experiments in parallel. And her approach is adaptable, allowing them to tackle diverse biological problems.

Among her many projects are investigating how the proteins that regulate gene expression in cells decode their DNA instructions, inventing a system to compress years of experiments on enzymes into weeks, and developing a method to better predict which antigens will trigger specific immune cells to act by mimicking the physical forces acting in the body.

Other researchers build different kinds of tools that can be inserted directly into cells, tools that harness the power of and manipulate the machinery in our cellular construction sites.

Lei Stanley Qi
Bioengineering

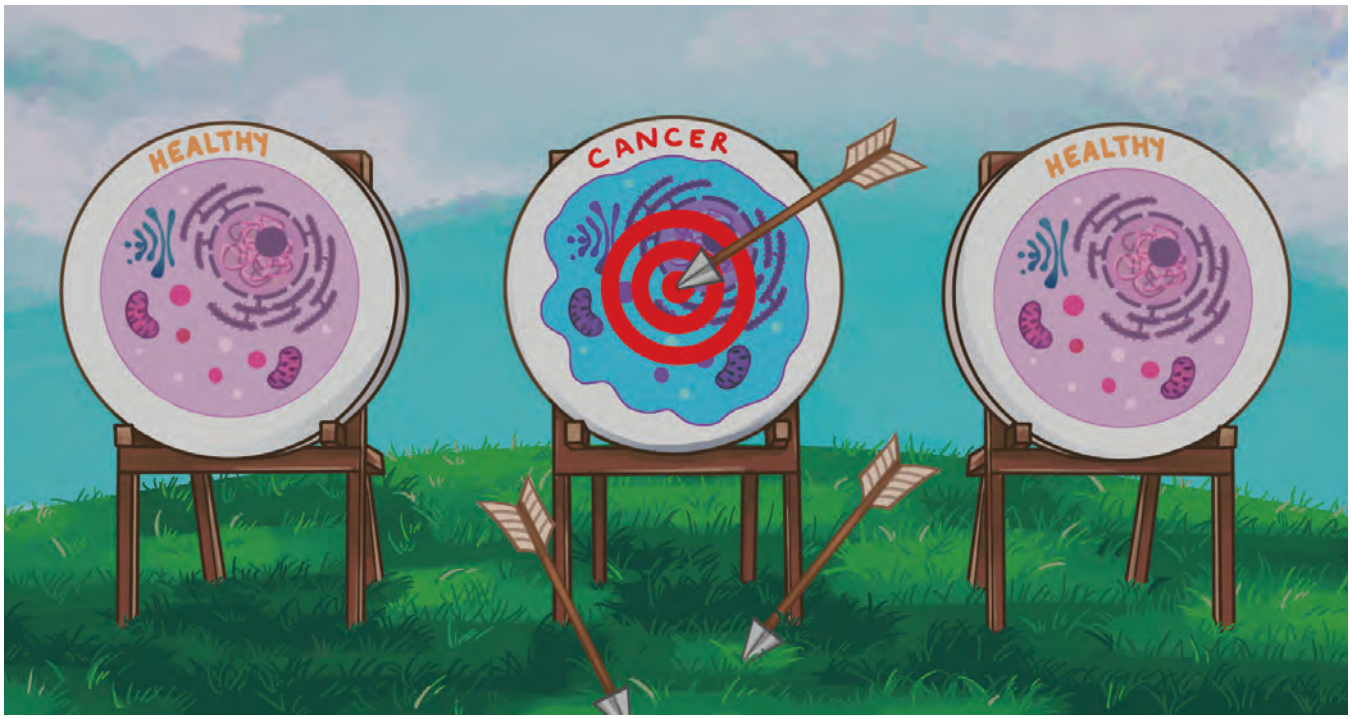
Lei Stanley Qi has made groundbreaking contributions to the field of genome editing using the CRISPR toolbox. With his visionary approach, he has taken CRISPR technology beyond traditional gene editing and opened a new frontier for studying the genome and treating diseases. His innovative approach centers on manipulating how the genome is translated into protein, thereby manipulating cellular functions, without altering human genetic codes. This allows him to investigate the underlying messages encoded in the genome that lead to disease, and to correct those messages with minimal damage.

Among Qi's many breakthroughs is a miniaturized CRISPR system that is orders of magnitude easier to deliver into cells than the traditional CRISPR system. He has also developed a tool that allows for real-time visualization of gene editing as it occurs in living tissues. Additionally, his CRISPR "tweezers" precisely pinch off and relocate genes within a cell's three-dimensional genome, a new level of precision in gene editing. His breadth of vision is perhaps most visible in his response to the COVID pandemic. He developed a new CRISPR method that destroys the viral genome, intercepting the virus's ability to infect cells and replicate itself. By expanding the CRISPR toolbox while investing in methods to improve clinical safety and efficacy, his research promises to change the way we understand, diagnose, and treat disease.

Steven Banik
Chemistry

Expanding cellular rewiring beyond gene editing, **Steven Banik** is a new kind of cellular engineer. He combines chemical and genetic tools to leverage and redirect natural cell functions, envisioning a future in which scientists can convince a cell to use its own machinery to solve biological puzzles or even treat underlying diseases. Proteins and nucleic acids naturally perform many functions within cells, so what else could they be convinced to do, and how?

His lab is tackling a major problem that stands in the way of advancing promising protein and gene therapies: how do we get these medicines across cell membranes and into cells, where they can have their therapeutic effect? When a cell internalizes a protein, it swallows it and keeps it stored in intracellular bubbles called endosomes, and Banik is discovering new ways to hijack this process. However, as long as that therapeutic cargo remains tucked inside those bubbles, it has no effect on the cell at all. Without something to encourage the surface of these endosomes to rupture, even the most promising new drug remains inert. Banik is developing tools that tag along with the valuable cargo until it gets wrapped up in the endosome, at which point it chews through the endosomal membrane to allow the intact cargo to be released into the cell. Banik is leveraging cellular sensor systems which can provide signal amplification readouts upon gain, loss, or relocalization of a protein to help develop these new therapeutic strategies and discover biological mechanisms.



Cancer drug hunters

Next generation cancer therapies

Despite tremendous advances in the last century in understanding the molecular underpinnings of cancer, most cancers remain incurable. The scientists at Sarafan ChEM-H are digging deeper into cancer's biology to understand and ultimately dismantle each of cancer's defenses in their quest to hunt down new kinds of cancer therapeutics. By zeroing in on three different kinds of biomolecules—proteins, DNA, and sugars—these scientists are leaving no stone unturned.

Nathanael Gray
Chemical and Systems Biology

Cells are busy places, and proteins are often at the center of the action, orchestrating processes like making and recycling molecules, launching an immune response, and helping your muscles contract. They also are at the center when those processes go awry in different diseases, making them alluring drug targets. Traditional drugs work by sliding into and blocking key pockets in these proteins. Many of the most promising cancer drug targets lack this pocket and remain "undruggable" using currently available technologies. **Nathanael Gray** is a drug hunter, inventing new approaches to drug proteins by applying the principles of chemistry to increasingly complex therapeutics. His lab has developed innovative approaches that leverage and redirect cellular functions to help cells fight back against cancer.

One approach involves targeting proteins that allow the immune system to select cancer cells for destruction. Their drug prototype convinces the cell to degrade a certain protein, thereby activating T cells to better kill tumor cells. In a second approach, his team collaborated with the lab of **Gerald Crabtree** to develop a new class of drugs that trick cancer-causing proteins to activate apoptosis, a natural cell suicide program. By convincing cancer-drivers to signal cell death, the new drugs rapidly

Illustration credit: Cindy Lin.

eliminate tumors in experimental mouse models. Both approaches are part of a broader effort called "proximity-based" therapeutics, so named because they reprogram cellular function by bringing two proteins together.

Paul Mischel
Pathology

For decades, clinicians and scientists have been troubled by an observation: cancer cells evolve faster than classical genetic inheritance rules dictate. Beyond merely a curiosity, it's dangerous; that power allows cancers to become resistant to drugs before the drug has a chance to work, and it may be why the most aggressive cancers are so difficult to treat. Solving that puzzle could change the outcome for millions of people worldwide who every year develop cancer. **Paul Mischel** got to the bottom of the mystery. He peered into cancer cells and found circles of DNA floating outside chromosomes, the home of DNA in healthy cells. By untethering themselves from chromosomes, these circles, which contain cancer-causing genes, drive aggressive tumor growth and enable cancers to change their genomes quickly. Hiding in plain sight, extrachromosomal DNA or ecDNA is a formidable challenge, affecting at least 20% of people with cancer. This work has catalyzed a paradigm shift in the field. Mischel has assembled a team of world-renowned scientists through the Cancer Grand Challenges Program funded jointly by Cancer Research UK and the National Cancer Institute to tackle ecDNA. In collaboration with **Howard Chang** and an international team of researchers, clinicians, and patient advocates, Mischel is learning more about how ecDNA works and developing new ways to better diagnose, monitor, and treat patients with the most aggressive cancers.

Bertozzi faced an early roadblock in her quest to unravel the secrets of sugars: the tools to study them did not exist. To learn more about these sugars, she needed a way to attach a label to and follow them. By developing chemical reactions that can proceed inside living cells without disrupting normal cellular function, collectively called bioorthogonal chemistry, Bertozzi catalyzed an explosion in glycobiology and was recognized with the 2022 Nobel Prize in chemistry.

Carolyn Bertozzi
Chemistry

While Mischel looked into the cell, others looked outside the cell for answers. **Carolyn Bertozzi** is fascinated by a different pressing mystery: what is the role of the dense forest of sugar molecules, or glycans, that decorate the surface of all the cells in our bodies? This is a pressing question for Bertozzi. For more than 50 years, scientists have wondered why cancer cells have drastically different surface sugar landscapes than their healthy counterparts, including a dramatic increase in the amount of one sugar called sialic acid.

All immune cells have on their surface protein receptors called Siglecs, and Bertozzi and others suspected Siglecs could be turning "off" immune cells in response to binding sialic acid. Could blocking the sialic acid/Siglec interaction uncloak the cancer cells and provide the immune system a chance to attack?

Since sialic acids are also present on healthy cells, she needed a way to block that interaction only on cancer cells. Her solution was a sialic acid lawn mower, a drug that first parks itself on a cancer cell and then cleaves all the sialic acids from the surface. In mouse studies, it cured breast cancer tumors that were resistant to all other therapies, including other immunotherapies. This strategy is the basis of a drug now in clinical trials.

Molecular trackers

Metabolism and molecular messages

In breaking down the food we eat, our cells produce a huge number of metabolites, molecules that the cell puts to work in building up new pieces of the cell, sending messages between cells, and regulating a complex suite of functions. Many diagrams of metabolic pathways are overly simplified, and mind-boggling numbers of metabolites—perhaps millions—remain undiscovered or poorly understood. By identifying and learning how, when, where, and why metabolites are made, Sarafan ChEM-H researchers are uncovering links between metabolism and health and discovering new ways to treat metabolic disorders like diabetes, neurodegenerative diseases, and cancers.

Jonathan Long
Pathology

Jonathan Long is puzzled by a deceptively simple question: how does our body process and use energy? The metabolic tissues of our body—muscles, heart, liver, fat, stomach—are all involved in a joint effort, coordinated by metabolites, to process energy. These metabolites are connected through a web of enzymes that make them, transporters that ferry them across cell membranes, carriers that shuttle them between tissues, and receptors they act on. He aims to create new maps that help us navigate the largely uncharted ground of mammalian metabolism.

Of particular interest to Long is exercise. What, molecularly, is happening when we exercise? And are those molecules linked to the intensity of the workout? To answer his questions, he used mass spectrometry, a set of tools that helps scientists determine the weights and identities of molecules in a mixture. First in mice, and then in racehorses and humans, he saw something remarkable: after high-intensity exercise, one molecule in the blood always spiked, dwarfing the changes in all other small molecules.

Illustration credit: Cindy Lin.

This metabolite is called lac-phe, a shortened name of lactate and phenylalanine, the two compounds that are fused together in this molecule, and the team learned that it's responsible for suppressing hunger after intense exercise. They even found that mice given this "anti-hunger molecule" without exercising ate 30% less than those not given any lac-phe. By better understanding how lac-phe works, they hope to gain a deeper picture of the molecular pathways involved in exercise and their connection to metabolic disorders.

Monther Abu-Remaileh
Chemical Engineering & Genetics

Others look inside cells to uncover new metabolites. Small but mighty, lysosomes play a surprisingly important role in cells despite their size. Making up only 1-3% of the cell by volume, these sacs are the cell's recycling centers, home to enzymes that break unneeded molecules into small pieces that are then assembled to form new ones. Lysosomal dysfunction can lead to a variety of neurodegenerative or other diseases, but without ways to better study the inner contents of lysosomes, the exact molecules involved in diseases—and new drugs to target them—remain elusive. **Monther Abu-Remaileh** has developed a method to uncover all the small molecules floating around in any lysosome in a mouse.

Using their method, called LysoTag, his lab members can selectively collect all the lysosomes in particular cells of a mouse at any time, like after fasting or feeding them a specific food. They can then break apart the lysosomes and identify the molecules that had been tucked inside. Those that grow or shrink would point scientists to certain pathways or functions.

Using this tool, he has learned more about the cause for Batten disease, a currently untreatable neurodegenerative disease. He found that molecules called glycerophosphodiesters, or GPDs for short, which naturally form during degradation of the fatty molecules that make up cell membranes, grow to potentially toxic levels. This finding could give scientists a new way to monitor and one day treat the disease.

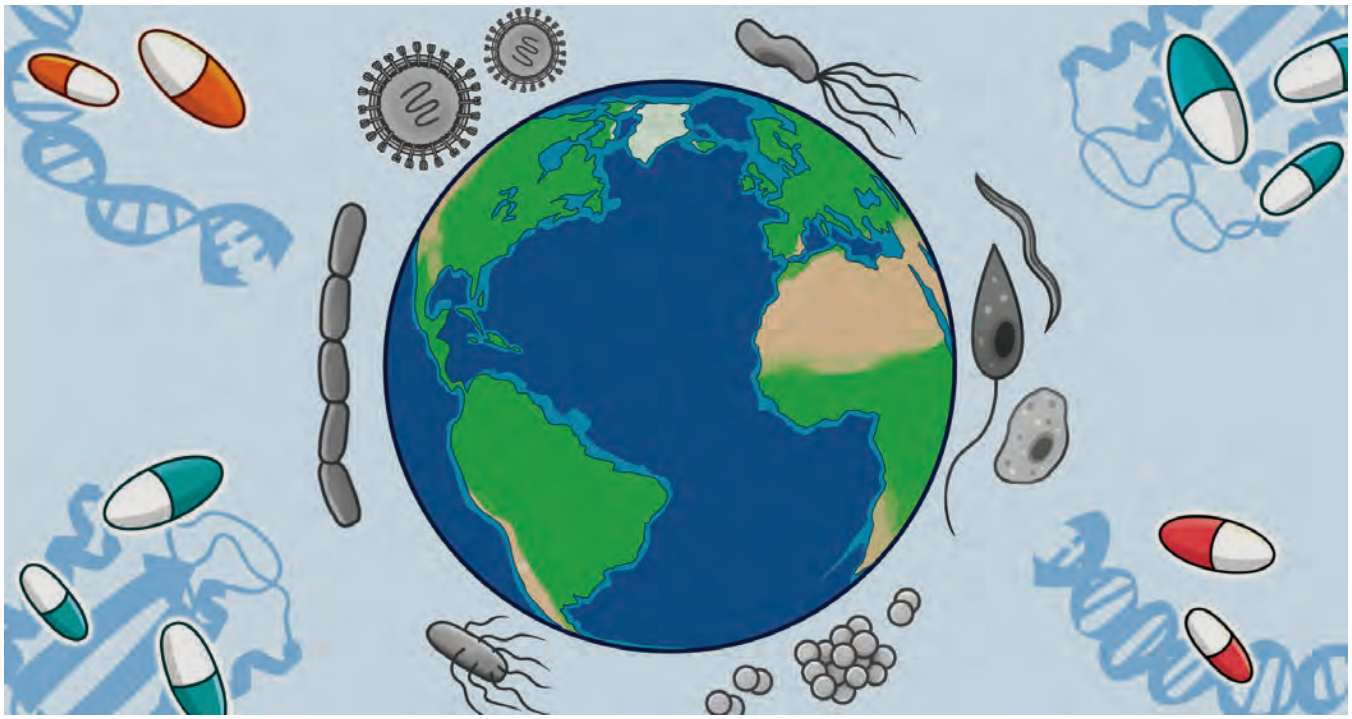
These mice are freely available to the scientific community in the hopes that they could help researchers learn more about the role of the long-overlooked lysosome in disease.

Nicole Martinez
Chemical and Systems Biology & Developmental Biology

Beyond the metabolites that flow between and within cells, our bodies rely on another important molecular messenger: messenger RNA (mRNA). DNA is the cell's permanent genetic material, contained in its entirety in every cell in our body and comprising the instructions for making all the proteins any cell could ever need. DNA first gets transcribed into precursor mRNA or pre-mRNA, which, like all types of RNA, is made up of four unique building blocks or bases, represented by the letters A, C, U, and G, organized in one long sequence.

Through splicing, some segments, called exons, are stitched together, while others, called introns, are discarded, to form mRNA. Exons are like words that can be pieced together in different ways, and it's the final mRNA sentences that determine which protein is made. The different ways of splicing (alternative splicing), plus chemical modifications in pre-mRNA and mRNA, are part of the cell's complex process of gene regulation, the series of mechanisms that dictate what proteins get made and when. **Nicole Martinez** studies pseudouridine, a modified version of the canonical base uridine. She discovered that pseudouridines are found in critical pieces of pre-mRNA, like near splice sites and in regions that bind to proteins. And the enzymes that install pseudouridines impact alternative splicing, effectively changing the genetic messages in a cell. Those enzymes are also connected to cancer, autoimmune diseases, and neurodevelopmental disorders. But why, and how?

Martinez wants to know more about the role of these pseudouridines, how they affect splicing, and why they appear in certain places, hoping to better understand gene regulation and ultimately reveal new drug targets.



Emerging disease fighters

Antibiotics, antivirals, and infectious diseases

Drug resistance and emerging infectious diseases are among the biggest global health challenges facing society. By uncovering the molecules involved in how pathogens elicit and evade immune responses, and discovering the complex relationships between our immune system and the human microbiome, Sarafan ChEM-H scientists are pioneering a new generation of anti-infectives.

Christine Jacobs-Wagner
Biology & Microbiology and Immunology

For **Christine Jacobs-Wagner**, fighting pathogens starts with fundamental scientific discovery. She has long been fascinated by self-replication, one of the most critical functions of cells. She has focused on studying the replication of bacteria, both because they are important to human and environmental health and also because they are simpler than other kinds of cells. They are the ideal "playground" to study the most basic ways cells reproduce so that we may one day be able to develop ways to manipulate cellular replication.

Jacobs-Wagner has combined approaches from biophysics, quantitative imaging, genetics, and biochemistry to overturn simplified pictures of bacteria and recast them as highly organized. By closely regulating the movement and concentration of biomolecules throughout the cell, bacteria can control their cellular functions and morphologies. Among her most recent discoveries is how the intermolecular interactions between DNA and the cellular cytoplasm lead to the highly compacted yet organized structure of bacterial DNA.

And what started as curiosity-driven science has ballooned. If she could identify unique ways that different bacteria self-replicate, could she find ways to selectively target bad actors while leaving the other bacteria untouched? She has zeroed in on the Lyme disease-causing agent *Borrelia burgdorferi*. Her group

Illustration credit: Cindy Lin.

has discovered unusual chemistry in the bacterium's cell wall, which is made of a material called peptidoglycan. This cell wall material can cause inflammation and linger in the joints of Lyme disease patients, even months after antibiotic treatment. By better understanding the unusual biology of bacterial pathogens like *Borrelia*, scientists could develop new ways of treating not just bacterial infections but also complex symptoms.

Laura Dassama
Chemistry & Microbiology and Immunology

To develop better antibiotics and predict those that will have the best effect, we first need to understand why existing ones fail. **Laura Dassama** is investigating the problem of multi-drug resistance. Many pathogens have proteins that shuttle out antibiotics and other toxic molecules upon entering the cell, which buys them time while they develop other drug resistance strategies. Dassama is studying some of these efflux pumps to figure out which antibiotics can be transported this way and how.

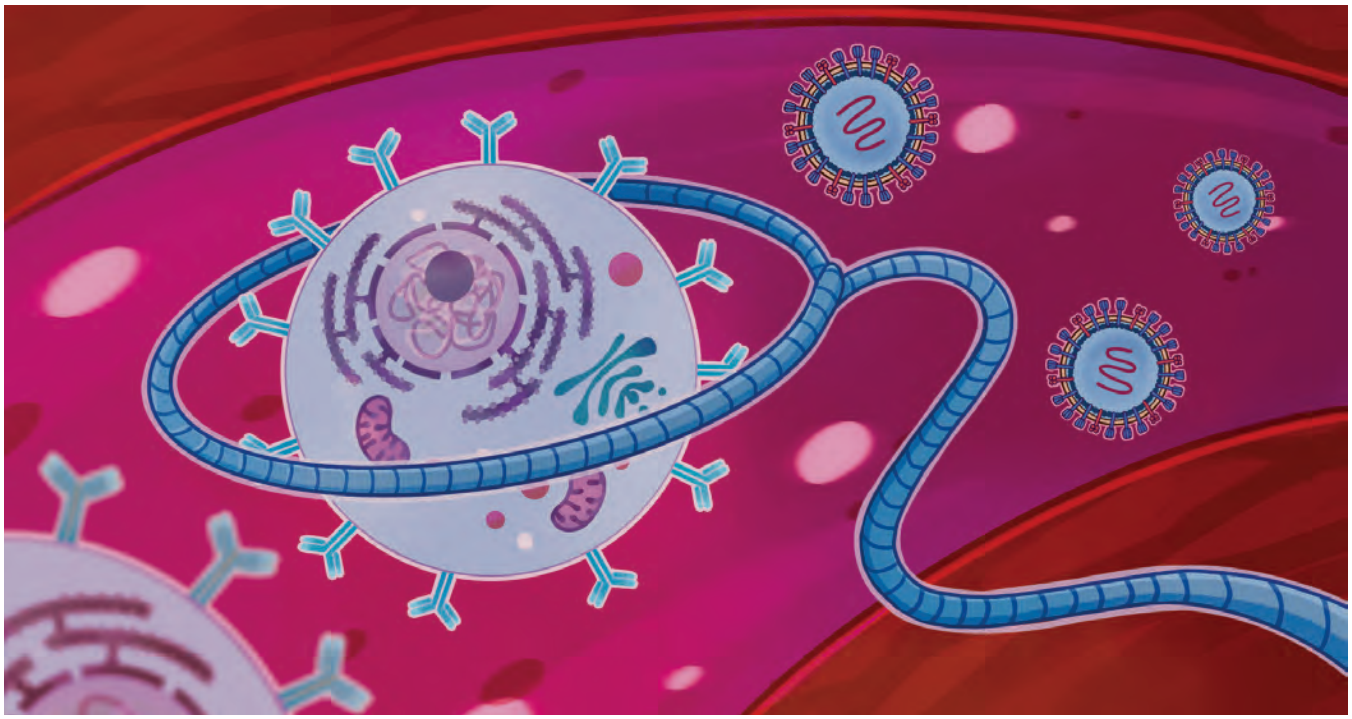
But learning how and why certain drugs get pumped out of cells before they have an effect is only half the challenge. Identifying those drugs that just might evade these resistance mechanisms—and figuring out ways to make them—is the other half. And that means developing ways of making a wide variety of structurally similar, bioactive molecules. Dassama has turned to nature for inspiration. Many of our antibiotic, antiviral, and antimicrobial agents are natural products, made every day by cells found in organisms around the world, and nature has developed ways of making complex products in modular ways. She is exploring one such class of modular molecules known as ribosomally synthesized and post-translationally modified peptides (RiPPs). These are compelling candidates because they allow for two dimensions of structural variety: the sequence of the peptide backbone chain and the identity of the chemical modifications that are installed on that sequence. By studying how small modifications impact efficacy, she hopes to engineer improved antiinfectives.

Chaitan Khosla
Chemical Engineering & Chemistry

In his quest to build new antibiotics, **Chaitan Khosla** also looks to nature. He studies a kind of molecule-making assembly line known as polyketide synthases, and they are responsible for making antibiotics like erythromycin. Polyketide molecules are large and complex, but these synthases make them time and again and with astonishingly few mistakes. He envisions that a more complete picture of how these assembly lines work with such precision will allow scientists to engineer them to make new antibiotics that are more effective against mankind's most problematic pathogens.

Each synthase contains anywhere between three to 30 sequentially organized enzyme "modules." Each module is a workstation in the assembly line that introduces an additional piece of molecular complexity to the overall structure of the polyketide molecule. Passing from module to module, the polyketide is incrementally elaborated upon until it eventually rolls off the conveyor belt in its final form.

The Khosla lab has tackled fundamental questions about how these assembly lines maintain such control, among them: how does the polyketide synthase ensure that its growing polyketide product always advances forward, not backward, along the assembly line? They identified what they call a "turnstile" mechanism, whereby each module adapts an asymmetric pose that both ensures it works on only one molecule at a time and helps propel that molecule to the next step.



Immune system wranglers

Vaccinology and immunology

Our immune cells are constantly patrolling our bodies to find signs of infection or disease. They maintain a balance between eliminating dangerous cells and protecting healthy ones through a complex series of molecular and physical triggers. Sarafan ChEM-H faculty are untangling those triggers and developing new tools to study and manipulate the immune system to develop new vaccines and therapeutics.

Hawa Racine Thiam
Bioengineering & Microbiology and Immunology

When **Hawa Racine Thiam** looks at an immune cell, she sees more than a living thing responsible for carrying out the processes that allow us to fight off infections. She sees a physical object that interacts with other cells and tissues that are soft or stiff, goes through channels that are wide or narrow, and experiences and exerts forces. To her, immune cells that weave their way through tissues and destroy pathogens are like elite athletes, capable of extreme cellular behaviors when pushed.

Among the extreme behaviors she studies is a process called NETosis in which a kind of immune cell called a neutrophil self-destructs, releasing its DNA outside the cell to form networks that trap invading pathogens. This process helps us combat bacterial or viral infections, but it can also be harmful in diseases like diabetes, rheumatoid arthritis, and cancer.

Another example of unusual cell behavior in neutrophils is in the shape of their nuclei. Most cells in our bodies have round, ovoid nuclei, and deviation from that rounded shape is one of the tell-tale signs of malignancy. But irregularly shaped nuclei are perfectly normal in many immune cells; neutrophils, for instance, have multi-lobed, doughnut-shaped nuclei.

Illustration credit: Cindy Lin.

By better understanding how and why immune cells adapt these behaviors, and what role physical forces have in biological functions, Thiam envisions that we might be able to engineer them—and other cells—to treat different conditions.

Christopher Barnes
Biology

To better leverage the immune system to fight infection, **Christopher Barnes** zooms in to see what is happening at the molecular level at the interface between immune cells and viral pathogens. He uses different tools of structural biology to learn more about the structures of antibodies and the viral proteins that stimulate their production, called antigens.

Using state-of-the-art techniques, like cryogenic electron microscopy (cryo-EM), he has focused on broadly-neutralizing antibodies, which target multiple strains of a virus, and their epitopes, the features on the surface of the virus that these antibodies bind to. If we could design a vaccine that elicits these superhero-like antibodies, then the body could be protected against any of multiple strains, and using those antibodies themselves as drugs could help stimulate a body already fighting off an infection. Techniques like cryo-EM allow him to create detailed molecular pictures starting from fuzzy outlines that transform into high-resolution models, whereby he can zero in on the key atoms present where antibody meets epitope and begin to understand which interactions are most critical to a productive immune response.

Long interested in developing a new vaccine for HIV, he shifted his research focus with the emergence of SARS-CoV-2 to try to unravel how antibodies target the spike protein that juts from the surface of the virus. He helped characterize several antibodies that were in clinical trials, and, more recently, has uncovered broadly neutralizing antibodies that could be useful to defend against future outbreaks of SARS-CoV-2 variants and emerging coronavirus strains.

Peter Kim
Biochemistry

Peter Kim discovered a pivotal component of how proteins cause many viral membranes to fuse with cells—a critical step in infection—including those of influenza, HIV-1, Ebola, RSV and SARS-CoV-2. He designed novel compounds to stop membrane fusion by HIV-1, and pioneered efforts to create an AIDS vaccine based on similar principles. He was president of Merck Research Laboratories for 10 years and oversaw development of more than 20 new medicines and vaccines, including drugs that treat diabetes (Januvia), HIV-1 (Isentress), and cancer (Keytruda), as well as vaccines against cervical cancer (Gardasil), shingles (Zostavax) and rotavirus (RotaTeq). He returned to academia and joined Sarafan ChEM-H in 2014, eager to apply chemical, biochemical, structural biology, and immunological techniques to understand antibody-mediated immune responses, with a focus on HIV-1, Ebola, and the flu, all with an eye for translation.

That focus informed his efforts towards developing a potential vaccine for SARS-CoV-2. His goal is to create a globally available vaccine that provides longer-lasting immunity against present and future viral variants. He developed a nanoparticle vaccine consisting of a spherical core decorated with modified versions of the viral spike protein present naturally on the virus. To enable global accessibility, his lab generated a cell line that can enable production of thousands of vaccine doses per liter of cell culture and showed that the vaccine maintains potency for at least 2 weeks even when stored above room temperature. The vaccine elicits a strong and long-lasting immune response in animals and is on track to be tested in humans in 2023.

Bertozzi wins Nobel Prize

On October 5, 2022, at 1:43 am, Carolyn Bertozzi woke to news that she had just won the Nobel Prize in chemistry for inventing the field of bioorthogonal chemistry, the set of chemical reactions that allow researchers to study molecules and their interactions in living things without interfering with natural biological processes. She shares the prize with Morten Meldal, professor at University of Copenhagen, and K. Barry Sharpless, professor at Scripps Research, for jointly developing click chemistry.

> "I am incredibly grateful to the students, postdocs, and researchers in my lab who brought this grand vision of performing reactions inside cells to life."
>
> Carolyn Bertozzi

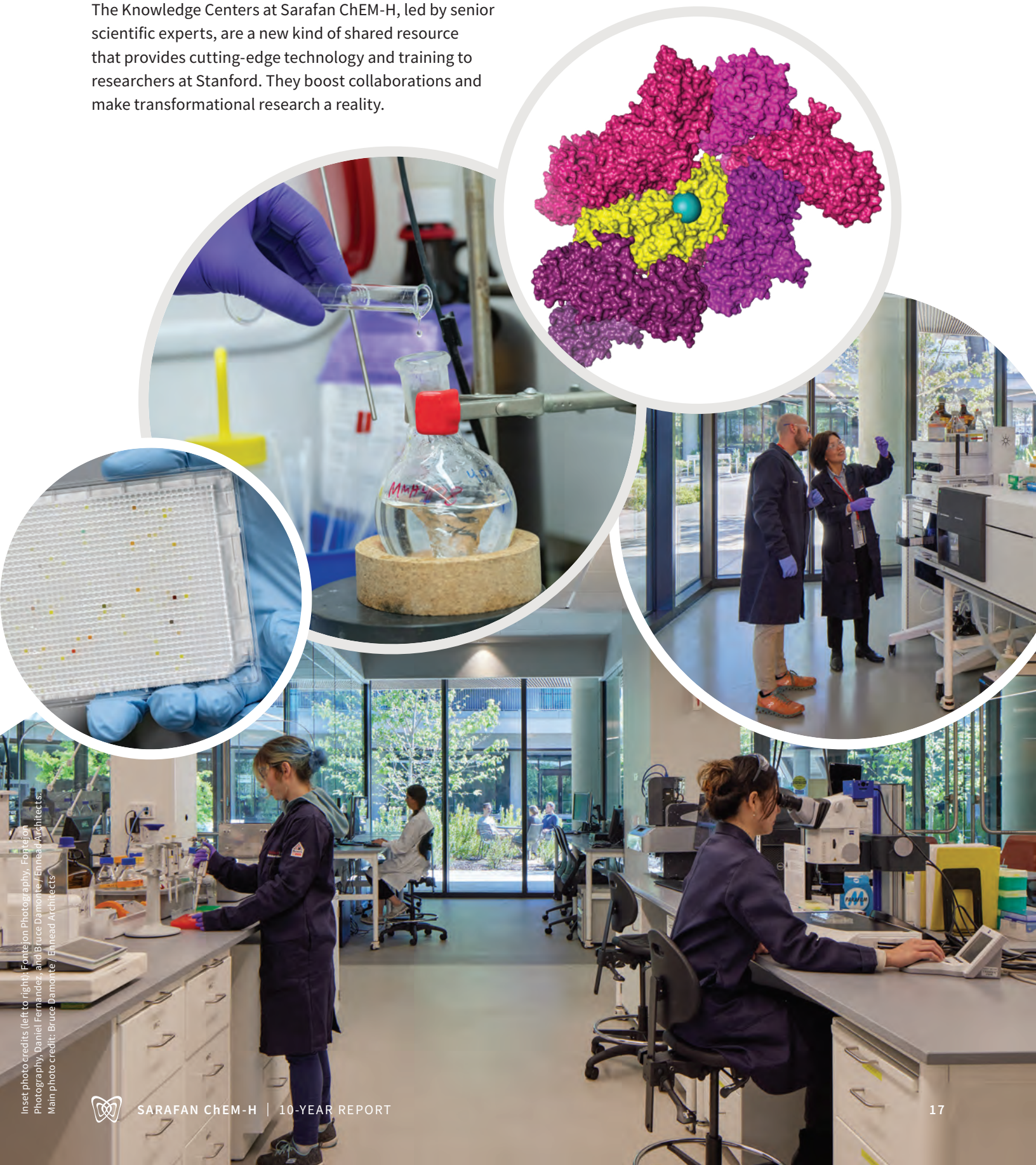
Her development of the field of bioorthogonal chemistry was born from necessity; she wanted to identify the roles that complex sugar molecules, or glycans, played in cells. She realized that if she could attach fluorescent tags directly onto those molecules, she could observe what they were doing in their natural environment. But attaching that tag without wreaking havoc on the cell was challenging.

Her quest to develop the first bioorthogonal reaction involved a lot of trial and error, but after digging up a hundred-year-old reaction known as the Staudinger ligation, her team had a winner. For the first time, they could visualize sugars in living cells. And this opened the door to countless applications in both visualizing and manipulating molecules in cells, among them new cancer treatments and energy storage materials.

> "Research at the interface of chemistry and biology has always been where I practice, and having a Nobel Prize in chemical biology is really great for the field. This is a celebration of chemical biology, of curiosity-driven basic science, and of collaboration."
>
> Carolyn Bertozzi

The Knowledge Centers at Sarafan ChEM-H

The Knowledge Centers at Sarafan ChEM-H, led by senior scientific experts, are a new kind of shared resource that provides cutting-edge technology and training to researchers at Stanford. They boost collaborations and make transformational research a reality.



Inset photo credits (left to right): Fontejon Photography, Fontejon Photography, Daniel Fernandez, and Bruce Damonte / Ennead Architects.
Main photo credit: Bruce Damonte / Ennead Architects

Bringing cutting-edge resources to Stanford labs

Bringing together scholars motivated to solve interdisciplinary problems is only part of the equation. Scientific problems, techniques and instrumentation can accelerate and pivot quickly, and Sarafan ChEM-H was built to anticipate and adapt to the rapidly changing landscape of human health research.

At the heart of this flexibility are the Knowledge Centers at Sarafan ChEM-H, collaborative labs staffed by experts in their fields who have the technical skill, experience and equipment to help researchers at the point when their project transitions from something purely biological or chemical, for example, into something interdisciplinary. And by welcoming researchers from across campus, these centers are democratizing access and ensuring that creative solutions are not stifled by expertise limitations in any given lab.

Medicinal Chemistry

Translating biochemical pathways or targets into drug prototypes

Mark Smith
Director of Medicinal Chemistry

Metabolomics

Identifying and quantifying small molecules in cells or tissues

Yuqin Dai
Director of Metabolomics

Macromolecular Structure

Visualizing the three-dimensional structure of biomacromolecules pathways or targets into drug prototypes

Daniel Fernandez
Director of Crystallography

High-Throughput Screening

Fishing a potential therapy from a sea of tens of thousands of drug-like molecules

Bruce Koch
Director of High-Throughput Screening

Protein Engineering

Designing antibodies and other proteins to probe or drug biological pathways

Adrian Hugenmatter
Director of Protein Engineering

Removing cancer's camouflage

Lingyin Li is fascinated by our immune system's ability to fight off cancer, and by figuring out how and why cancer cells sometimes avoid our immune system's advances. In her quest to uncover cancer's ability to evade the immune system, she has zeroed in on STING, an innate immune pathway that is responsible for monitoring our cells for suspicious signs and triggering the immune system to act. Her lab, which bridges chemistry, cancer biology, and medicine, has been busy unraveling how cancer camouflages itself and developing new ways to remove that disguise.

Jacqueline Carozza, a student in the Sarafan ChEM-H Chemistry/Biology Interface (CBI) Predoctoral Training Program, discovered, while working in Li's lab, that a small molecule called cGAMP is naturally pumped out of cancer cells and alters immune cells to attack. Unfortunately for patients, though, some cancer cells also have a way of hiding this vulnerability by making an enzyme called ENPP1 that chews up the "danger signal" before the alarm can sound. Could blocking ENPP1 pull the camouflage off cancer and allow the immune system to better attack?

To answer that question, Li's team turned to two of the Knowledge Centers at Sarafan ChEM-H. Working with **Mark Smith**, the Director of the Medicinal Chemistry Knowledge Center, Carozza, Li, and their team designed a set of molecules that would bind to and prevent ENPP1 from chewing up cGAMP. Injecting their molecule into mice resulted in not just shrinking tumors but also in completely curing 10% of mice when used in combination with cancer therapies.

And to develop an even better drug prototype, they turned to **Daniel Fernandez**, the Director of Crystallography at the Macromolecular Structure Knowledge Center. **Jenifer Brown**, another grad student in the lab, led the team that helped unravel the three-dimensional structure of ENPP1. Knowing more about the structure of the enzyme gave the team new insights to develop a new molecule that could block ENPP1 even more strongly. The team is hopeful that this could lead to a better way to treat cancer.

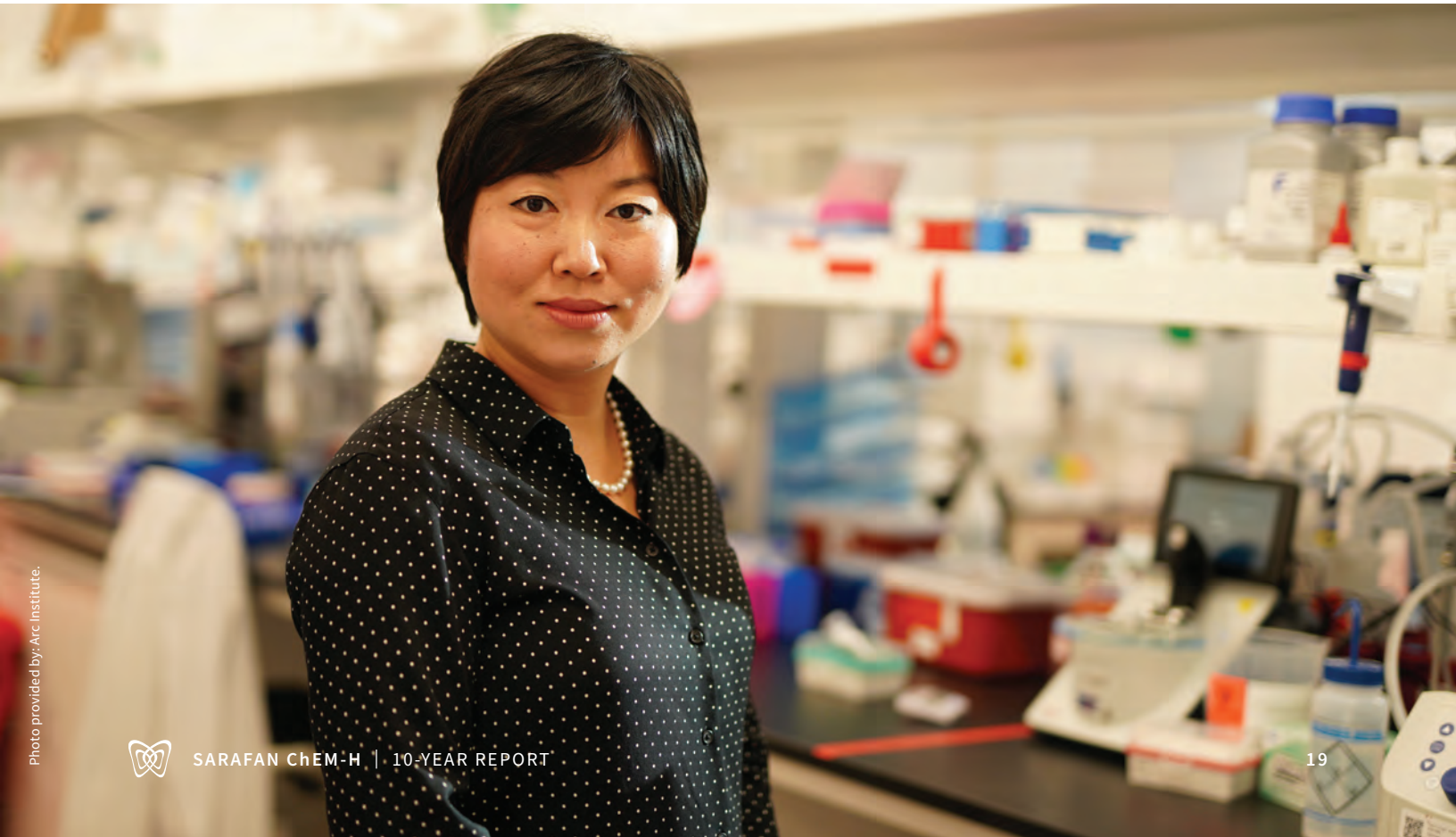


Photo provided by: Arc Institute.

Photo credits: Andrew Brodhead (upper left)
All other photo credits: Fontejon photography

Training the next generation of scientific leaders

Sarafan ChEM-H believes that to push the boundaries of our understanding of the biological mechanisms underlying human health, we need to leverage the power of diversity: diversity of disciplines — life, physical and clinical sciences — and most importantly, diversity of people. Central to our mission is training the next generation of scientists who are fluent in more than one scientific language, who are excited by problems that require collaboration across disciplines. As we transform human health through new discoveries, we simultaneously seek to contribute to the transformation of the biomedical workforce by increasing the diversity of highly skilled scientists in the pipeline.

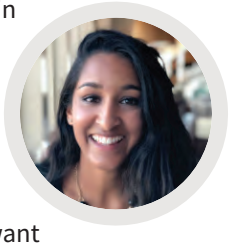
The first stage of Sarafan ChEM-H's institutional life has been characterized by the recruitment and training of young scientists poised to tackle important problems that do not fall neatly within disciplinary boundaries.

A new cadre of interdisciplinary graduate students

The **Chemistry/Biology Interface (CBI) Predoctoral Training Program** at Sarafan ChEM-H equips graduate students with the tools to solve big problems in human health through cross-disciplinary training. The program welcomes trainees from departments in the schools of Medicine, Engineering, and Humanities and Sciences, and teaches them to communicate across fields and identify areas ripe for discovery or collaboration.

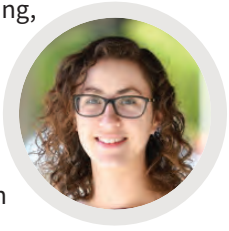
Over the course of the program, trainees take courses in chemical biology and translational medicine; participate in seminars, career panels, conferences, and retreats; and are given opportunities for professional development and community building.

"The CBI Program enriches the educational and research landscape of Stanford. It is the jewel in the crown of Sarafan ChEM-H," said Chaitan Khosla, the founding director of Sarafan ChEM-H, who serves as a faculty mentor for the program.



"Even if I can't be fluent in all the different fields represented by CBI, there is value in being able to think like another scientist, in going through their design and troubleshooting process. It is amazing to have this support system and source of inspiration as I carve out where I want to go with my career and think about the kind of short-term and long-term impact I want to have on human health."

Tara Murty, O'Leary-Thiry Graduate Fellow in Biophysics



"Research isn't easy. Even if you are working on something that you find very exciting, research can be challenging, stressful, and exhausting. And the only way to do it is with the support of the people around you, and I've found that in my lab and in ChEM-H"

Julieta Gomez-Frittelli, CBI student in Chemical Engineering

Diversifying the pre-graduate school pipeline

Started in 2021 by Sarafan ChEM-H and the Stanford Innovative Medicines Accelerator, the **Postbaccalaureate Program in Target Discovery** aims to help passionate early-career scientists traverse the gap between completing an undergraduate degree and matriculating into competitive graduate programs. This is a unique opportunity for recent college graduates to conduct full-time research for two years in a Stanford lab alongside experienced mentors and gain valuable experience while building their professional network.

With a focus on fostering diversity, equity, and inclusion, the program prioritizes the recruitment and retention of historically under-represented groups and seeks to level the playing field and make a lasting impact in the scientific community. By providing access to research opportunities and mentorship, the Postbac Program in Target Discovery is helping to build a more diverse and vibrant scientific community.

Entrepreneurial undergrads develop new therapeutics

Since 2016, the **Undergraduate Entrepreneurship Program** has invited teams of Stanford undergrads to leverage their academic training, curiosity, and vision to develop an idea for a new biotechnology company to address an unmet medical need.

After six months of developing a scientifically viable idea and a solid business plan under the guidance of academic and industrial mentors, the teams present their pitch to a panel of faculty and biotech executives. The winning team then receives $50,000 to pursue their plan.

The winning teams have tried to find solutions to diverse problems, from human papillomavirus, to antibiotic resistance and degenerative retinal disease.

In 2021, **Cesar Armas** ’21, **Karen Chen** ’22, and **Phillip Ipock** ’23 knew they wanted to tackle ovarian cancer. Ovarian cancer remains difficult to treat, partly because of its ability to manipulate the body’s immune system.

Team “Tremsara,” as Armas, Chen, and Ipock are known, impressed the judges with their sophisticated understanding of the clinical need for ovarian cancer treatments and clever idea for taking the brakes off the immune system.

In addition to research funds, the team also received access to the Medicinal Chemistry Knowledge Center, a state-of-the-art chemical and drug development lab in Sarafan ChEM-H. The Knowledge Centers house cutting edge equipment and employ professional scientists to help Stanford researchers turn fundamental discoveries into potential drugs.

The members of Tremsara spent over a year becoming medicinal chemists, first by reading up on cancer immunology and then by getting into the lab to build and test their therapeutic prototype.

In their search through papers, the students found that there was a protein within the tumor environment that seemed to dampen the body's immune response to cancer. The three students realized that if they could develop a way to get rid of that protein, the immune system would have a better chance of attacking the cancerous cells.

The next step was designing a drug. They ultimately settled on a molecule that would trick a natural cellular pathway into degrading the problem protein, which they hope will kickstart the immune system.

For Chen, who from the start advocated to her teammates about the need for better ovarian cancer treatments, the experience has been empowering. "It's helped me realize that if I see a problem, I have to go solve it, because maybe no one else has reason to," said Chen. "I feel more of an obligation to work on drug development in the future because now I know that I'm capable. And if I don't do it, who will?"

Building community, fueling collaboration

How Sarafan ChEM-H events catalyzed new research directions

CBI retreat sparks new understanding of flu infection

The flu virus relies on using human cells to reproduce and spread. But before it even gets to the cell surface, the virus must navigate the tall, dense forest of sugar-coated proteins on the cell surface known as the glycocalyx. Unraveling how the virus navigates these bushy proteins could be key to preventing infections.

Bette Webster and **Corleone Delaveris**, students in the labs of **Steven Boxer** and **Carolyn Bertozzi**, respectively, began collaborating after a conversation over breakfast at the 2017 Chemistry/Biology Interface Retreat. The pair recognized their shared interest in how mucins on cell membranes affect viral infection.

Mucins drew their interest for two big reasons. First, when cells are infected with viruses, they often begin making a lot more mucins. Though the genes involved in the process have mostly been identified, why cells do this is unknown. Second, mucins often contain a specific sugar, called sialic acid, that could tether the virus to a cell and help position it to bind to receptors on the cell surface.

They found that increasing the density of mucins on the surface inhibited two major steps of influenza A infection: the virus binding to the surface of the cell and the virus fusing its membrane with the host cell's membrane to release its genes into the host. These findings help explain the cell's natural response to infection and provide a foundation to better understand and treat the flu and other respiratory viruses. The team also hopes that their method will help researchers tackle other viruses that infect individuals through places like the lungs and respiratory tracts, which have mucin-rich mucous coatings.

Photo credit: Rebecca McClellan.

Postdoc retreat ignites new exploration of how cells self destruct

In 2015, **Jennifer Cao** and **Cole Dovey**, then postdoctoral scholars in the labs of **Scott Dixon** and **Jan Carette**, respectively, met at the Sarafan ChEM-H Postdoc Retreat and discovered that they shared an interest in cell death pathways.

Controlled cell death is a vital part of normal embryonic development and the destruction of disease-afflicted cells, but too much or too little cell death can mean disaster. With better understanding of why, when, and how cells self-destruct, scientists could use cell death signaling molecules as diagnostic markers or as switches to turn cell death on or off.

Two cell death pathways quickly came to the forefront of Cao and Dovey's conversation. Cao had been pulling apart ferroptosis, an iron-dependent process, while Dovey had zeroed in on necroptosis, a kind of cell death that involves the insides of the cell leaking out through an expanding, ballooning membrane.

Cao and Dovey were granted funding through the Sarafan ChEM-H **Postdocs at the Interface** program, then in its first year. This seed grant funds collaborative research between postdocs to answer questions at the interface of chemistry, biology, and medicine that could have big implications for human health. The team's complementary expertise and strategies let them attack cell death from multiple angles.

Together, the team discovered a gene that influences a cell's vulnerability to ferroptosis and that inducing ferroptosis could help kill cancers that are conventionally difficult to drug. They also found that a particular sequence of small molecules, which they refer to as a "death code," is partially responsible for the cascade that leads to the destruction of the cell membrane during necroptosis.

Design credit: Graham McLeod and Cole Dovey.

Sarafan ChEM-H impact in action

Accelerating new therapeutics

Sarafan ChEM-H was built with the expectation that by bringing creative scientists together, encouraging them to follow unconventional paths, and supporting interdisciplinary research, new ways to improve human health would naturally arise. And when faced with the challenge of how to support these targeted directions, Sarafan ChEM-H is committed to helping those ideas flourish by bringing together the people and resources that turn a promising vision into new therapeutics. The rich, diverse playground of Sarafan ChEM-H has so far launched two major Stanford-wide initiatives: the Stanford Innovative Medicines Accelerator (IMA) and the Stanford Microbiome Therapies Initiative (MITI).

Main photo credit: Andrew Brodhead.
Inset photo credits: Fontejon Photography

Stanford Innovative Medicines Accelerator (IMA)

Despite incredible advances in human health research at Stanford and beyond, too many promising discoveries are never translated into real medicines, and too many patients suffer from diseases whose cures may lie in these unexplored avenues. Led by **Chaitan Khosla**, the founding director of Sarafan ChEM-H, the Stanford IMA aims to transform more Stanford discoveries into medicines, creating a new therapeutic landscape with new classes of medicines that address unmet clinical needs.

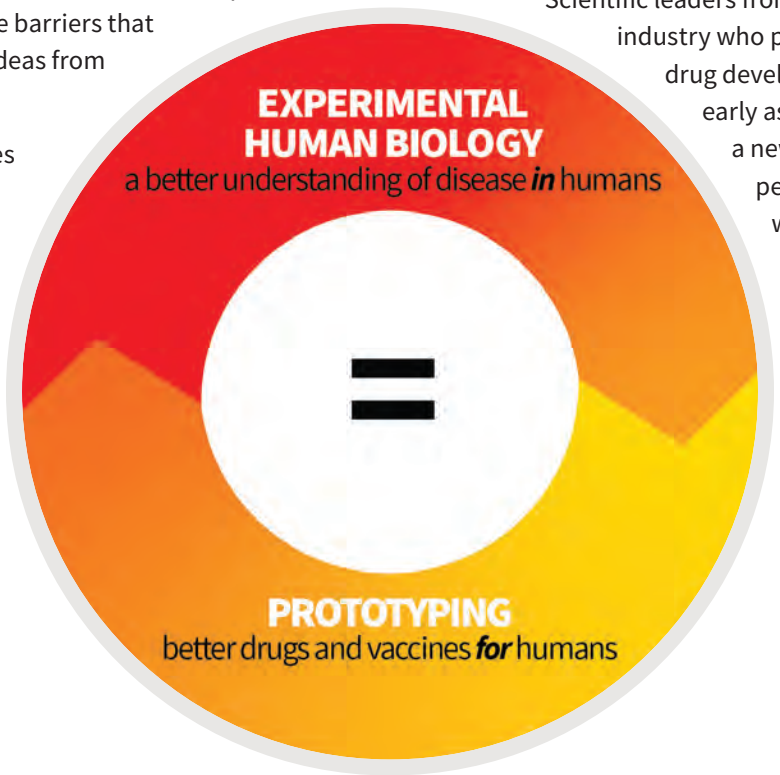
Chaitan Khosla
Founding director of Sarafan ChEM-H
Director of the Stanford Innovative Medicines Accelerator

The IMA builds upon a foundation established by Sarafan ChEM-H, Stanford Medicine, and other Stanford interdisciplinary life sciences institutes that foster collaboration and innovation. This rich ecosystem has inspired Khosla, the Director of the Stanford IMA, and other campus leaders to build the IMA and help researchers overcome the barriers that prevent their promising ideas from being translated.

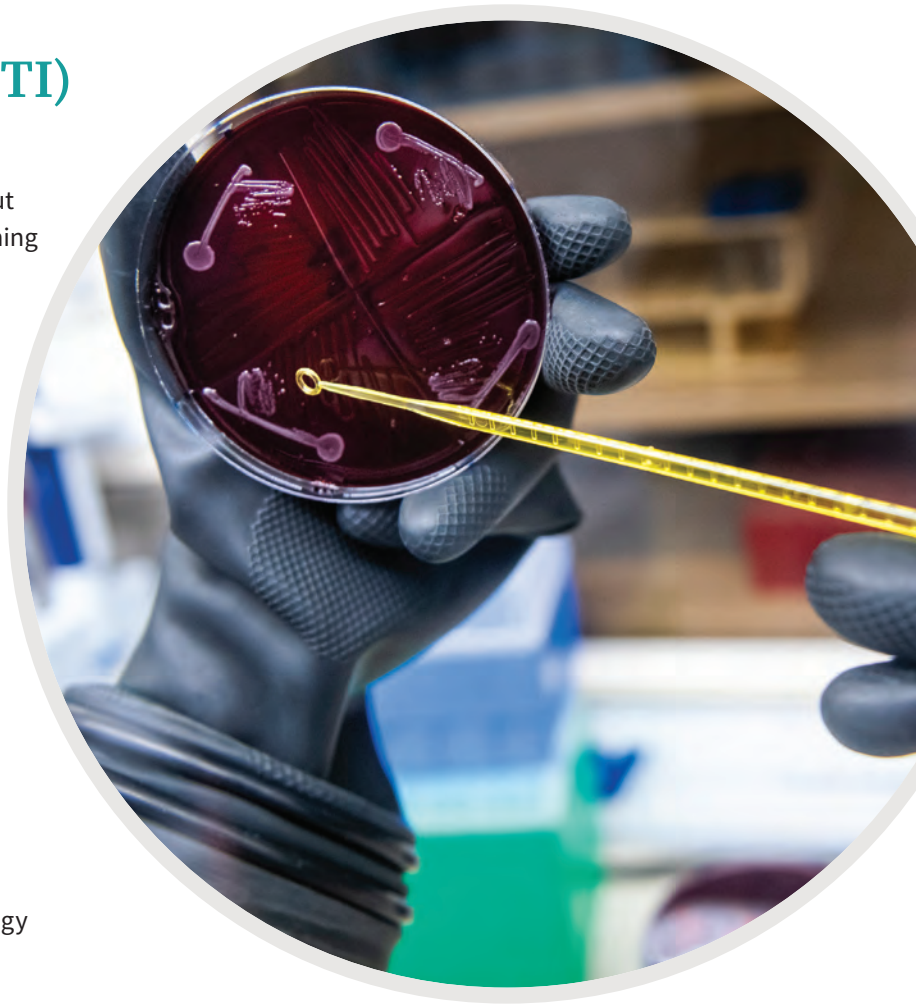
Among the biggest hurdles to realizing the potential of a new drug target is validating it using a prototype medicine. Industry partners are likely to only carry forward well validated targets, and academia traditionally is ill-equipped to create drug prototypes and demonstrate their effectiveness. Even among highly validated targets, there is still a high failure rate for medicines once they reach clinical trials because of our incomplete understanding of human biology. There are currently few mechanisms that allow for feedback between the clinic and the lab early in the drug development process, which could improve the likelihood of successful outcomes.

By providing expertise, equipment, and infrastructure, the IMA has created two distinct but complementary programs: **drug prototyping** and **experimental human biology**. By creating both an in-house process for generating advanced drug prototypes and mechanisms to extract more information about human biology from clinical trials, the IMA generates a drug development feedback loop. Both drug prototyping advances and a more complete understanding of why and how patients respond in certain ways to medicines allows scientists and clinicians to nimbly correct drug failures and address emerging diseases.

Central to the initiative's success is the new kind of human capital the initiative has attracted from industry. Scientific leaders from the biopharmaceutical industry who provide insight into the drug development process as early as the initial discovery of a new target. This industrial perspective, combined with the incredible diversity of expertise on Stanford's campus and the freedom to pursue projects regardless of potential profitability, make the IMA a unique breeding ground for developing new kinds of therapies.



Stanford Microbiome Therapies Initiative (MITI)



The microbes that live in, on, and around us are inextricably linked to human health. These small but mighty bugs are each a mini chemistry lab, performing reactions that break down and build up molecules, reactions that our bodies' cells could never carry out. These residents of our bodies are welcome tenants—they, after all, break down foods we otherwise could not digest—but dysfunction in the microbiome is linked to diseases from ulcerative colitis to heart disease to cancer to neurodegeneration. Putting those chemistry labs to work and creating an engineered microbiome specifically designed to address a patient's conditions could revolutionize medicine. The Stanford Microbiome Therapies Initiative (MITI) will deliver on the as yet unrealized promise of microbiome-based drugs.

Michael Fischbach
Bioengineering & Microbiology and Immunology

Led by Institute Scholar **Michael Fischbach**, their vision is as clear as it is ambitious: create first-of-their kind microbiome therapies. They are forging through the next frontier of personalized medicine, envisioning a future in which engineered microbiome communities, swallowed as a pill or swiped on the skin as cream, can shrink a tumor, turn off dangerous autoimmune disorders, or prevent the spread of infectious diseases.

In the age of personalized medicine, microbiome therapies are the next frontier. The scientists at MITI are developing the genetic tools to better understand and manipulate individual microbes, the manufacturing technology to construct perfectly balanced populations of hundreds of microbes, and the infrastructure to translate basic science discoveries into a class of therapeutics that does not yet exist.

In one of the first demonstrations of their progress, Fischbach recently reported that his team has built the most complex and well-defined synthetic microbiome, creating a community of over 100 bacterial species that was successfully transplanted into mice. They built their "Noah's Ark" community, which contains bacteria that represent the natural variety found in humans, by mixing stocks of each particular species. That piecewise addition, which gives researchers the ability to add, remove, and edit individual species, will allow scientists to better understand the links between the microbiome and health, and eventually develop first-in-class microbiome therapies.

"We built this consortium for the broader research community. We want to get this into as many hands as possible to have an impact on the field," said Fischbach.

Photo credit: L.A. Cicero.

Message from Elizabeth Ponder, Executive Director

Strength through transitions

I think back on the building of Sarafan ChEM-H over the last 10 years as a time of big transitions at Stanford. Sarafan ChEM-H benefited from the support of two university administrations and two Deans of Research; the leadership of two different faculty directors; and the opportunity to launch both the Stanford Innovative Medicines Accelerator (IMA) and the Stanford Microbiome Therapies Initiative (MITI). As employee number two at Sarafan ChEM-H, I arrived in April 2014 and had the privilege to witness how our institute reacted to these and other transitions. What has impressed me the most is how well our leaders have worked together, first in the campaign to establish Sarafan ChEM-H, then to bring new initiatives to campus, and finally to stabilize our programs.

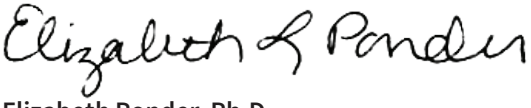
And the world around us has changed, perhaps most obvious when we look at the impact of the COVID-19 pandemic on society, healthcare, economics, academia, and beyond. Our strength lies in our response to a changing world: recognizing and embracing change, identifying the role we can and should play, and rallying people and resources around a shared vision. In the early days of the pandemic, that meant launching the IMA while still building it to ensure that projects with the potential to lead to new vaccines or treatments were accelerated.

The transitions we have lived through highlight not only the strength of Sarafan ChEM-H but the necessity of Sarafan ChEM-H; the more we understand about the molecular basis of health and disease and the better we learn to engage deeply across disciplinary boundaries, the more prepared we will be to respond to emerging diseases and any challenge to human health.

Behind each milestone we accomplished over the last decade are countless people who made our hopes a reality, people I would like to enthusiastically thank. They are the faculty who believed that our institute could cultivate their research programs; the students and postdoctoral scholars who trusted us to prepare them to be scientific leaders; the staff who established our programs and initiatives, supported our researchers and programs, and shared their expertise; the leaders who lent their time, knowledge, and patience to us; the partners inside and outside Stanford who supported our vision; and many others who ensured that our people can thrive, our programs can succeed, and our facilities continue to run.

It is truly a pleasure to work alongside you all as we look forward to the next decade of Sarafan ChEM-H. Your partnership in building an institute that leverages the power of diversity to improve human health is not only necessary for our success but also inspiring. It is because of you all that we have come this far and can continue to be ambitious in our vision for the future.

With sincere thanks,



Elizabeth Ponder, Ph.D.
Executive Director, Sarafan ChEM-H

Photo credit: Fontejon Photography.

Sarafan ChEM-H by the numbers

Training Programs

Sarafan ChEM-H has supported:

117 undergraduate students through the Undergraduate Scholars Program and the Undergraduate Entrepreneurship Program

108 graduate students through the Chemistry/Biology Interface (CBI) Predoctoral Training Program and the Stanford Interdisciplinary Graduate Fellowship Program (SIGF)

10 postbaccalaureate scholars through the Sarafan ChEM-H/Stanford Innovative Medicines Accelerator Postbaccalaureate Program in Target Discovery

Seed Grants

Sarafan ChEM-H has funded:

71 faculty across **40 departments** through **49 research projects**

58 postdocs across **24 departments** through **29 seed grants and fellowships**

Sarafan ChEM-H has awarded more than **100 grants** to teams of researchers tackling interdisciplinary problems

Knowledge Centers

Our **5 Knowledge Centers** contributed to **97 publications** with **47 Stanford faculty co-authors** that represent **24 departments**

Main photo credit: Bruce Damonte / Ennead Architects; inset photo credits (left to right): Fontejon Photography, Kate Alfieri, and Fontejon Photography

Sarafan ChEM-H
Stanford University

Stanford ChEM-H Building
290 Jane Stanford Way, Stanford, CA 94305
United States

chemh.stanford.edu

T 650-498-6484
E chemh-info@stanford.edu