Spring 2022 Issue 42

berkeley science review

berkeleysciencereview.com

berkeley science review
Spring 2022 Issue 42
berkeleysciencereview.com

Editor in Chief
Andrew Saintsing

Editors
Julie Fornaciari
Amy Kynman
Shannon O'Brien
Sierra Lear
Héctor Torres Vera
Sophia Friesen

Copy Editors
Erin Akins
Amy Price

Managing Editor
Julie Fornaciari

Art Director
Julia Torvi

Designers
Abigail Estes
Chenyu Zhang
Erica Pledger
Jennifer Cummings
Kristina Boyko
Liya Oster
Madeleine Snyder
Nicolette Puskar
Shannon O'Brien

Photographer
Kazuomori Lewis

Blog Editor in Chief
Samvardhini Sridharan

Blog Editors
Anneliese Gest
Chris Jackson
Audrey Short
Samvardhini Sridharan
Stephanie Reeves

Blog Copy Editors
Jennifer Hill
Andrew Plebanek

Blog Designers
Gabriel Sturm
Jaquesta Adams
Marsalis Gibson
Meghan Turner
Tsai-Ching Hsi
Vanha Pham

Web Director/Social Media
Samvardhini Sridharan

Printer
Sundance Press

from the editor

Dear Readers,

I've been working on the *Berkeley Science Review* in various roles for the past four years, and it's always been a blast. The magazine provides an amazing opportunity for graduate students to refine their communication skills and find their voice, while sharing stories about the exciting science happening at UC Berkeley. Reading through these pages, you'll learn a lot about the research being conducted here on campus. But you'll also have the opportunity to see what's important to our authors, who represent the next generation of scientists just now starting their careers.

Like many early-career scientists, our authors have come of age witnessing the effects of climate change and the collapse of biodiversity. They acknowledge the duty that the scientific community has to take action on issues affecting the wider world. In their articles, they grapple not only with the science behind climate change in "Out of the soil, into the atmosphere," but also with its social impacts in "The real cost of carbon." In "Protocols for the people," Sophia Friesen provides an explanation of how insulin is synthesized to support a larger story about trying to fight back against out-of-control prices.

Of course, some issues that human beings face don't necessarily have scientific solutions, but our authors chose not to be silent about them. When Russia invaded Ukraine halfway through our editorial process, Kalie Knecht chose to acknowledge Ukraine's distinct national identity and sovereignty by switching to the Ukrainian spelling of Chornobyl in her "From the field" article.

Today's challenges are daunting, but not insurmountable—if we work together. Many of our authors have chosen to write about centers and platforms established to propel fields forward. The features "Sana, sana, colita de rana" and "From molecules to memories," the brief "Breaking the mold," the labscope "The real cost of carbon," and the toolbox "CRISPRbrain" all describe entities established with the mission of bringing people together to solve common problems. Science is about pushing outward against the bounds of human knowledge, but obstacles in that pursuit often require teamwork to overcome. Our authors embrace that fact and want to work in a community that does as well.

Of course, we at the *Berkeley Science Review* know all about the importance of teamwork. We have an incredible group of editors who really honed these articles, and I'm always amazed at the artwork produced by our designers. A special thanks to our departing Managing Editor Julie Fornaciari and Art Director Julia Torvi. Both have excelled in their roles over this past year. I would also like to welcome our new Blog Editor in Chief Samvardhini Sridharan, who simultaneously managed to take over that role and write a feature for this issue. Lastly, I'd like to thank all our donors and subscribers, whose contributions keep our magazine going. The Karmon family in particular continues to be an important and generous supporter.

I hope you enjoy reading Issue 42 as much as we enjoyed making it!

Sincerely,

Andrew Saintsing
Editor in Chief

contents

DEPARTMENTS

FEATURES

CURRENT BRIEFS

COVER & TABLE OF CONTENTS:
Photography, Design & Illustration by Julia Torvi

© **2022 Berkeley Science Review.** No part of this publication may be reproduced, stored, or transmitted in any form without the express permission of the publishers.

Financial assistance for the 2020-2021 academic year was generously provided by the Office of the Vice Chancellor of Research, the UC Berkeley Graduate Assembly (GA), the Associated Students of the University of California (ASUC), and the Eran Karmon Memorial Fund. ***Berkeley Science Review*** is not an official publication of the University of California, Berkeley, the ASUC, the GA, or Lawrence Berkeley National Laboratory. The views expressed herein are the views of the writers and not necessarily the views of the aforementioned organizations. All events sponsored by the BSR are wheelchair accessible. **For more information** email sciencereview@gmail.com. **Letters to the editor** and **story proposals** are encouraged and should be emailed to sciencereview@gmail.com. **Advertisers:** contact sciencereview@gmail.com or visit berkeleysciencereview.com.

faculty profiles

LIANA LAREAU

by Sierra Lear

"If someone asks me if I want to do this or that, I always think: *why not both*? "

Says Dr. Liana Lareau, professor of bioengineering at UC Berkeley. This philosophy has defined much of Lareau's professional journey, and she now leads a thriving research lab at the intersection between biology and engineering.Halfway through Lareau's postdoc, the lab she worked in shut down. Rather than find a new lab and start afresh, Lareau chose to finish her project. She gained her own funding and two graduate students to co-advise, which served as a trial run at being a professor and helped Lareau determine the type of science she would later pursue. She explains, "Because I had done a postdoc in a biochemistry lab, I came out thinking, 'OK, here are these really cool biochemistry questions' … But in terms of where my unique contribution comes from, it turned out I'm not actually a biochemist." Instead, Lareau decided she is a bioengineer.

The Lareau group is interested in understanding how information stored in DNA affects RNA and using this basic science to engineer therapeutics. In cells, DNA is first transcribed into RNA before interacting with cellular machinery to make essential proteins. Lareau's work shows that the specific sequence of the DNA can change the RNA that is transcribed, which in turn alters the protein. Knowing why this occurs and the fundamental rules underlying how RNA is controlled is vital for developing RNA therapeutics, which have recently come into prominence with COVID-19 vaccines.

Although Lareau didn't expect to end up in bioengineering, she notes that she always had an "engineering 'let's see if we can make this happen' mentality." For the past decade, in fact, she has been involved in an Oakland-based art collective that creates sculptures for Burning Man, including a Dance Dance Revolution rig that bursts into flames if the player—dressed in a fireproof suit—makes too many mistakes. In this creativity lies Lareau's talent: combining her seemingly disparate interests, whether they be science and art, or RNA biology and clinical therapeutics.

Sierra Lear *is a graduate student in bioengineering.*

JAMES NUÑEZ

by Meghan Pressimone

Dr. James Nuñez feels both at home and in uncharted waters as a new principal investigator (PI) at his alma mater. A Department of Molecular and Cell Biology (MCB) PhD graduate, Nuñez is excited about returning to Berkeley to create a lab true to his tenets of curiosity and inclusivity. Nuñez has made extensive contributions to CRISPR gene-editing technology in his graduate and postdoctoral research, but his goals diverge from pure technology development towards a fundamental question: "How do cells know what genes to turn on and off?" Nuñez investigates the modifications that activate or silence genes by mimicking those marks across the entire genome. This remarkable DNA coverage is made possible by using the CRISPR-Cas system to target nearly every DNA code. The popularity of CRISPR comes with intense competition, but Nuñez's fascination with basic biology keeps him grounded in his research. His passion also alleviates the stress of being a new PI.

DESIGN & PHOTOGRAPHY: CHENYU ZHANG

"No one sits you down and tells you, 'This is how you start a lab,' "

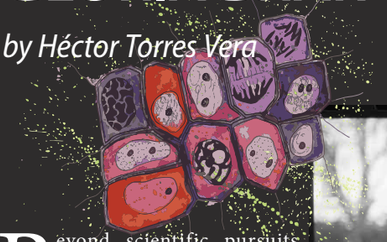
Nuñez reflects on the transition from a research-centric postdoc to the leader of a lab. Nuñez acknowledges that "it's a big undertaking, but there's a network of supportive PIs in the field, especially at Berkeley." A faculty position offers the freedom to do science as he sees fit, which Nuñez cites as a reason he chose academia over other careers. This freedom applies to lab culture as much as the research itself. Nuñez comments, "I felt like starting my lab was a great place to essentially create an environment that I didn't get to have, [one] for people of color or marginalized groups." Nuñez has already extended support even before taking grad students by organizing meetings to connect with MCB students that share his Filipino heritage. His mentees' enthusiasm keeps him optimistic about his future at UC Berkeley. The potential for both social and scientific progress underlies the exciting start to Nuñez's career as a PI.

Meghan Pressimone *is a graduate student in molecular and cellular biology.*

DESIGN & PHOTOGRAPHY: CHENYU ZHANG

GLORIA BRAR

by Héctor Torres Vera



Beyond scientific pursuits, research is also a means for human connection. This idea is paramount to how Dr. Gloria Brar runs her lab as an assistant professor of molecular and cell biology at UC Berkeley.

"You figure out how to do great science by learning a series of different things from people with different strengths that you want to emulate," says Brar.

Throughout her career, Brar worked alongside scientists whose different personalities and approaches she admired. Now, Brar continues to foster scientific collaboration by running a lab together with co-PI Dr. Elçin Ünal. Brar explains, "Besides being fun, it allows each of us to supplement our shortcomings. Nobody is good at everything, but we can be greater than the sum of our parts because she [Elçin] is better at things I'm not great at, and vice versa."

The collaborative nature of the eponymous Br-Ün Team Lab is crucial for studying Brar's research focus: meiosis. Meiosis is the process by which a single cell divides and produces four reproductive cells, or gametes, each containing half the original amount of genetic information. Gametes ultimately form new generations of organisms, carrying a unique assembly of genetic information from their parent cell. This uniqueness underlies much of the complexity of meiosis. "You're not just trying to make one cell into two cells that look similar to what you started with [like in mitosis]," Brar explains. Brar asks, "In meiosis, you're absolutely restructuring everything so that you end up with something different." This cellular reorganization is complex, and many mysteries still surround it. "What to keep? What to get rid of? How do cells change their components to better suit the intermediate stages and the final product?"

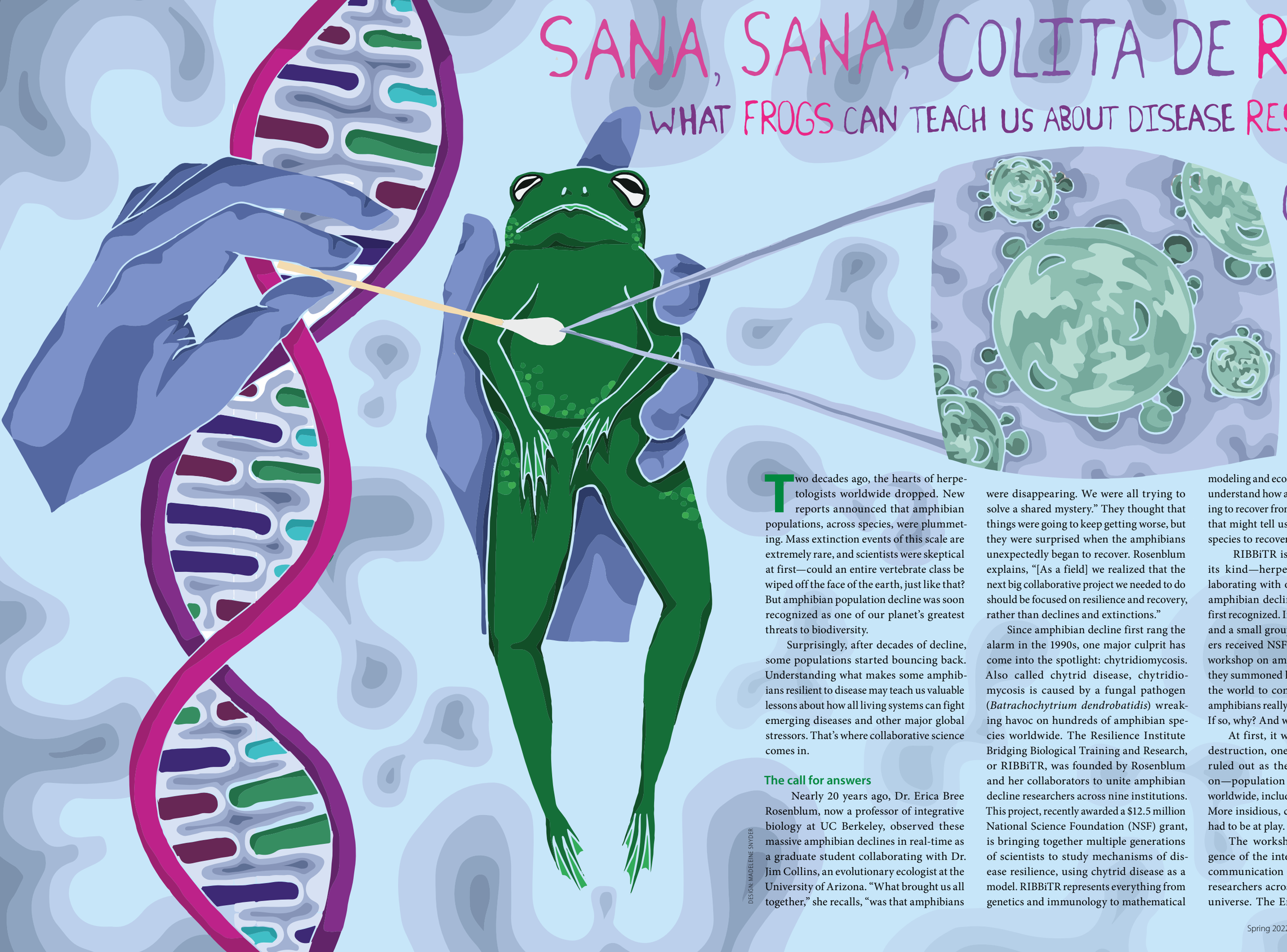
To answer these questions, Brar uses yeast to study gene regulation—the process of turning genes on and off under specific conditions—which she suspects is the true conductor of meiosis. Her ultimate goal is to learn about cell differentiation, the general process by which dividing cells change shape and function. Brar says, "There's every reason to believe that when we expand this to study cellular differentiation in more complex organisms, we'll find many of these unexpected core features to be conserved amidst even greater complexity."

Héctor Torres Vera *is a graduate student in molecular and cellular biology.*

SANA, SANA, COLITA DE RANA

WHAT FROGS CAN TEACH US ABOUT DISEASE RESILIENCE

CELIA FORD



Two decades ago, the hearts of herpetologists worldwide dropped. New reports announced that amphibian populations, across species, were plummeting. Mass extinction events of this scale are extremely rare, and scientists were skeptical at first—could an entire vertebrate class be wiped off the face of the earth, just like that? But amphibian population decline was soon recognized as one of our planet's greatest threats to biodiversity.

Surprisingly, after decades of decline, some populations started bouncing back. Understanding what makes some amphibians resilient to disease may teach us valuable lessons about how all living systems can fight emerging diseases and other major global stressors. That's where collaborative science comes in.

The call for answers

Nearly 20 years ago, Dr. Erica Bree Rosenblum, now a professor of integrative biology at UC Berkeley, observed these massive amphibian declines in real-time as a graduate student collaborating with Dr. Jim Collins, an evolutionary ecologist at the University of Arizona. "What brought us all together," she recalls, "was that amphibians were disappearing. We were all trying to solve a shared mystery." They thought that things were going to keep getting worse, but they were surprised when the amphibians unexpectedly began to recover. Rosenblum explains, "[As a field] we realized that the next big collaborative project we needed to do should be focused on resilience and recovery, rather than declines and extinctions."

Since amphibian decline first rang the alarm in the 1990s, one major culprit has come into the spotlight: chytridiomycosis. Also called chytrid disease, chytridiomycosis is caused by a fungal pathogen (*Batrachochytrium dendrobatidis*) wreaking havoc on hundreds of amphibian species worldwide. The Resilience Institute Bridging Biological Training and Research, or RIBBiTR, was founded by Rosenblum and her collaborators to unite amphibian decline researchers across nine institutions. This project, recently awarded a $12.5 million National Science Foundation (NSF) grant, is bringing together multiple generations of scientists to study mechanisms of disease resilience, using chytrid disease as a model. RIBBiTR represents everything from genetics and immunology to mathematical modeling and ecology. The project's goal is to understand how amphibian species are starting to recover from chytrid disease, and what that might tell us about the ability of other species to recover from their own ailments.

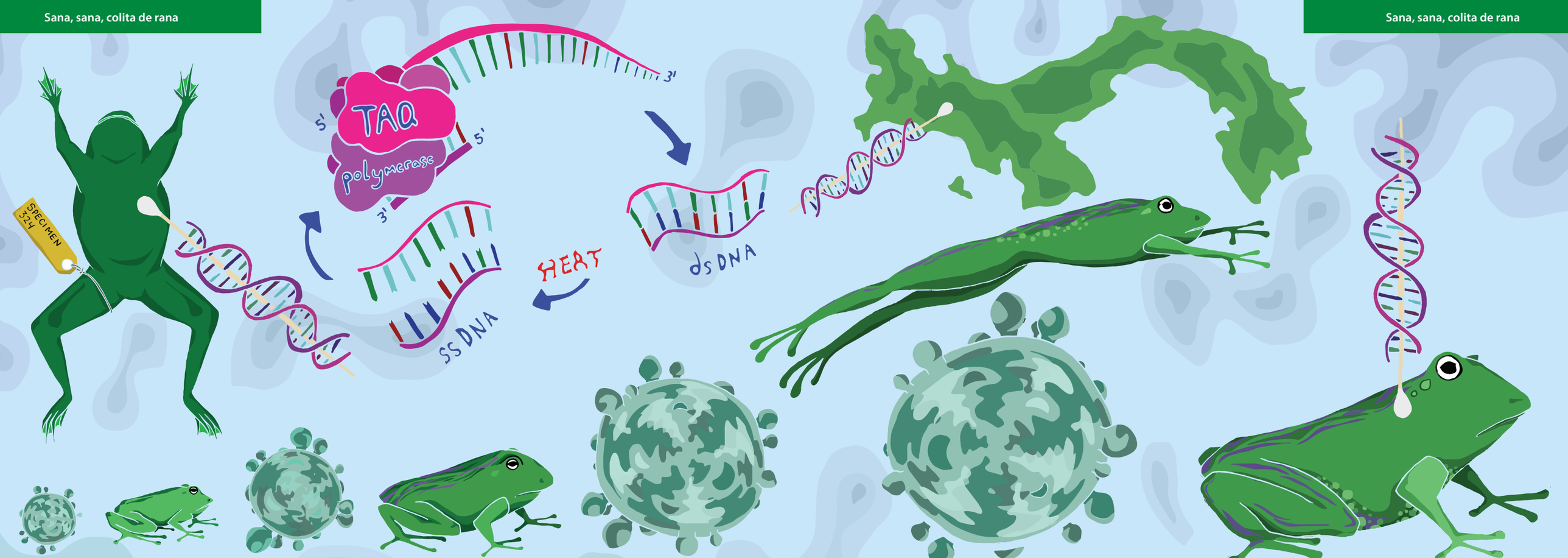
RIBBiTR is not the first institute of its kind—herpetologists have been collaborating with other researchers to study amphibian decline since the problem was first recognized. In the late 1990s, Dr. Collins and a small group of like-minded researchers received NSF funding for an academic workshop on amphibian decline. Together, they summoned herpetologists from across the world to come together and ask: Are amphibians really under threat of extinction? If so, why? And what can we do to stop it?

At first, it was all a mystery. Habitat destruction, one obvious contender, was ruled out as the primary problem early on—population declines were observed worldwide, including on protected reserves. More insidious, complex, and subtle forces had to be at play.

The workshop, alongside the emergence of the internet and modern global communication networks, connected star researchers across the amphibian science universe. The Environmental Protection

DESIGN: MADELEINE SNYDER

Sana, sana, colita de rana



Agency covered toxic chemicals while virologists and mycologists, who study viruses and fungi, respectively, tackled infectious disease. NASA studied climate change while conservation biologists investigated habitat change. After years of interdisciplinary work, one particularly destructive culprit stepped into the spotlight: the aforementioned fungal pathogen, *B. dendrobatidis*.

Under an electron microscope, a *B. dendrobatidis* spore looks like a serene, gray orb—not particularly threatening. But these spores are capable of incredible destruction, swimming through bodies of water until they reach the skin of an unsuspecting amphibian. The resulting infection is chytrid disease, and it is every epidemiologist's worst nightmare: highly infectious, highly lethal, and tricky to fight. Amphibians exposed to chytrid disease develop excessive thickening and shedding of skin, an especially nightmarish set of symptoms for animals who use their skin to absorb nutrients, release toxins, and breathe.

Unlike viruses and bacteria, fungal pathogens are eukaryotes, with organelles and DNA packaged up in a nucleus like members of the animal kingdom. Antivirals and antibiotics target pathogens that are very different from animal cells, making it easier to attack the virus or bacteria without killing the animal's cells. But any treatment that might kill a fungus is likely to kill parts of the animal's cells, too. While there are over 100 types of antibiotics, there are only four main classes of antifungals. Fungal diseases don't yet occupy much space in our collective consciousness, but climate change and globalization are enabling their spread to new environments and pushing these cool-loving pathogens to adapt to warm body temperatures. A highly transmissible fungal disease could pit us against a pandemic that is highly infectious and painful to treat. Understanding how fungal pathogens interact with hosts, and how host populations develop resilience and recover from these outbreaks, will help us prepare for the worst-case scenario.

100-year-old frogs reveal hidden truths about the present

There are three main players in any disease system: the host, the pathogen, and the environment. If any of those players makes a sudden move, the disease changes. Major global phenomena like climate change play a big role in shaping disease systems, enabling problematic pathogens to spread to new territory, exposing unsuspecting hosts. But disease evolution implies major genetic shifts in the host, the pathogen, or both.

The Rosenblum lab is trying to understand why evolutionary adaptation is leading some amphibian species to recover, while others continue to struggle. While historically the problem of amphibian decline was mainly being tackled by ecologists, Dr. Rosenblum says, "I was a geneticist by training, so there was an open niche: what can we learn about chytrid disease under the hood, if we marry an ecological perspective with a genetics perspective?" Today, her group is leading RIBBiTR's genetics efforts with a two-pronged approach, studying the history of chytrid disease from the perspective of both the host and the pathogen.

DESIGN: MADELEINE SNYDER

To do this, they sequence host genomes, reading DNA to compare amphibians to one another, and to compare the same host species at different points in time. Scientists trek through the amphibians' natural habitats and snag genetic samples by swabbing the critters' belly skin with a Q-tip. This process is easy for the amphibians but presents some challenges for the scientists: samples collected via swabs are often of lower quality than samples collected in more controlled lab environments. To get around this, the Rosenblum lab developed new custom tools to retrieve high-quality genetic data from lower-quality samples, like those collected from decades-old frogs preserved in museums, or those swabbed at field sites outside a controlled lab environment.

Dr. Allie Byrne, a former Rosenblum lab graduate student, is now a postdoctoral scholar at RIBBiTR who specializes in these techniques. "There are preserved frogs in jars stored in museums all over the world," she explains, "and we're swabbing these specimens to see what their genomes were like before chytrid, relative to what they look like now." To get modern-day samples, she hikes along tropical rainforest streams at a field site in Panama. "It's day after day of that," Byrne says. "It's grueling work, but it's so fun seeing all the amphibians and really feeling like you're a part of it."

As amphibians adapt, so does the disease. The Rosenblum team also runs polymerase chain reaction (PCR) tests on frog belly swabs to find molecules of *B. dendrobatidis*. To sequence these genomes, Byrne first runs a qPCR (short for quantitative PCR) test, a more informative version of the same PCR tests occupying a lot of space in the public eye over the past two years as one of our best tools for detecting COVID-19. PCR tests amplify DNA, enabling researchers and clinicians to detect even the small quantities of genetic material produced by microscopic pathogens (like *B. dendrobatidis* and SARS-CoV-2, the virus that causes COVID-19). While a sample from a swab might contain lots of different genetic material from lots of different organisms, scientists use primers—short, single-stranded bits of DNA matching a chunk of the pathogen's DNA—that selectively target only the genetic material of the pathogen of interest. If a PCR doesn't amplify any DNA, then the pathogen was probably not in the initial sample. While PCR tests can only show whether a pathogen is present or absent, qPCR also reveals how much pathogen DNA was found.

Byrne uses primers that match *B. dendrobatidis*. To make sure that they can still spot this genetic material in low-quality samples, like time-worn DNA on the skin of 100-year-old museum frogs, her research group designed special primers that go straight for segments of the *B. dendrobatidis* genome that are most diagnostic for different lineages of the pathogen. Testing both museum samples and live frogs across the world and comparing genetic data of disease in decades-old and modern-day samples, can reveal the historical emergence and spread of *B. dendrobatidis*. "We don't just know

DESIGN: MADELEINE SNYDER

whether or not the pathogen was there at a particular place and time," Rosenblum explains, "but we actually know what strain of the pathogen was there, and how closely it relates to others." By tracing the waxing and waning of pathogen strains over time, scientists can map out its evolution and better understand how its mutations shaped the history of chytrid disease.

Disease is an ever-moving target

Over two years and multiple variants deep into our own global pandemic, we've become intimately familiar with the potential impacts of pathogen evolution. "To me," Byrne says, "the most interesting parallel with COVID is this genetics question." When a disease infects a giant population, there's more opportunity for pathogens to mutate and evolve. Byrne explains, "Just like we're concerned about whether new variants of COVID are more infectious or more deadly, we're worried about chytrid evolution."

To understand emerging infectious diseases, we need to understand the world through which they spread, past and present. "We can't treat diseases like they just appeared from outer space," Rosenblum says. "Everybody talks about emerging infectious diseases like they're one thing, rather than complex organisms with fascinating evolutionary histories. It matters a lot, in terms of how we respond and treat disease outbreaks."

"Many people would argue that chytrid is the most important infectious disease system that we've ever seen, or that's ever been recorded in the history of understanding diseases," Dr. Jamie Voyles, associate professor at the University of Nevada, Reno and co-director of RIBBiTR, says. In the past, scientists largely assumed that infectious diseases were not capable of driving a species to extinction. As infectious and deadly as the coronavirus pandemic has been for humans across the world, we've never feared our literal extinction. The understanding was that, as potential hosts get sick and die, the pathogen loses opportunities for transmission. Eventually, infection rates wind down, giving the host population a chance to catch its breath. Chytrid, and the sheer scope of its destruction, challenged everything scientists thought they knew about infectious diseases.

Learning from amphibian resiliance

The research efforts led by RIBBiTR and its predecessors will not only teach us about amphibian resilience to chytrid disease, but it may give us the key to understanding human infectious disease systems—including the one we're battling right now. Tackling the chytrid crises required scientists to face just how little they understood about host-pathogen biology and the environment. Using the host-pathogen relationship between amphibians and *B. dendrobatidis* as a model, scientists began solving basic science questions to chip away at the mystery of amphibian decline and recovery. This story—a specific scientific mission leading to unexpected innovation along the way—is familiar. For example, it took a global coronavirus pandemic to launch mRNA vaccine technology into the public sphere. Likewise, figuring out why amphibians are dying is showing us how to anticipate and react to emerging infectious diseases.

> "Fundamentally, it's about how we handle people and things moving around the planet."

It perhaps isn't surprising, but the COVID pandemic and the spread of chytrid share an underlying cause: globalization. "There are some foundational similarities in the stressors affecting us," Rosenblum says. "Fundamentally, it's about how we handle people and things moving around the planet." After first being identified in Wuhan, China, the coronavirus hitched a ride with humans traveling worldwide on airplanes and cruise ships, enabling its global spread. Similarly, the global scale of chytrid disease was likely brought on by human-facilitated movement. Dr. Voyles explains, "Amphibians are actually moved around the world, and have been since the 1950s, for all kinds of things, like pet trade, food consumption, and science education." A 2009 *Science* article reported nearly 28 million live frogs (62% of which tested positive for *B. dendrobatidis*) were traded globally between 2000 and 2005. Both COVID and chytrid are emerging infectious diseases that came about because of the human-facilitated movement of pathogens around the world. So, perhaps the same mitigation techniques—frequent testing, quarantines, limiting transmission, travel restrictions—may help both us and amphibians get through our respective crises.

It's difficult to imagine now, but pandemics end. Even at a much shorter timescale than evolution affords, Voyles points out, "We have great hope, in that we have an immune system with the ability to learn to recognize pathogens." We don't necessarily need to wait for evolution to run its generational course—as we're exposed to variants of a pathogen, like SARS-CoV-2, our bodies learn to adapt and respond.

Pandemics are also unpredictable. Rosenblum takes the unexpected post-chytrid recovery of some amphibian species as a good sign for us, too. She says, "There are some rays of hope, even though we don't have the benefit of hindsight in the middle of this human pandemic. Things do change. Hosts evolve, pathogens evolve." Part of what's been so fascinating about studying chytrid over the past 20 years, she adds, "is how unexpected it's been. We couldn't predict the outcome or trajectory of the disease systems we studied from what we knew when the pathogen first arrived."

Given our current media landscape, parallels between chytrid and COVID are tough to ignore. However, for conservation biologists, the intrinsic value of understanding amphibian population decline can't be overstated. Chytrid is disturbing the entire amphibian vertebrate class, which includes thousands of species worldwide. As important players in both aquatic and terrestrial environments, losing them will disrupt two entirely different ecosystems.

"There's inherent value in our world's diversity," Voyles says. "There's definitely a benefit to having all organisms and all species within our world." It may not be immediately obvious why a threat to amphibian biodiversity also threatens human health, but as Rosenblum explains, "Amphibians are part of the middle layer of the food webs of most ecosystems, and there's a colossal impact when you lose that whole layer." Other organisms lose their food sources, still others lose their predators.

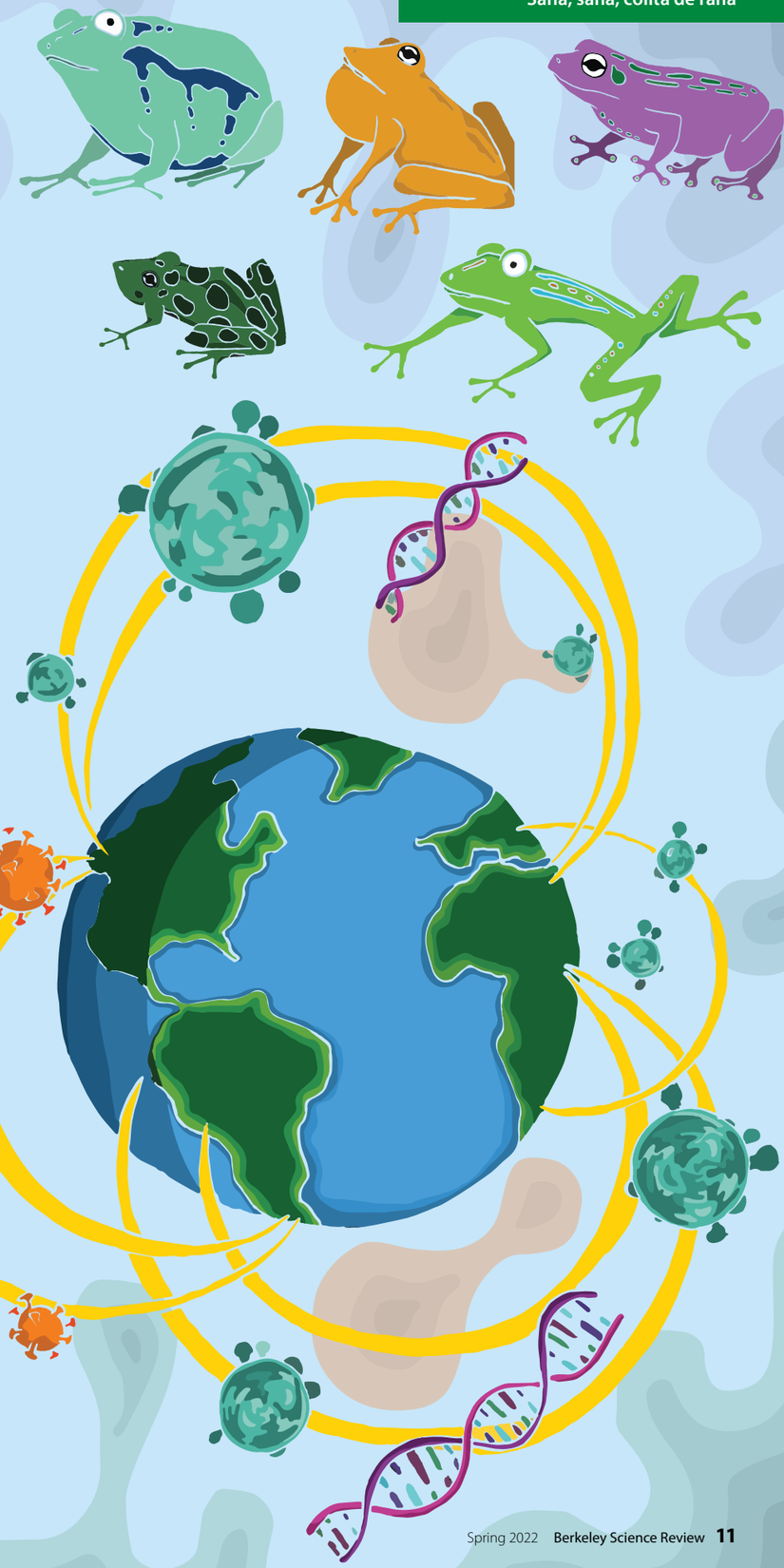
Big problems need collaborative solutions

If this disease system and its environment sound overwhelmingly complicated, that's because it is. Without grant funding for large scale interdisciplinary research institutes like RIBBiTR, studying problems of this global scale is nearly impossible. "We're studying complex, interdependent, irreducible phenomena that involve many different host species and many different pathogen strains in many different environments across the world," Rosenblum explains. "Honestly, I think anyone not doing interdisciplinary research on complex biological systems is operating from complete hubris, thinking that they're going to be able to understand anything themselves."

By bringing together a community of passionate, like-minded researchers with a broad range of expertise, large, elusive problems can be broken down from all sides. However, Rosenblum argues, it isn't enough to assemble an interdisciplinary team based on academic specialty alone. "Putting together teams that have complementary expertise and a real foundation of trust is really different from putting together teams that just check the right boxes." RIBBiTR was founded by a team of people who have been working together, off and on, for 20 years. "Some of us are dear, close friends," Rosenblum says, "and some of us are each other's advisors. The sense of trust we've built is important. We don't just need public trust in scientists. Scientists should also feel like they have a base of shared understanding, so they can challenge each other."

With NSF funding secured, the RIBBiTR team is looking towards the future. Between their collaborators, the institute has field research teams in Panama, Brazil, and several sites in the United States. With swabs in hand, they are ready to uncover the amphibian community's secret to achieving disease resilience. Data scientists at their home institutions are preparing to discover genomic patterns connecting these global communities. University professors and conservation biologists are preparing coursework and outreach programs to educate people on the importance of biodiversity. There are a lot of pieces to coordinate, but Rosenblum points out, "The reason we study complex things in complex ways is because that's reality."

Celia Ford *is a graduate student in neuroscience.*



DESIGN: MADELEINE SNYDER

Current briefs

Protocols for the People

COMMUNITY SCIENTISTS TAKE INSULIN MANAGEMENT INTO THEIR OWN HANDS

Since its first use a century ago, medical insulin has been a critical part of diabetes treatment. This lifesaving molecule promotes the uptake of blood sugar into the body's tissues, making it possible for many people with diabetes to keep their blood sugar at a healthy level, even though their bodies produce little or no insulin. But medical insulin only works when people can afford to use it, and this medicine has been increasingly out of financial reach for many. In the United States, insulin is 10 times more expensive than it was in the 1990s. This increased price has little to do with the manufacturing costs and more to do with perverse financial incentives in the American health care system.

Even though insulin itself is off-patent, explains Professor of Health Policy and Management James Robinson, a handful of insulin manufacturers have kept a stranglehold on production by "being very creative about secondary patents." Basically, they patent every step of the process that they can. This near monopoly is further strengthened by economies of scale: larger manufacturers can produce insulin more cheaply. Control of the insulin market lets manufacturers and middlemen jack up the prices and rack up the profits, while people who can't afford insulin ration doses, suffer preventable health problems, and even die. Many states have implemented insulin price caps to try to address this crisis, but California has no such policy protections, says Camila Hurtado, a research fellow with the California Initiative for Health Equity & Action and a medical and graduate student of the UC Berkeley-UCSF Joint Medical Program. Two recent state bills that could have lowered insulin prices have already been shot down, and though one insulin price-capping bill is still pending, Hurtado explains, "Even a five-dollar copay can be a barrier for accessing insulin."

But what if the monopolies could be bypassed entirely? What if smaller communities, like individual cities, could make and distribute their own insulin? This is the vision of Open Insulin, a team of self-described biohackers who aim to create and release "open-source" protocols for small-scale, affordable insulin production. Open Insulin's Oakland branch, where the now-global organization began, operates out of a small community lab, and hopes to ultimately give similar labs the power to make their own safe, accessible, and affordable insulin.

Open Insulin's basic strategy for producing insulin is to genetically engineer bacteria and yeast to make insulin analogs. It's the same strategy that large insulin manufacturers have used for decades, but that doesn't mean insulin is simple to make, especially for a community lab. "There are some technical things that are not a roadblock for a huge company, that are for a small operation … What industry calls small-scale is like 1,000 times the size of what we do in our [graduate] labs," says Max Ferrin, a graduate student in the Department of Molecular and Cell Biology and an Open Insulin volunteer who helps manage the bioengineering team.

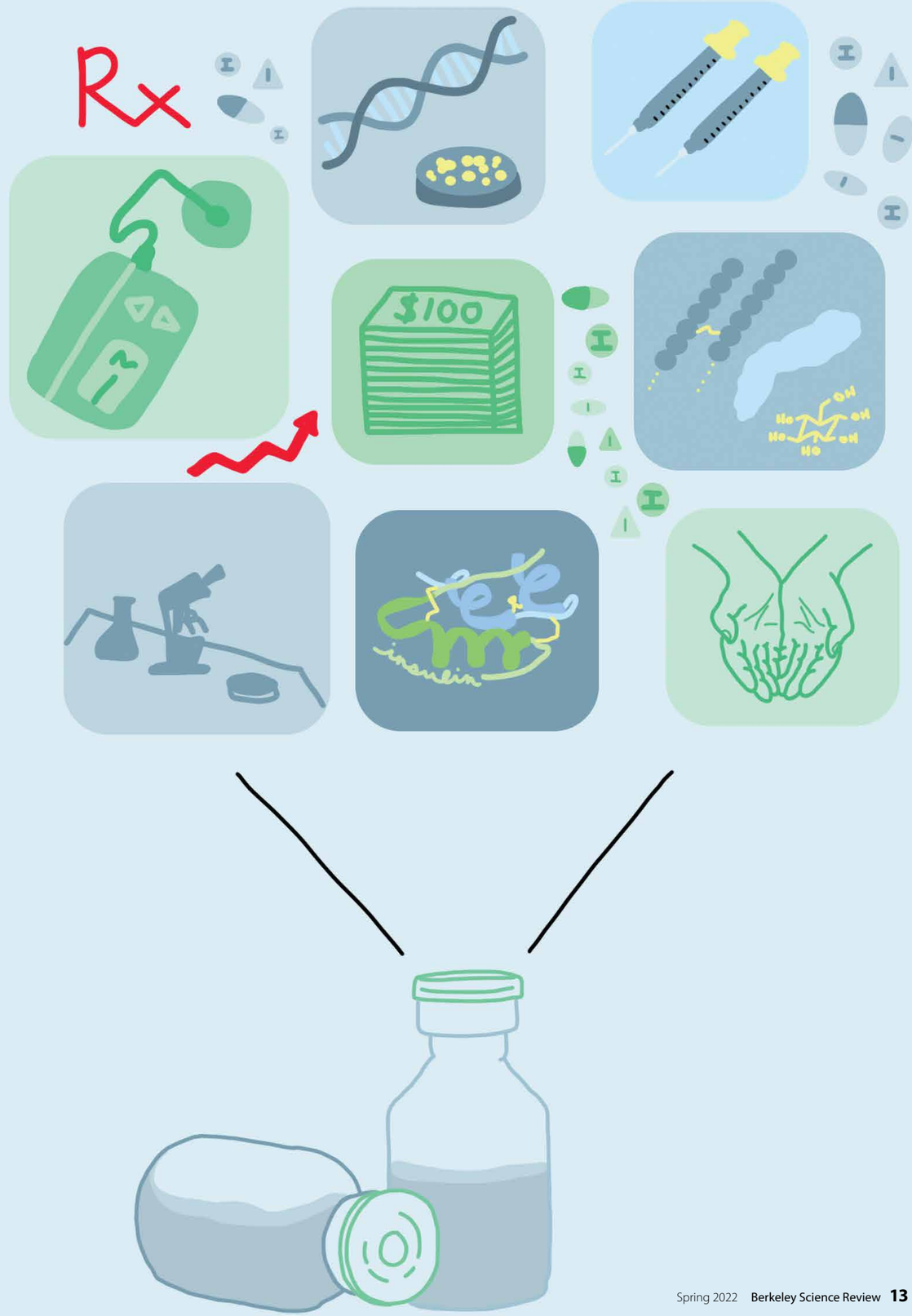
Ferrin explains that for a molecule of insulin to be functional, it needs to fold into the correct three-dimensional structure—a process that often goes wrong when making insulin. Industrial scale production can deal with this problem by simply producing massive amounts of insulin and using the fraction with the right structure. Smaller-scale operations, however, may have to rely on producing the functional form of insulin more efficiently. Open Insulin's current strategy is to try to direct the insulin to a specific bacterial compartment, where the chemical environment favors the correct form, but production efficiency remains low.

That said, Open Insulin has made progress. The company is working to synthesize two insulin analogs that are free from patent protection. Open Insulin researchers have engineered bacterial and yeast strains that express detectable amounts of the necessary precursor for each molecule, which is no mean feat. While Big Pharma can use robots to do the time-intensive, scientific grunt work to engineer a useful yeast strain, Open Insulin relies on human volunteers. Robinson remains skeptical that such small operations will ever succeed in a world where their competitors are already so powerful. "Pharmaceutical production has huge economies of scale. The notion that you're going to have little mom and pop not-for-profit things—if you think you're going to compete against China, good luck."

Yet, despite the many hurdles that remain, the researchers at Open Insulin remain hopeful that their work will make a difference. As Ferrin puts it, "Even if we get stopped, and big pharma finds a way to shut us down, there's still the exercise of showing that, eventually, a ragtag team of DIY scientists can produce this thing that pharmaceutical companies are telling you is worth extra hundreds of dollars … Actually, it's total bulls**t and it doesn't have to be that way." By setting out to produce insulin independently, the project rejects the idea that the current status quo is unchangeable. Ferrin says, "It's an avenue to expand people's imagination of what's possible."

Sophia Friesen *is a graduate student in molecular and cell biology.*

DESIGN: ABBY ESTES



Breaking the mold

UC Berkeley research center open doors—and minds—to new perceptions of psychedelics

In the late 1950s, Western scientists became aware of a class of compounds that produced psychoactive effects unlike anything that had been described in the scientific literature. These molecules, which elicited changes in consciousness ranging from visual hallucinations to mystical experiences in those who ingested them, were termed psychedelics, grouped together by a shared affinity for the serotonin receptor 5-HT2A. Though they showed great therapeutic potential in the treatment of a host of psychiatric disorders, research on psychedelics was soon stifled by drug criminalization. Recently, however, promising results from clinical trials have rejuvenated the field, and a new generation of psychedelic research centers began popping up like mushrooms after a long period of rain. Among them is UC Berkeley's Center for the Science of Psychedelics (BCSP), launched in late 2019 and now poised to become a leader in the growing movement. The BCSP's three mutually supportive programs—research, training, and public education—have been thoughtfully designed by an interdisciplinary team of scholars to advance our understanding of psychedelic compounds and the many different ways humans interact with them.

While clinical trials of psychedelic-assisted therapies are underway at other psychedelic research centers, the field is still developing a unified framework describing how these molecules reshape thought patterns. The BCSP's research arm is filling this gap by supporting projects focused on unraveling the cognitive and biochemical mechanisms underlying psychedelic experiences. Researchers like Optometry Professor and inaugural BCSP Director Michael Silver are leveraging the profound sensory effects of psychedelics to investigate how sensory perception creates conscious experience.

Silver explains that light entering the retina is just one step in a processing cascade that allows the brain to perceive and interpret visual stimuli. "It feels like we're all just pointing our eye-cameras at locations in the visual environment and simply recording whatever's out there, but perception is actually a very active process." To translate sensory input into perception—for you to see the image on this page and interpret it as a mushroom, for example—the brain relies on predictions based on its previous experience called "priors." In many cases, priors are very stringent, informed by a lifetime of making reasonably correct inferences about the identities of objects in our visual field.

Overstimulating the brain's 5-HT_{2A} receptors with psychedelic compounds, however, appears to upend this perceptual hierarchy. This shift underlies the leading framework used to describe the compounds' therapeutic effects, called relaxed beliefs under psychedelics (REBUS). Proposed by BCSP team member Robin Carhartt-Harris, REBUS purports that psychedelics allow the brain to reroute the perceptual flow of information, bypassing the prior-informed filter and instead permitting a bottom-up integration of immediate sensory experiences. For individuals suffering from mental illnesses that involve harmful repetitive thought patterns, psychedelics could provide a temporary reprieve from prior-driven thinking, and a window of opportunity for the patient to re-write the negative mental models coloring their experience.

Directly testing the REBUS theory will be challenging, but Silver's lab will use the visual system—the neural basis of which, he says, is much better understood than a higher-order cognitive process like generating a sense of self—to test how psychedelics alter the relative contributions of prediction and sensory information to perception. The lab uses a set of optical illusions that can be interpreted multiple ways, depending on the extent to which a person is relying on prior assumptions or bottom-up integration.

Though the therapeutic potential of psychedelics is driving increased interest from the public and funding agencies, the legacy of backlash against the first wave of psychedelic research continues to cast a shadow around which researchers must tread cautiously. "Until recently," explains Silver, "psychedelics weren't widely seen as a possible revolution in mental health. Instead, they were portrayed primarily as drugs of abuse." The center's public education program, directed by author and UC Berkeley professor Michael Pollan, represents a concerted effort to create reliable sources of information about psychedelics that will be freely accessible to the public. "There's a lot of misinformation and disinformation about psychedelics out there," says Silver, "but the fact that our public education group is working with scientists who are actually conducting the research makes their message more powerful. They're actually at the front line of science together with the researchers."

The conspicuous niche that psychedelics occupy in the American zeitgeist makes the BCSP's work both challenging and vital. Through interdisciplinary collaborations, a commitment to open science principles, and continued involvement with the public and other stakeholders, the center is carving out a careful path to develop a robust research program that can withstand the pressures of ever-shifting political, cultural, and commercial interests. According to Silver, "There's really nothing like it in the history of US science."

Rachel Weinberg *is a graduate student in environmental science, policy, and management.*

DESIGN: CHENYU ZHANG

Dr. Fill in the blanks

An AI wins it all at the American Crossword Puzzle Tournament

Here's a puzzle for you: which eight-letter word describes the events of April 24, 2021, at the annual American Crossword Puzzle Tournament? Did you guess historic?

For the first time in crossword history, the tournament winner was not human, but instead a puzzle-solving algorithm developed in part by a team of UC Berkeley scientists. This tournament was certainly not the first time that a computer has beaten us at our own games. Deep Blue shocked both the worlds of artificial intelligence and chess when it defeated world champion Garry Kasparov in 1997, and then in 2011 IBM's Watson won first place in the trivia game show *Jeopardy!*. But both of these competitions play to the strengths of computers, such as rapidly calculating finite permutations. Chess is a strategy game with a limited number of outcomes, and *Jeopardy!* tasks contestants with recalling facts. In contrast, crosswords are often full of double meanings and wordplay that require a sophisticated understanding of human language.

The idea of teaching crosswords to computers was first taken up a decade ago by Dr. Matt Ginsberg, a programmer and mathematician who lives in Oregon. Ginsberg designed a computer program with a massive database and the lightning fast ability to read a crossword clue, search its memory for similar clues it has encountered before, and then figure out which possible answers fit best into the surrounding puzzle. He debuted his program—creatively christened "Dr. Fill" —at the American Crossword Puzzle Tournament in 2012. On its first try, Dr. Fill placed 141st out of 650 entrants. It slowly inched up the leaderboards each successive year, placing in 14th place by 2019, but never quite managed to edge out its competitors. While Dr. Fill was far faster than the best human solvers, it made too many mistakes.

Then, for the first time, Dr. Fill showed up with a teammate in tow. Ginsberg had partnered with the Natural Language Processing Group at UC Berkeley to improve the algorithm. The UC Berkeley scientists noted that Dr. Fill was already excellent at searching through its memory of crossword clues and placing answers within the grid. According to Nicholas Tomlin, a Department of Electrical Engineering and Computer Science graduate student on the team, Dr. Fill could even handle some types of wordplay, such as "mixing up letters within words, reversed words, or even answers that jump over black squares in the grid." But if the computer was presented with a clue that didn't use any of the same words as the clues it had already seen, it was stumped.

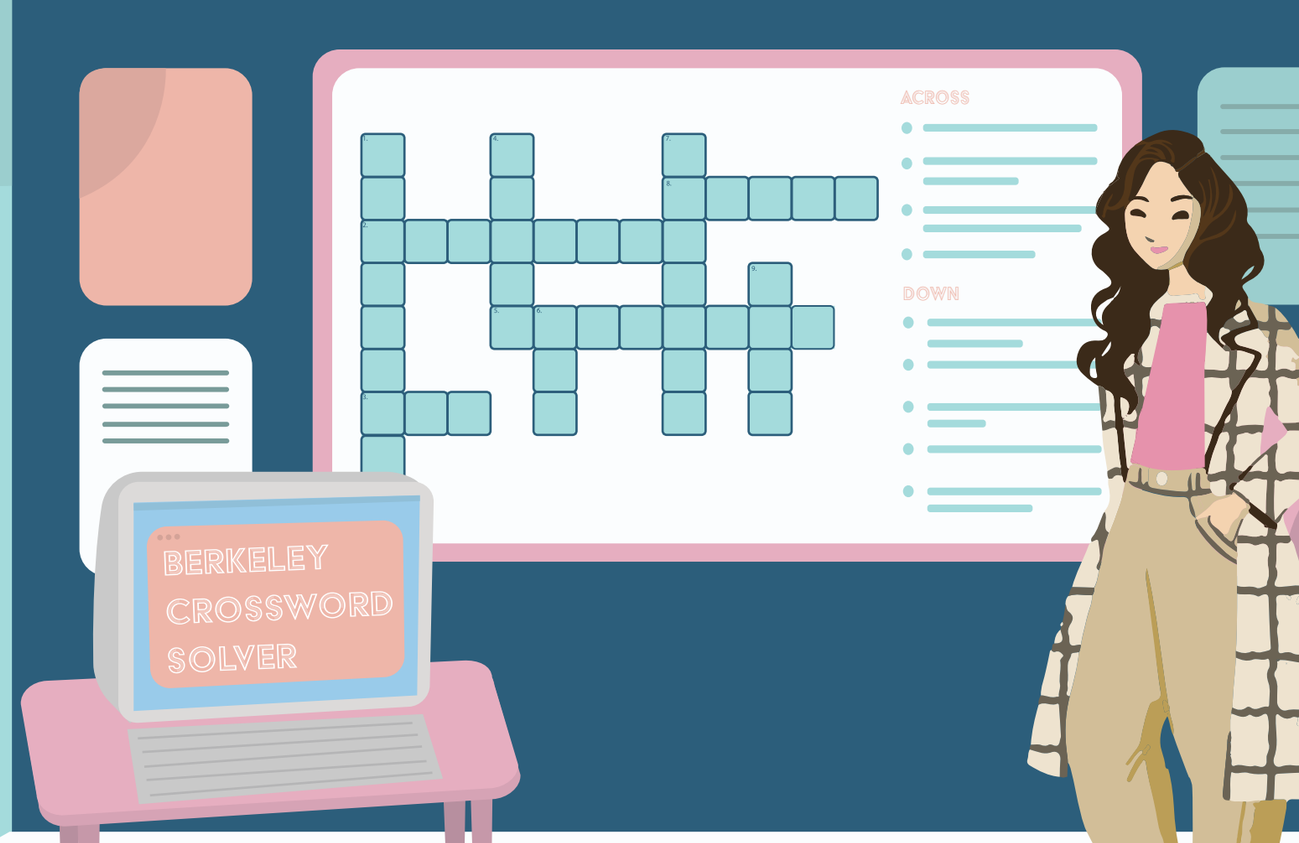
To help Dr. Fill, the Berkeley team turned to a different subfield of artificial intelligence. They developed a neural network—a complex model that mapped millions of crossword clues and answers by how close together they were in meaning. With this model, Tomlin said, "If two clues have very similar meanings but don't use any of the same words, the algorithm can pick up on that and predict that they're likely to have similar answers."

In essence, Dr. Fill had been trying to solve crosswords like a computer: assigning probabilities to millions of possible answers in the blink of an eye, without quite understanding the meanings of the clues beyond their individual words. The Natural Language Processing Group trained Dr. Fill to think more like a human, a task that requires an understanding of the emergent meaning of human language beyond the definitions of individual words. Dr. Fill's new design finally catapulted the computer into the ranks of crossword-solving elites. In a nerve-wracking end to the 2021 tournament, the algorithm racked up a score of 12,825, edging out the top human competitor by 15 points.

What's next for Dr. Fill? After the victory, Ginsberg announced that he would be retiring Dr. Fill from crossword competitions. But training a computer to meaningfully understand human language has implications far beyond puzzle solving. Language interpretation algorithms are transforming many other aspects of our society already, from translation and speech to text services to digital assistants like Alexa and Siri. Tomlin notes that computers can still struggle to understand meaning in the same way as humans, describing them as "increasingly convincing, but not always increasingly competent" over the years. He says that the field's current models "do a great job of producing fluent English, but it's not always meaningful. We trust artificial intelligence more than we used to, but we probably shouldn't." In games like Two Truths and a Lie, players often benefit from personal knowledge of one another. In other games, such as Monopoly, they must negotiate with their competitors. These are tasks that continue to be difficult for computers. So don't worry about robots beating you at all your favorite games just yet—they still have a lot to learn!

Reena Debray *is a graduate student in integrative biology.*

DESIGN: SHANNON O'BRIEN



Eran Karmon Editor's Award

In memory of Eran Karmon, co-founder and first Editor in Chief of the Berkeley Science Review, this award is given annually to the Editor in Chief of the BSR thanks to a generous donation from the Karmon family.

REELING IN THE MYSTERIES OF AGING

BY SAMVARDHINI SRIDHARAN

One fish, two fish, rockfish, new fish

Off the coast of California exists one of the most diverse group of animals in the world: the rockfish. Over 150 different species of rockfish have evolved in the last 10 million years, an explosive burst of diversity rarely seen in nature. For UC Berkeley Professor of Integrative Biology Peter Sudmant, this biodiversity is a treasure trove of possibilities for research in his lab. Not only do the number of unique rockfish make them a great model for studying evolution, but they are also useful in studying longevity thanks to their range in lifespans—from 11 to over 200 years.

Although rockfish have never traditionally been used in research labs, the Sudmant lab is leading efforts to develop tools to study them. Their recently published study and ongoing projects have resulted in several new discoveries in aging, evolution, and species diversity, thanks to rockfish's special attributes. "I was really enthralled by the diversity of life span among organisms on earth," Sudmant explains. "I wanted to find a set of species that were closely related, and yet had differences in lifespan. I almost couldn't believe how extraordinary rockfish were when I first learned about them."

Methuselah's Zoo: exceptionally long-lived animals

Stories about longevity appear in almost all cultures and religions. Professor Steven N. Austad at the University of Alabama, Birmingham, wrote a paper in 2009, refocusing the scientific interest in human longevity—and coining the phrase "Methuselah's Zoo." Methuselah is one of the oldest Biblical characters, living for nearly 970 years. Rockfish may not have lifespans as long as Methuselah, but they have achieved lifespans that alchemists from long ago only hoped. This fact, combined with rockfish's variance in lifespan, makes them one of the most important animals in Methuselah's Zoo.

Nature contains a remarkable diversity of lifespans. The mayfly has an adult lifespan of only 24 hours, whereas the Greenland shark can live for over 300 years. How long an animal can live is typically explained through its unique biology and needs. To better understand the longevity of a species, scientists often assay an organism's life history—the patterns of survival and reproduction events during the life of an organism. For example, longevity has a strong correlation with body size. The hypothesis is that larger animals live longer than smaller ones. For many years, lifespan was said to be the inverse of metabolic rate, or the number of calories an organism burns as they perform basic life-sustaining functions. Larger animals tend to do everything more slowly. Since they do not have to worry about fleeing from as many predators, they often move more slowly and are pregnant for longer. Adding to this trend, larger animals tend to age more slowly too.

Of course, any natural trend is created to be broken. Rockfish stand out as a potential exception to the trend, since they can live for almost 200 years despite their relatively small size, especially when compared to larger species like sharks and whales. While their unusual size-to-lifespan ratio may be partly explained by the environment they live in—the longest-lived rockfish spend their lives in frigid, deep waters where their metabolism is extremely slow—this exception is still remarkable and studying why and how rockfish age could answer several questions about aging.

The newest non-model organism on the block

Although rockfish may be the perfect species to understand aging and evolution, most scientists have not yet developed the necessary techniques to best study them. Instead, researchers are more likely to use model organisms, non-human species that they raise in the lab, to better understand biological processes. Typically, model organisms are easy to maintain and breed in laboratory settings, often by having short generation times, small body sizes, and short lifespans. Current examples include mice, fruit flies, nematodes, and yeast. These organisms are synonymous with science—they are the species names that repeatedly come up in textbooks, papers, and pop culture.

Working with model organisms affords scientists more protocols, infrastructure, and resources to rely upon. "When I was working in a yeast lab," explains Department of Molecular and Cell Biology graduate student Sophia Adler, "I could Google protocols and find 20 to 30 papers with different examples and conditions, which was super helpful. If I try to do that in [a non-model organism], I might get one paper—but also maybe none at all—and that happens all the time."

Studying non-model organisms such as rockfish requires overcoming many more hurdles. While entire journals are dedicated to experiments in model organisms such as yeast and mice, only a handful of articles

have been published about rockfish. When researchers work with non-model systems, one of the biggest challenges they must overcome is developing and fine-tuning new protocols. Although many methods can be adapted from other systems, much of the foundation must be laid from scratch.

Luckily, rockfish check many boxes that might also make them easier to study than most other non-model organisms. Many species of rockfish can be brought into the lab space and survive in aquariums. It is also relatively easy to gain access to them through commercial fisheries and farming, oftentimes without having to kill the fish in the process. Additionally, UC Berkeley is uniquely situated very close to the Gulf of the Farallones, located just outside the Golden Gate Bridge, where dozens of rockfish species live.

"We are very lucky that many species of rockfish live off the California coast," says Sudmant. "A graduate student in my department, Alexander Stubbs, is a commercial fisherman, and he had a boat. So, we went fishing! We also enlisted the help of other fishermen, the National Oceanographic and Atmospheric Association (NOAA), and a number of museums."

Sudmant's collection of rockfish samples also implies that studying non-model organisms is no longer as difficult as it used to be. "People use worms and yeast to study lifespan, because they are wonderful organisms you can grow in the lab," Sudmant says. "You can even do that with mice—even though they live for two years. But you can't do that with rockfish because their lifespan is longer than a researcher, let alone a graduate student. Rockfish are never going to be a model organism in that sense."

"But the world is changing now," Sudmant continues. "Technologies allow us to completely deconstruct the genomes of all kinds of organisms. Simultaneously, technological advances in the lab are allowing us to make cellular models for the first time, and do all kinds of very cool experiments."

So, while rockfish may never have the traditional and vaunted status of model organism in the old sense of the word, they have become one of the first species to herald a new age of biological science research. In this innovation, the Sudmant lab leads the charge in developing the first protocols and techniques to determine how to best study rockfish and, in a larger sense, non-model species as a whole.

Going fishing on a scooter

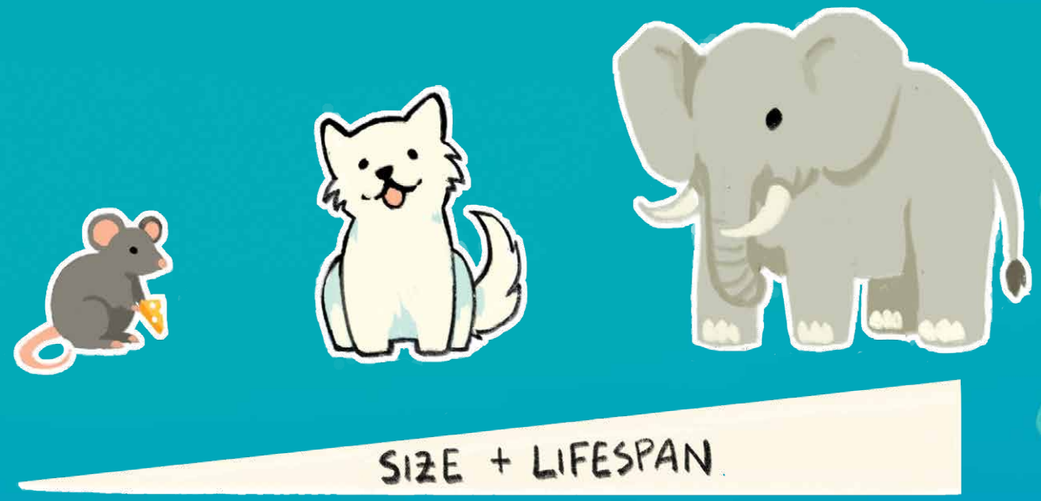
Department of Integrative Biology graduate student Stacy Li is one of the first researchers to take on the challenging and oftentimes daunting task of developing the proper protocols and techniques necessary to prepare rockfish for specific laboratory experiments.

Earlier this year, the Sudmant lab was receiving samples of "fin clips," small hole-punches of fish fins that are a relatively non-invasive way of collecting DNA samples. Based on technical application notes about DNA extraction, Li believed that they would be able to collect high molecular weight DNA. This type of DNA is intact and contains long reads of sequences. High molecular weight DNA is of particular importance as it has haplotype information. Haplotypes are blocks of DNA which are typically inherited together, but are sometimes broken up over many generations, resulting in genetic variation. By extracting high molecular weight DNA, researchers may be able to use haplotype information to understand how rockfish evolved.

But Li was not seeing these haplotypes in the fin clips they were processing. There was no DNA present in their samples, let alone the long DNA they'd need for computational analysis. "If the problem was the biological sample," explains Li, "I didn't want to waste any more of the precious ones we've been sent—I was just going to have to find some more fish fins." Collaborator samples were limited, and Li was keen to minimize the number of samples that needed to be collected due to the significant effort involved.

So, Li hopped onto their trusty scooter,

DESIGN: LIYA OSTER



took their bag and some cash, and went over to Monterey Fish Market. Through the store's Instagram page, Li had noticed that they sold several varieties of rockfish. At 9 a.m. on a weekday morning, Li went up to the fishmonger who was laying out some rockfish on ice.

"My first question to him was: 'How long has it been since this died?'" says Li. "Time from death and temperature storage are two of the biggest contributors to determining whether or not we'd be getting high molecular weight DNA, but he didn't know the exact answer—guessing that it could be anywhere between one and three days."

While this number is excellent for human consumption, it wasn't the best condition for DNA. This experience confirmed Li's fears: even exemplary standards for fish storage for human consumption were not ideal conditions to study biology. Regardless, Li wanted to give it a shot and scooted back to campus with their bounty.

Back on campus, Li made careful notes and decided to collect samples from their fish's organs. They planned out storage conditions and cleaned their fish for processing. Generally, the fish fin, heart, blood, spleen and gonads should contain the most amount of high molecular weight DNA.

"As I'm clipping away at this fish with a picture of fish anatomy as a reference, my whole lab was standing around me guessing what the organs were," Li laughs. "It was a fun and weird thing. All the biology I'd done before had been in petri dishes and little tubes."

Several hours later, Li was left with tubes of samples containing high molecular weight DNA, and the body of their mutilated fish—which they proceeded to take home for dinner.

Understanding the evolution of aging

What Li successfully obtained from their rockfish samples lay the framework for the Sudmant lab to answer several questions about the evolution of aging. Rockfish are powerful models to study evolutionary relationships because they make up a clade, or group of organisms believed to have evolved from a common ancestor, for over 10 million years. This large amount of time means that individual species had more time to accumulate mutations, while conserving bits and pieces from a common ancestor. Mutations change the structure of genes, and usually occur at a steady rate. The more species that exist means that more pieces of the common ancestor have been conserved. Thus, by having more species that evolved from the same ancestor, researchers have more data to put together the original genome of the original ancestor. In the process, they can also figure out what genetic changes underlie the presentation of certain traits in the organisms of today.

When assembling genomes, scientists often rely on a high-quality reference genome. Making a reference genome is a complex process. In an ideal world, the entire length of the genome would be read by a machine, outputting the different nucleotides of the genome sequence (A, T, G, and C) as it goes. However, because this technology doesn't exist yet, scientists must assemble the genome from small fragments of DNA.

This process is akin to taking 10 copies of a newspaper and shredding it. Some of the pieces will overlap, allowing you to rebuild the pages. If a particular page or fragment has seven copies of the same words at the same position, the "read depth" is said to be 7x. Parts of the rebuilt newspaper may have only one or two copies, and would therefore have a lower read depth. A lower read depth gives scientists less confidence that they truly have the correct sequence of words and that a typo was not introduced—but many times that's all they have to work with. Ultimately, by chopping many copies of the genome into fragments, researchers can then sequence those fragments, called "reads". By noting where the reads overlap, scientists can put the DNA fragments in the right order.

Previously, reads were around 1,000 nucleotides long, which made some parts of the genome, especially where there were many repeats, unclear. However, the Sudmant lab was able to use recent long-read sequencing technologies, which increased the length of the reads to up to 100 thousand nucleotides. Longer reads allow for more clarity. In other words, each individual shred of the newspaper is longer, so instead of using just letters to put the page back together, you are using sentences, phrases, and paragraphs. When it comes to rockfish genomes, not only do long reads make for a more accurate assembly, but they also allow for more confidence. By

DESIGN: LIYA OSTER

using this method, the Sudmant lab was able to build high-quality reference genomes for many of their rockfish.

These long-read sequences allow scientists to faithfully reconstruct the evolutionary history of every gene in the rockfish. With this capability comes an incredible power to detect any genetic changes associated with the longevity of long-lived rockfish relative to short-lived rockfish. In fact, researchers in the Sudmant lab worked with 88 different rockfish species to pinpoint 137 genes that were correlated with an increased lifespan. However, lifespan in rockfish is strongly correlated with both body size and environmental factors. What this finding means is that some of the genes associated with lifespan may primarily act by influencing growth or may facilitate adaptations to cold, deep-ocean environments where long-lived rockfish are more likely to live, rather than directly promoting longevity.

To identify genes associated primarily with longevity, the group had to parse out which genes were associated with lifespan independently of body size and environment. The group used a statistical model to identify 56 genes that were independent of rockfish body size and the ocean depth at which they were found. These included several genes that were known to increase lifespans across other animals, including insulin and glucose signaling and butyrophilins, genes which regulate the rockfish immune system and are known to suppress inflammation in aging humans.

From fish to humans: what would translation look like?

"We found that butyrophilins have a higher 'copy number' in ultra-long-lived species," Sudmant explains. "This highlights a specific set of genes and pathways that might be important to follow up in humans."

Insulin signaling, identified as another one of the primary genes related to longevity in rockfish, is one of the most important pathways in aging. Rockfish also have their own insulin-like factors which have undergone different changes due to mutation. Speculatively, scientists could use an insulin-like factor in long-lived rockfish and observe changes when inserted into the genome of short-lived rockfish. If the new gene indeed extends the fish's lifespan, then these factors could be inserted into genomes of mammals more closely related to humans than fish. Extensions in lifespan in model organisms may suggest that these factors could be used in humans next.

However, the lead author on the study, postdoctoral researcher Dr. Rohit Kolora, is cautious when talking about the translation of longevity in rockfish to humans. "Longevity from rockfish is not something we can directly translate into humans," Kolora explains. "Something that increases longevity in deep-sea fish may not work in freshwater fish. What works in freshwater fish might not work in birds. And what works in birds might not work in humans."

But Kolora still has big plans for rockfish and the problems they might solve some day. From better sequencing reads to molecular manipulation, Kolora is hopeful that better genetic datasets and tools will keep rockfish studies moving forward. "We have the capability to culture rockfish cells, and manipulate them with genomic tools to remove specific genes from the rockfish and see how the removal impacts the health of cells," Kolora says. "There's a lot more to learn when it comes to rockfish longevity."

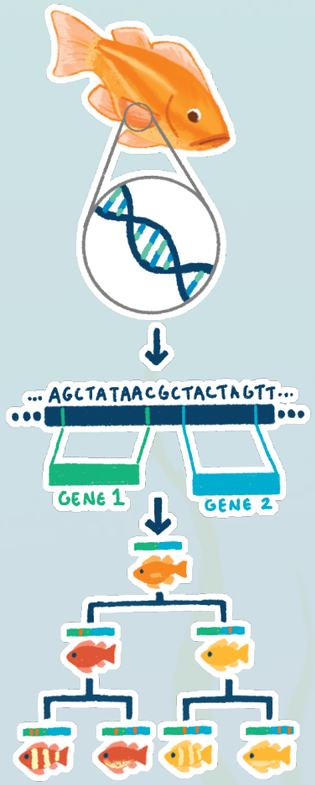
Besides lifespan, translational studies from rockfish would also provide insight into health span—or how long an individual stays healthy. One of the criticisms of current human aging research is that there is little use to living for a long time if it means being tied to machines, medications, and end-of-life care for years or even decades. Because rockfish are wild animals, who spend their 200 years eating and hunting, they must maintain fitness into old age.

What would health span studies look like in humans? Studying longevity isn't feasible because such research would require a clinical trial in which a participant may outlive the clinician. Instead, researchers may look at certain diseases which arise only in old age, such as Parkinson's or Alzheimer's disease. They could then see if a cohort treated with a drug mimicking a rockfish biomolecule suffers from fewer cases of the disease.

While it may be years before rockfish studies are translated into humans, we may see these genes manipulated in mammals, and perhaps even our pets, sooner than that. "Aging is a disease that can be solved," says Dr. Juan Manuel Vazquez, a postdoctoral researcher in the Sudmant lab. "It is no longer an intractable problem."

Rockfish through history—from bountiful to collapse

Even besides aging and evolution, rockfish can answer other questions, such as the role humans play on rockfish ecology, and on the environment as a whole. A staple fixture in the Sudmant lab is the fish freezer (nicknamed "British Columbia" as a nod to Sudmant's Canadian roots), filled with dozens of samples of rockfish collected over several fishing expeditions. One of the frozen residents is the boccacio. This species of rockfish was once prevalent off the California Coast, and its large size lent itself for human consumption. Boccacio live for almost 50 years—much longer than most fish species that are farmed. However, because of their long lifespan, when the population was



DESIGN: LIYA OSTER

One fish, two fish, rockfish, new fish

decimated in the early 2000s due to overfishing, it left the younger fish to repopulate. Because the boccacio are so long-lived, changes in their population structure have persisted a long time.

"This population collapse created a massive human-shaped hole in the boccacio population," explains Li. "It's important to study this phenomenon because California is flush with resources for human consumption and living—especially in the Bay Area. We obtain so much of our diet from local production—and that includes rockfish. If we are not careful about the way we conduct stewardship of our natural resources, we could end up decimating more populations."

Boccacio fisheries have been recovering since 2004 due to careful management from California Fish and Wildlife. But in this situation, rockfish present an interesting study of a human-made phenomenon that impacts a species that lives for an unusually long time. And most importantly, their ecology is tightly entangled with ours.

Modern examination of rockfish is one way the boccacio population structure is being studied. The other method is to examine historical rockfish to understand the human impact on rockfish over time. This kind of study can only be done longitudinally—a research design that involves repeated observations of the same variables over long periods of time—and the Sudmant lab is one of the few researcher groups able to lead a project due to their extensive groundwork on how to process rockfish samples in the laboratory.

In a collaboration with NOAA and Dr. Milton Love, a research biologist at the Marine Science Institute at University of California, Santa Barbara, the Sudmant lab obtained boccacio samples over the course of 15 years—from 2004, when boccacio fishing became regulated by the federal government, to 2019. The lab received 400 samples.

The clips, about a hole-punched millimeter in size, were used to get short fragments of DNA, which were compared to a reference genome. A representative subset of these samples would allow the researchers to see how the immense depletion in 2004 to 2019 would affect the genetics of a population.

"This isn't just a story about fish," Li elaborates. "It's also a story about how humans are affecting the world around them. If we are not careful, we could end up creating population changes and affecting the genetics and genomics of the population for generations to come."

Just keep swimming: what's next for the rockfish?

"The thing that I find most exciting about our study is that we identify both the causes and the consequences of extreme lifespan," describes Sudmant. "It means that not only are there genetic changes that allow these fish to live so long, but, because they live so long, long life is also reshaping patterns of genetic diversity."

There is still more work to be done. Statistical methods allowing researchers to look back in time have shown that there is a very tight linkage between size of a population and lifespan. That is, longer lived species have smaller population sizes than shorter ones.

"We are continuing to study the genetic diversity of these fishes, particularly at the population level," Sudmant explains. "This project was more about comparing between species, not within species and I am really excited to understand the relationship between the extraordinary lifespan of these fishes and their rapid speciation."

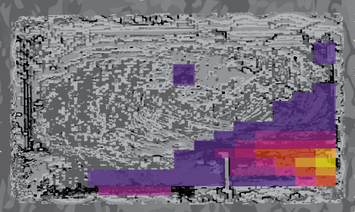
The lab also plans to strengthen their understanding of the functional consequences of some of the genes they found, by growing fish cells in the lab and manipulating them. Similarly, there are also efforts to build more long-read reference genomes. "If we have better reference genomes," Kolora explains, "we may be able to make stronger and better conclusions about the evolution of aging."

In the meantime, the Sudmant lab is already revolutionizing our understanding of aging and evolution. "Aging is as fundamental a biological trait as DNA is part of cells," explains Vazquez. "It is a programmed process. Rockfish are simultaneously helping us understand one of the most fundamental processes of life, but also helping us understand how that process came to be."

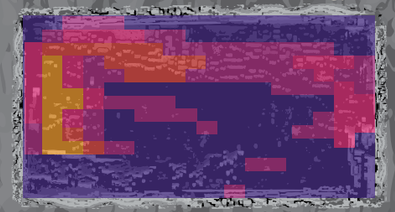
Samvardhini Sridharan *is a graduate student in molecular and cell biology.*

from the field

Late in the night on April 26, 1986, Chornobyl Nuclear Power Plant Unit 4 was scheduled for routine safety testing. Preparations for testing left the reactor in an unstable condition, resulting in a meltdown followed by explosions that destroyed the reactor building and released radioactive material for many days after. To many, Chornobyl remains a symbol of why nuclear energy should not be widely adopted. Despite this event, Ukraine sees benefits in remaining largely dependent on nuclear energy. Nuclear energy provides Ukraine a carbon-free source of energy without having to rely on fossil fuels from Russia. However, as history has made clear, there are risks associated with this technology. While the probability of an accident like what happened at Chornobyl is low, the impact can be long-lasting. Through technology recently developed at UC Berkeley and Lawrence Berkeley National Laboratory (LBL), we can better explore this impact to understand the risks of nuclear power 35 years after an accident.

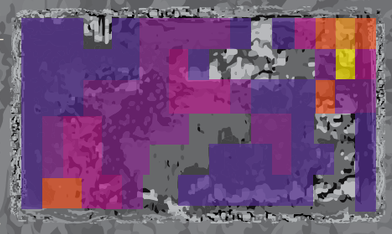


In May 2018, a team of scientists from Professor Kai Vetter's group at the UC Berkeley Department of Nuclear Engineering and LBL visited Chornobyl and the surrounding areas with a gamma-ray imaging system to construct maps of the remaining contamination. Graduate student Jake Hecla, who visited the site, explained, "We went to Chornobyl because it was effectively a field test of our technology applied to its ultimate purpose. The whole point of this technology is to map and eventually quantify radiation environments for worker safety and a variety of other reasons."



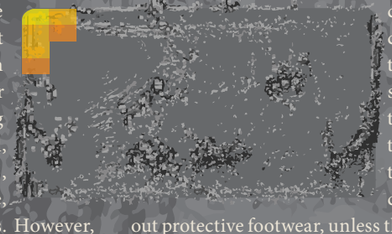
As the team scanned the exclusion zone using the imager, the system gathered data from its contextual sensors (a laser-based LiDAR, a visual camera, and an inertial measurement unit) to perform simultaneous localization and mapping (SLAM). SLAM constructs a 3D map of the environment and determines the location of the gamma-ray imager within that map during the measurement. This information paired with radiation data unlocks the ability to estimate where radiation is emitted from while freely moving through a contaminated environment. This technology, developed by LBL, and called Scene Data Fusion, can build large 3D maps of contamination remaining from an accident just by briefly walking through an area.

One of the main environments of interest during the measurement campaign was Pripyat. Pripyat was built in the 1970s alongside the plant to house the workers and their families. Although the town has remained abandoned since its residents were evacuated following the accident, Pripyat has emerged as a site of modern public interest. Ukraine, facing poverty and war, has utilized Pripyat tourism as a resource to support its economy and finance expenses associated with decommissioning Chornobyl. One of the dreams that Ukraine has envisioned for Pripyat is a science and technology park to educate the public about what happened at Chornobyl and to reflect on the risks and benefits of nuclear power. Understanding the radiation environment at Pripyat is vital not only for the safety of its workers and tourists, but also for enabling its decontamination so it can be used for education.



Among the amenities in Pripyat is a town center which houses the Palace of Culture Energetik, a community center for residents to enjoy recreational activities, such as swimming, watching films, and dancing—the building even contains a shooting range in its basement. In the town center, there are a number of fountains that were once enjoyed by Chornobyl workers and their families on their days off. The 3D radiation map of this area shows that, today, those fountains see little activity, save for the occasional tourist and the radioactive cesium (Cs-137) contamination leftover from the accident. As rainwater falls and pools in the bottom of the fountains, it attracts the nearby Cs-137. When the water evaporates, the contamination remains.

The Pripyat amusement park completed construction in 1986 and was slated to open for May Day celebrations. Should the disaster not have occurred, May 1st would have seen families with their children riding the Ferris wheel, bumper cars, paratrooper ride, and swing boats. However, when the accident occurred just days before its opening, the May Day celebrations were canceled, and the amusement park remains abandoned, without ever having been operated. The radiation map of the amusement park shows the Ferris wheel itself contains negligible activity, but some Cs-137 contamination can be found in the nearby soil. The bumper cars sit on an elevated platform, and the radiation map reveals that any contamination that had accumulated among the cars has long been washed away to the platform edges by rainfall.



Radiation mapping has seen many advances since the 1986 accident at Chornobyl. With Scene Data Fusion, we can now perform rapid reconstructions of radiation in 3D environments. We can see in detail where contamination remains in Pripyat, and use this knowledge to protect visitors; they could be cautioned to avoid stepping in the fountains or near the bumper cars without protective footwear, unless they want to leave their shoes behind when they go home. The maps can also guide workers to focus on specific areas for further decontamination, so the area can be fully reopened. Cleaning up the area can lead to a "return to normal," where people can visit without radiological controls to learn about the risks and rewards of nuclear power and see that even when the consequences are dire, such as in Chornobyl, eventually we can see life return.

Kalie Knecht *is a graduate student in nuclear engineering.*

DESIGN: NICOLETTE PUSKAR

From molecules to memories

How UC Berkeley's neuroscientists are taking a multidisciplinary approach to understanding neurodegenerative disease

Gergey Alzaem Mousa

DESIGN: KRISTINA BOYKO

This past October, UC Berkeley's Helen Wills Neuroscience Institute (HWNI) held its annual retreat. Gathered within Cal's football stadium, professors and students from across the institute presented novel research developments and future directions. However, the most striking feature of the gathering wasn't the research being presented per se. It was the sheer breadth of science present. Cognitive scientists rubbed shoulders with cell biologists and systems neuroscientists alike, all in the same intellectual space. It was a refreshing sight, and a far cry from the archetypal academic environment where researchers are often found publishing and presenting only within their specialized fields.

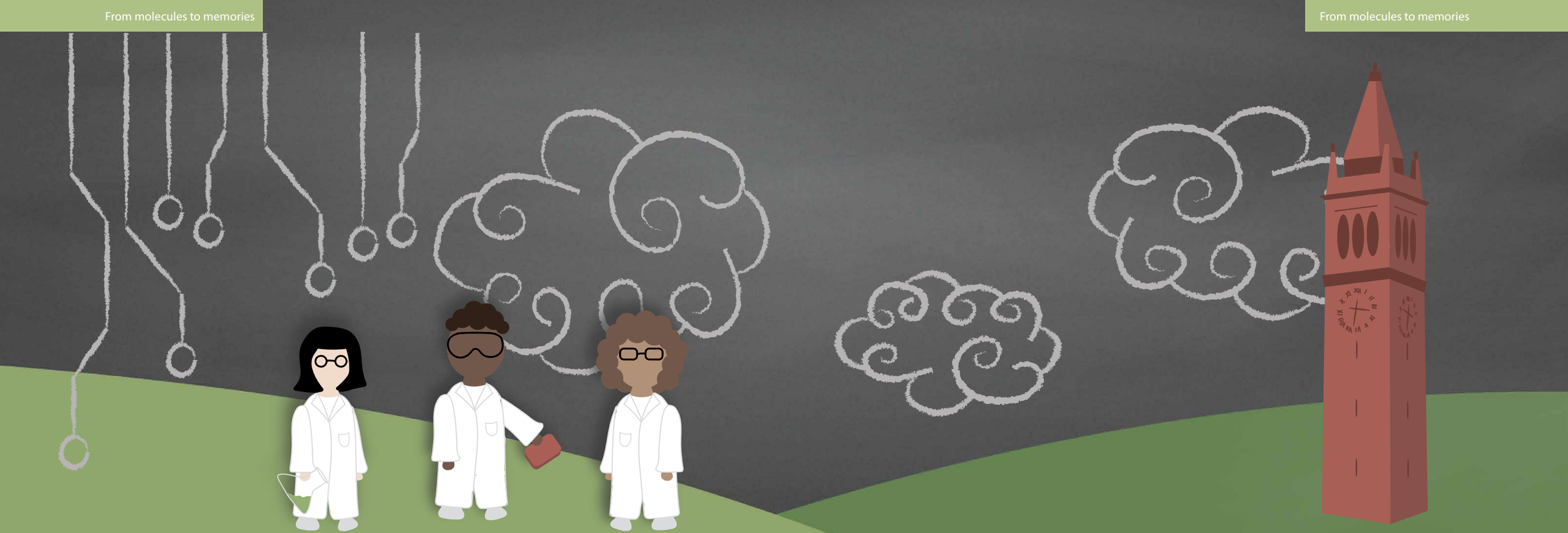
Neuroscience research increasingly necessitates approaches from multiple subdisciplines. Any one approach alone would likely fail to capture the complexity of a given neural phenomenon. Take memory, for example. At the broadest level, cognitive neuroscientists assess memory by measuring activity in specialized regions of the brain and monitoring how a subject's memory may be perturbed under certain conditions. On a deeper level, systems neuroscientists disentangle how neurons wire together to process information and yield memory formation and recall. Deeper still, cellular and molecular neuroscientists probe how the individual neurons that make up the neural circuits of memory develop and function. Importantly, it's only when all three domains are considered together that such an immensely complicated concept as memory can be comprehensively understood.

Within UC Berkeley's cross-departmental HWNI, discoveries in and across cognitive, systems, and cellular and molecular neuroscience are being made in pursuit of understanding a devastating set of pathologies: neurodegeneration. Neurodegeneration encompasses a group of diseases—including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis—characterized by neuronal death and loss of neural functions such as memory, cognition, sensory perception, and motor abilities. An estimated 6.5 million Americans over the age of 65 are living with Alzheimer's disease alone. Furthermore, neurodegeneration poses an increasingly significant public health burden over the next few generations, as increased age represents the largest risk factor for neurodegeneration and the aged demographic is growing rapidly worldwide (it is estimated that a fifth of Americans will be over the age of 65 by the year 2030). Unfortunately, however, the field's understanding of these diseases and their causes is incomplete, and current treatments to address them remain limited. To tackle these questions, researchers at UC Berkeley are leveraging neuroscience's multidisciplinary nature and investigating these diseases across subdisciplines.

A molecular perspective: halting neurodegenerative protein aggregation

Starting at a microscopic scale, investigators are trying to understand the cellular and molecular drivers of neurodegeneration. In neurodegenerative disease, neurons and other cell types of the brain become damaged and eventually die when normal cellular processes go awry. Neurodegeneration demonstrates a variety of pathological features, from dysfunction in organelles (such as the

From molecules to memories



energy-producing mitochondria and the waste-disposing lysosomes) to immune activation and cellular stress. However, of all the cellular features of neurodegeneration, one is considered a key hallmark of neurodegenerative disease: protein aggregation. These aggregates take shape when specific proteins in neurons are misfolded and clump together. Nearly every neurodegenerative disease, from Alzheimer's to Huntington's, involves the formation of protein aggregates, though each disease involves a different protein or set of proteins. What gives rise to these aggregates and to what extent they drive disease progression is still an area of active research, but their correlation with neuronal dysfunction is well established. The Rapé lab, led by Professor Michael Rapé of UC Berkeley's HWNI and Department of Molecular and Cell Biology, is taking a unique approach to studying how these protein aggregates initially emerge in a cell.

Rapé broadly describes his lab's research as working to "understand the signaling pathways that allow cells to either obtain a particular fate or preserve it." To preserve a homeostatic, or stable and functional, cellular state, cells employ a series of quality control systems which act as internal self-regulating mechanisms. One focus of the Rapé lab is how ubiquitin, a cellular tag that marks proteins for degradation, plays a role in maintaining protein homeostasis. It was through investigating this quality control system that the Rapé lab serendipitously uncovered a connection to neurodegeneration. "Starting with a discovery by a graduate student that there are specific [ubiquitin] chains that are better signals for degradation," Rapé explains, "we see that there are different tiers of quality control. Some are really, really powerful, and they are focused on the aggregation-prone proteins."

It was this connection between quality control systems and protein aggregation that prompted the lab's foray into neurodegeneration. The lab began studying how specific E3 ligases, the class of enzymes that tag proteins with ubiquitin, mediate degradation of proteins that are susceptible to aggregation in neurodegeneration, and how mutations in these enzymes may be implicated in pathology. "The more we move into the quality control field, the more we come upon neurodegenerative diseases and discover enzymes that are mutated in neurodegenerative diseases," Rapé affirms.

Using E3 ligase-mediated degradation as a foundation, the Rapé lab has begun exploring how cells degrade a variety of protein aggregates implicated in numerous neurodegenerative diseases. This work represents neurodegenerative research at a deep, molecular level. Rapé shared how he envisions this work translating into therapies that could combat decline in human cognition and memory, functions that extend far past the cellular level. "If you want to focus on either small molecule strategies or even gene-editing strategies, I think you need to have a very clear understanding of the molecular machinery." Rapé elaborates, "For us, that's always been a driving force. We want to understand how it works, we want to solve the structures, we want to do all these things. Then we already have an extremely good starting point to go to the next step, which is how can we manipulate it in treating disease." Through researching protein aggregates as they form, the Rapé lab's work illustrates how the molecular features of a degenerating neuron can be picked apart to both better understand the basic cellular machinery involved and to synthesize novel approaches for treatment.

Aggregating proteins, however, represent just one step in a cascade of cellular events taking place inside a degenerating neuron, each of which has the potential to be therapeutically targeted. This broad assortment of diseased cellular processes is mirrored by the range of molecular neurodegeneration studied within UC Berkeley's Department of Molecular and Cell Biology. For example, the Bateup, Hockemeyer, and Rio labs are collaborating to investigate how different gene variants are implicated in Parkinson's disease using human brain organoid models. The Olzmann lab is identifying the mediators of ferroptosis, a newly defined form of cell death implicated in numerous neurodegenerative diseases. The Hurley lab is probing how the lysosome can stop the spread and aggregation of pathological proteins in neurodegeneration. Additionally, the Hurley and Park labs are collaborating to better understand how lysosomes can relieve the problems caused by mitochondrial dysfunction in Parkinson's disease. The Dillin lab is investigating how maintenance of the proteome, or the set of proteins expressed by a cell, declines in aging and neurodegeneration. And the Schekman lab is investigating the mechanisms through which alpha-synuclein, the protein aggregate implicated in Parkinson's Disease, is unconventionally secreted from neurons and spreads throughout the brain. Ultimately, whether it's through stopping protein aggregation or preventing ferroptosis, researching the molecular mechanisms underlying neurodegeneration allows for a better understanding of what could be driving the pathology and paves the way for therapeutic interventions to treat these diseases at the cellular level.

DESIGN: KRISTINA BOYKO

A systems perspective: using dopamine targets to treat Parkinson's disease

In parallel with research on a molecular scale, systems neuroscientists have a different perspective on neurodegenerative research. Their work seeks to understand the neural circuits that process the activity of individual neurons and transform them into behaviors. One approach to neurodegenerative research within this sub-discipline is that of the Dan lab, led by Yang Dan of the HWNI and the Department of Molecular and Cell Biology, which studies the neural circuits that mediate sleep and how those circuits are perturbed in Parkinson's disease. Another approach involves investigating a neural circuit by zooming in on the dynamics of neurotransmitters, the chemical signals passed between neurons. The Isacoff lab, led by Ehud Isacoff, who is also a professor in the HWNI and the Department of Molecular and Cell Biology, is probing how one such neurotransmitter—dopamine—functions in the specific neural circuits that mediate motor movement.

Although popularized as the "feel-good" chemical, dopamine plays a role in far more than just mood. It has a hand in movement, pain sensations, and bodily functions such as heart rate and blood vessel changes. "Dopamine, which is key, functions in just so many aspects of brain behavior," Isacoff explains. "Whether you're trying to dissect the functions of a circuit and understand what dopamine is doing, or you're trying to

understand the mechanism of pathology, or you're trying to develop a treatment for the pathology, in all cases you're confounded by the multifarious nature of dopamine signaling." In this way, dopamine research poses a catch-22: dopamine's broad range of functions highlights the need for a more detailed understanding of its role in specific contexts; however, trying to achieve a more detailed understanding is often confounded by how widespread its signaling is.

To overcome the challenges inherent to dopamine research, the Isacoff lab has developed a set of molecular tools to activate or block, in a timed manner, specific dopamine receptors in specific cells and brain regions. These tools build off optogenetics, a branch of neuroscience in which one can control the firing of neurons with light. This is commonly accomplished through artificially expressing a naturally light-activated channel, which was originally found in microbes, in a specific class of neurons. Shining a pulse of light over the brain opens these channels and induces those neurons to fire. The Isacoff Lab, in collaboration with UC Berkeley's Kramer lab and the Trauner lab (now at New York University), has instead focused on artificially activating the endogenous channels of the brain. They have developed chemical optogenetics in which the native signaling proteins of the nervous system are made sensitive to light, thereby gaining optical control over the physiological channels that control neural firing. In the past few months, the Isacoff lab reported the first photo-agonist (an optically controlled chemical that activates a receptor) for a specific subset of dopamine receptors, which can be targeted to one cell type in a circuit of the brain that controls movement. Activating these engineered agonists with light effectively simulates the natural signaling that occurs when dopamine is released onto those neurons. Overall, these photoswitchable dopamine agonists allow for a robust and highly controlled method for studying dopaminergic action by zooming in on dopamine's neuronal targets.

This technology becomes particularly relevant when trying to research Parkinson's disease. Parkinson's disease is characterized by the death of dopaminergic neurons that originate in a deep structure of the brain called the substantia nigra and then project out, releasing dopamine to other regions of the brain. Loss of dopamine signaling in Parkinson's disease causes problems with motor functions, with patients suffering from tremors, slowed movement, and stiffness, among other symptoms. Current treatments for Parkinson's disease focus on increasing dopamine levels indiscriminately in the brain. In contrast, the work of the Isacoff lab is oriented towards future treatments that can replace dopamine signaling to the neurons that have lost it, when they need it.

The connection to neurodegeneration is an exciting prospect for the Isacoff lab. "So far we have seen that our dopamine agonists can induce movement initiation in healthy animals. The next step is to test whether this also works in the Parkinson's models," Isacoff explains. This work would yield therapies that differ from treatments that try to prevent the death of the dopaminergic neurons. Instead, this systems-level research asks: where and how do the neurons that die interact with other neurons, and how can this interaction be compensated for? "This is a different approach. This is a prosthetic approach that's meant to correct for the loss, not prevent the loss," Isacoff affirms. Nonetheless, both strategies have the potential to improve lives and contribute to a more comprehensive understanding of neurodegenerative disease.

A cognitive perspective: tying cognitive decline to amyloid and tau in Alzheimer's patients

Molecular and systems neuroscience affords us a mechanistic understanding of neurodegenerative pathology on cellular and subcellular scales; however, a more global analysis of neuropathology, and one done with human subjects, is where the strengths of cognitive neuroscience lie. Generally, cognitive neuroscience seeks to understand how the brain mediates behavior in a broad sense and where in the brain different information is processed. The Jagust lab, led by William Jagust of UC Berkeley's HWNI and School of Public Health, uses brain imaging technologies to address these questions in the context of aging and Alzheimer's disease. "We're interested in how the brain produces behavior," Jagust explains, "and we're interested in how systems in the brain interact with pathology to produce abnormal behavior." The Jagust lab uses PET scanning to identify the location and concentration of certain pathological proteins in the brain. "We have the tools to, on the one hand, look at cognition and take it apart in various ways, and on the other hand, we have the tools to look at pathology in a living human," Jagust explains.

A driving force of the Jagust lab's research is to understand the relationship between the presence of protein aggregates and cognitive decline in Alzheimer's disease. A hallmark of Alzheimer's disease pathology is aggregation of the proteins beta-amyloid, which form plaques, and tau, which form neurofibrillary tangles. In the early days of this research, scientists only had the tools to visualize beta-amyloid in the brain, which led to a very unclear relationship between protein aggregates and cognitive dysfunction. "The first studies that came out showed no relationship between where the amyloid is in the brain and the kinds of cognitive loss a person had. In fact, there was an extremely weak relationship. In general, you could have quite a lot of amyloid in your brain and be cognitively normal," Jagust says.

However, when the tools to measure tau in the brain were developed, things began to click. "When we started to be able to visualize tau, we got a very different picture," Jagust explains. "The amount of tau in the brain is very correlated with how cognitively impaired you are and also with the type of cognitive impairment you have. There's also a relationship between the amount of amyloid in the brain and the amount of tau in the brain." These findings led to a new hypothesis connecting these two types of protein aggregates and cognitive decline. "What we think is happening is that amyloid is driving the tau and that tau is driving the cognitive dysfunction," says Jagust. Other work has substantiated this idea by correlating the location of tau in the brain and specific forms of cognitive impairment. To this end, Jagust explains how Alzheimer's disease patients with visual and spatial disorders, for example, have an increased concentration of tau in the occipital cortex, the region of the brain largely responsible for visual processing.

Establishing this kind of framework to describe the basic relationship between the presence of pathological protein aggregates and cognitive decline in humans has been fundamental to the field. This work has informed research on both how therapeutic modalities should target these proteins when trying to treat Alzheimer's disease as well as what molecular mechanisms could explain this disease progression in humans. To this latter point, the Jagust lab has an ongoing collaboration with the Kaufer lab, led by Daniela Kaufer of UC Berkeley's HWNI and Department of Integrative Biology, that seeks to uncover some of the underlying factors driving beta-amyloid deposition in aging individuals. Specifically, this collaboration investigates the relationship between the spread of beta-amyloid and blood-brain barrier deterioration. The blood-brain barrier constitutes the specialized blood vessels that prevent most molecules and cells from entering the brain as readily as they would in other organs. It gives the brain an extra layer of protection against pathogens or other potential threats. Previous studies from the Kaufer lab and others have demonstrated that this barrier gradually breaks down as one ages. Additionally, the Jagust lab, among others, have shown that amyloid deposition in the brain increases with age. Therefore, the questions asked by the Jagust and Kaufer labs are: does disruption of the blood-brain barrier lead to the deposition of beta-amyloid? Or does the deposition of beta-amyloid lead to disruption of the blood-brain barrier? Or are these two totally unrelated processes?

"To make a very long story short, we're still in early stages, but we think there's a correlation between the amount of beta-amyloid in the brain and the amount the blood-brain barrier is disrupted," Jagust explains. "But this still doesn't tell us the mechanism. It's just a correlation." That's why collaboration between the Jagust and Kaufer labs is critical. The Kaufer lab is able to probe this mechanism by strengthening and weakening the blood-brain barrier in mouse models of Alzheimer's disease that have beta-amyloid pathology. Overall, this collaboration represents a unique bridge connecting the cognitive and molecular ends of neurodegenerative research. "[This project] is a way to take observations in humans and dig into the mechanisms that underlie them, because if those things really are linked, then that's a whole new pathway for therapy," Jagust affirms.

From molecules to memory and from memory to molecules

Neuroscientists at UC Berkeley are taking robust, multifaceted approaches to understand the brain's vast complexity. Together, they contribute to a growing body of work that comprehensively probes the nature of neurodegeneration, from its origins to its potential treatments. Approaching this complex, multi-layered set of diseases requires new and unique tactics that increasingly cross the lines of sub-disciplines. Ultimately, the future of neurodegenerative research lies at the intersection of different specialties. The cross-departmental nature of UC Berkeley's HWNI has made it a leader in that effort.

Walking out of last October's HWNI retreat, having just heard from a myriad of scientists studying the brain on all levels, one was left awestruck with just how complex understanding the brain is. And yet, despite the daunting nature of that challenge, there was a persistent sense of hope that all those researchers, with their disparate interests and techniques, might just pull it off, together.

Gergey Alzaem Mousa *is a graduate student in neuroscience.*

DESIGN: KRISTINA BOYKO

labscopes

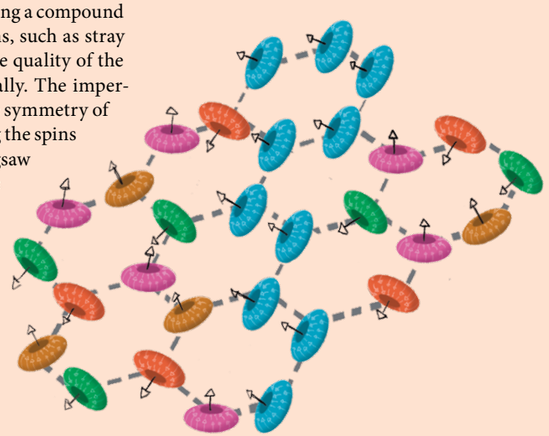
Spin to win

Although computer chips have been getting exponentially faster as the decades go by, we're fast approaching a fundamental limit on how many transistors, or microscopic switches, we can fit onto a chip. Scientists may be able to bypass this limit by replacing transistors with a new kind of switch: a "spintronic" switch. These devices rely on a quantum property called spin to toggle between on and off.

Even though electrons don't spin in the same way a top does, they do have a fixed amount of rotational momentum, which physicists call spin. The amount of spin can't be increased or decreased; only the orientation of the "rotation axis" can change. In a spintronic switch, the collective orientations of many spins can form two types of organized patterns which affect the material's electrical conductivity, and therefore whether the switch is on or off. Unfortunately, it takes energy to coax all the spins to reorient between the two states. On top of that, the organized spins quickly decay back into randomness.

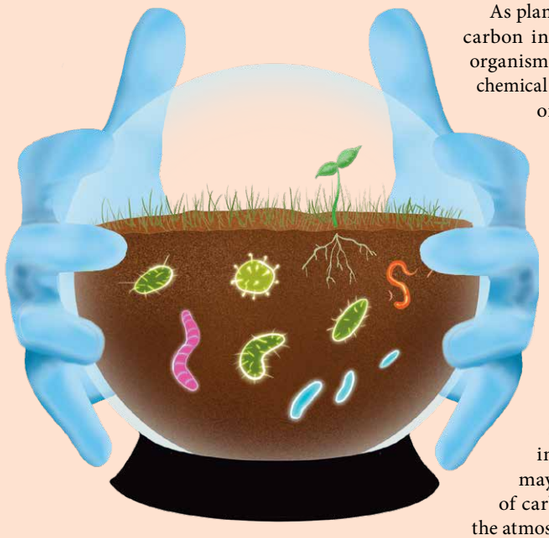
But recently, a research group led by UC Berkeley Professor of Physics James Analytis made a breakthrough: by using a compound with chemical imperfections, such as stray atoms of other elements, the quality of the switch increased dramatically. The imperfections ruin the crystalline symmetry of the electronic spins, causing the spins to lock to each other like a jigsaw puzzle. As a result, the spins can't reorient individually, so they're forced to move in tandem. This remarkable discovery makes the switch stable against random decay and reduces energy consumption by a factor of 100. As it becomes increasingly viable, researchers worldwide are eager to discover novel applications of this exciting new technology.

—DHRUVA KARKADA



Out of the soil, into the atmosphere

Like most climate scientists, Dr. Margaret Torn, an adjunt professor in the Energy and Resources Group at UC Berkeley and senior scientist at Lawrence Berkeley National Lab, is concerned about the increasing amount of greenhouse gases in the atmosphere. But instead of just looking up into the sky, Torn is looking down at the ground to study what might come out of the soil as the planet warms.



As plants grow, they sequester carbon in the soil. Tiny microorganisms living in the soil use chemical reactions to break down organic matter, which releases greenhouse gases back into the atmosphere. Usually, plants sequester more carbon than microorganisms can eat, so there's a storage of carbon in the soil. However, chemical reactions occur more quickly when more energy is available, so increasing soil temperatures may speed up the release of carbon dioxide back into the atmosphere.

To investigate this phenomena, Torn conducts soil warming experiments, in which scientists install large circular arrays of wire below ground to heat up the soil to specific temperatures. Torn's experiments have previously spanned environments ranging from temperate ecosystems to the icy Arctic tundra. Right now, her group is launching a new soil warming experiment closer to home, in Point Reyes National Seashore. The ecosystem is representative of other grasslands around the world, which may become important sources of carbon dioxide.

Torn's soil warming experiments provide a glimpse into the future to understand what ecosystems might look like under different climate conditions. Her experiments motivate action now to limit warming and prevent these greenhouse gases from being released from the soil.

—SOPHIE RUEHR

The real cost of carbon

From its founding in 2014, the Climate Impact Lab has worked to build the world's first empirically derived estimate of the social cost of carbon (SCC), which is the cost to society, in dollars, of emitting a metric ton of carbon. Solomon Hsiang, a professor of public policy at UC Berkeley and co-director of the lab, says that the SCC "had been written down in theoretical terms 30 years ago," but only recently have advances in data science and cloud computing made it calculable using real-world data. Today, SCC is mandated by the Environmental Protection Agency (EPA) and used by agencies to do cost-benefit analysis in their reviews of major investments, like power plants. SCC is also used by policymakers to estimate how much society benefits from avoided costs by reducing carbon emissions.

The Climate Impact Lab is unique in that it brings together leading climate scientists, economists, and computational experts through partnerships with academic and private organizations. The lab's research on SCC and other global climate models has demonstrated how climate change will further exacerbate inequality around the globe. This impact is clearly visible in the Climate Impact Map which is prominently displayed on the lab's website. Users can explore outcomes such as energy costs, temperature changes and mortality rates under different carbon emission scenarios up to the end of this century.

Going forward, Hsiang's lab is learning from their work with SCC to tackle challenges that society has yet to address. Hsiang says, "We take the ethos, methods, and tools that we have applied fairly successfully to climate and try to apply them to other problems as well. People in my lab are working on water pollution, biodiversity, fisheries—all sorts of large-scale policy problems that national governments are not dealing with or even thinking about correctly."

—GREG TULLY

Trickle up toxins

Many poisons protect plants from being devoured by insects, including manmade insecticides and natural toxins produced by plants themselves. One example is the milkweed plant, which produces a toxin known as a cardiac glycoside that disrupts a cellular pump important in animal hearts. While deadly to many animals, several insects, such as the monarch butterfly, have evolved defenses against this toxin. Milkweed-eating insects have mutations in this cellular pump that render the toxin ineffective. Consequently, monarchs can harbor the cardiac glycoside in their bodies for their own defense.

Despite their toxin hoarding, monarchs are still prey to predators and parasites. Recently, UC Berkeley Professor of Integrative Biology Noah Whiteman and UC Riverside Professor of Evolutionary Systems Biology Simon "Niels" Groen found that four species that prey on monarchs—a mouse, a bird, a parasitic wasp, and a worm—all carry mutations in the cellular pump like the monarch. This finding is the first example of a predator or parasite evolving in response to the diet of the animal it consumes. Not only that, but these are the first four distinct examples, showing the power of a plant toxin in shaping an ecosystem.

The evolutionary potency of plant toxins raises questions about how insecticides used in modern agriculture affect ecosystems. "We know more and more about resistance in insects to natural and manmade toxins," Groen mentioned, "but we still don't know much about how the predators and parasites of these insects deal with these toxins." Currently, the data are lacking to evaluate these impacts, but other toxins, including manmade ones, could be shaping the evolution of species beyond the insects they target.

—ANNA ROGERS

DESIGN: JENNIFER CUMMINGS

CRISPRbrain

There are over 20,000 genes in the human genome, and the functions of many of them are not yet understood. Advances in genome sequencing technology have revealed correlations between genes and diseases, but successful therapeutics require knowledge of a problematic gene's function. To address this gap, scientists mutate genes one at a time and check how cells respond. In recent years, CRISPR technology has greatly facilitated this process. Biologists use CRISPR screens to generate huge amounts of data on genes that regulate cancer cell proliferation, neurodegeneration, immune cell responsivity, and viral entry. Still, the sheer scale of available data makes understanding and sharing these CRISPR screen data sets a daunting challenge.

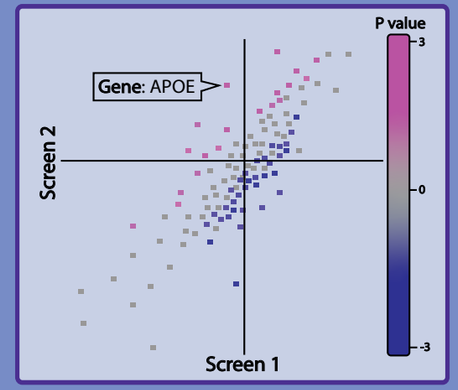
Dr. Martin Kampmann, a UCSF professor in biochemistry and biophysics, and Dr. Faraz Faghri, a collaborating computer scientist at the NIH Center for Alzheimer's and Related Dementias from Data Tecnica International, recognized CRISPR screen data proliferation as a growing problem. "We realized that there is going to be a major problem as more people are generating the same data," remarked Dr. Faghri. After initially planning how to visualize a CRISPR screen data set so that other researchers could access and interact with it, they quickly recognized the potential for a larger, more exciting project. Thus, in 2020, they launched CRISPRbrain, an online data commons for CRISPR screen data with features that bridge biology and data science.

Dr. Faghri exaplains, "We sat down and planned what a platform should look like in a way that would be scalable and provide value to … the biologist." CRISPRbrain offers an intuitive interface to visualize, explore, and cross-compare data sets without needing a bioinformatics background. Scientists can easily upload and explore their own data or search and compare across the repository of CRISPR screens for a particular cell type, cell function, or gene. CRISPRbrain facilitates biological exploration and adds confidence to biological findings when they emerge from multiple studies. Looking to the future, Drs. Kampmann and Faghri. alongside the rest of the CRISPRbrain team, plan to accommodate microscopy data, integrate machine learning algorithms, and add features for data scientists to access biological concepts and definitions in their queries.

"CRISPRbrain offers an intuitive interface to visualize, explore, and cross-compare data sets without needing a bioinformatics background."

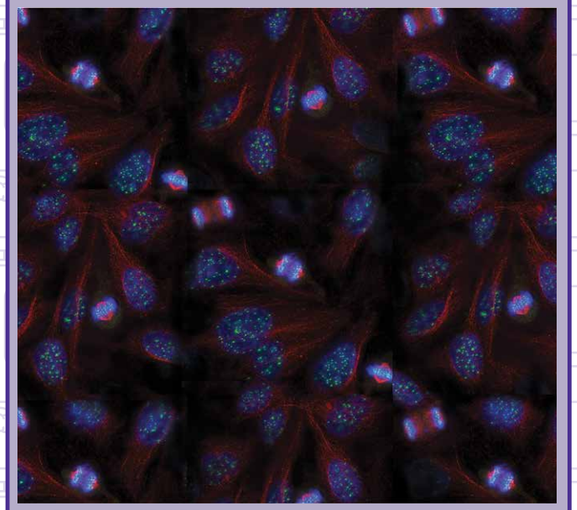
Ultimately, CRISPRbrain may facilitate much more rapid development of therapeutics. For instance, Kampmann and his lab have the expertise and equipment to determine a gene's role in the nervous system. They could use the information they gather to propose interventions for Alzheimer's and other neurodegenerative diseases. However, these same genes that affect the nervous system are present throughout the rest of the body. A therapeutic for Alzheimer's disease that targets a particular gene could have wide-ranging and unintended consequences for a living patient. While investigating all the risks associated with a potential therapeutic is essential, it often requires the work of many research groups with different areas of expertise. CRISPRbrain offers a platform that connects those groups to push each other forward in developing novel, exciting therapeutic discoveries.

Andrew Saintsing *is a graduate student in integrative biology and* Olivia Teter *is a graduate student in bioengineering.*



Easily compare CRISPR screens from different labs using CRISPRbrain

DESIGN: ERICA PLENGER



By using CRISPR, cancer cell proteins can be fluorescently tagged and visualized under a light microscope. The CRIPSRbrain team plans to accommodate microscopy data in the future.

amf
Alfred Mann Foundation

The **Alfred Mann Foundation** is a **nonprofit medical research** foundation, dedicated to bringing advanced medical technologies to the public to provide significant improvements to the health, security and quality of life for people suffering from debilitating medical conditions.

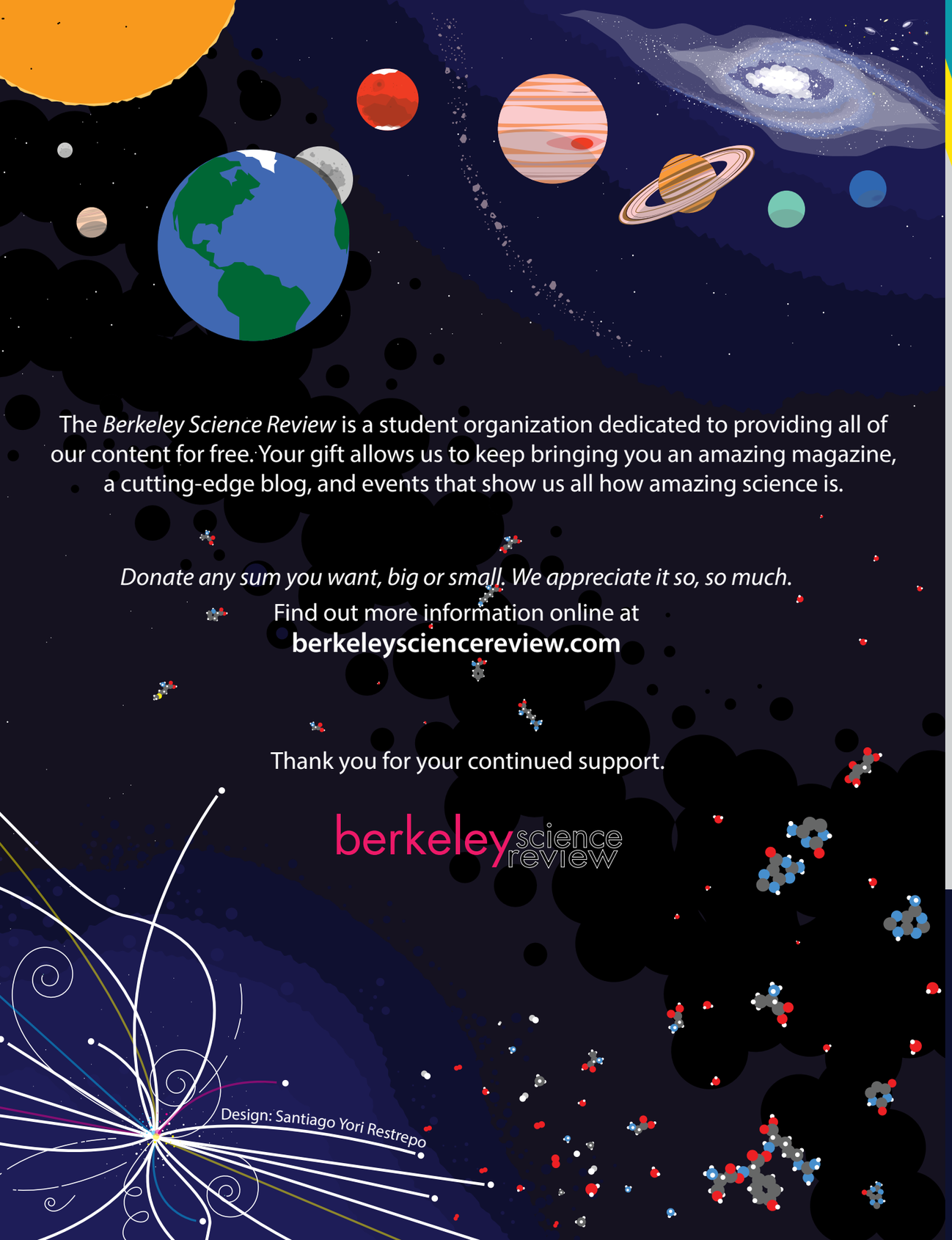
Feel free to visit our website: **www.aemf.org,** career section, from time to time to review our job openings.

NAVY
Strategic Systems Programs
From the Sea

"THERE ARE NO SMALL JOBS AT SSP"

Vice Admiral Johnny R. Wolfe, Jr.
Director, Strategic Systems Programs

If interested send resumes to:
SSPrecruitment@ssp.navy.mil



The *Berkeley Science Review* is a student organization dedicated to providing all of our content for free. Your gift allows us to keep bringing you an amazing magazine, a cutting-edge blog, and events that show us all how amazing science is.

Donate any sum you want, big or small. We appreciate it so, so much.

Find out more information online at
berkeleysciencereview.com

Thank you for your continued support.

berkeley science review

Design: Santiago Yori Restrepo

Toyon®
RESEARCH CORPORATION

Toyon's high caliber technical staff supports R&D efforts for the DoD.

We are looking for candidates with B.S., M.S., & Ph.D. degrees in engineering or the physical sciences. Opportunities exist in: CA, VA, AL, and CO.

- **Radar & Optical Sensors**
- **Algorithm Development**
- **Modeling & Simulation**
- **Systems Analysis**

For career opportunities:
www.toyon.com
U.S. Citizenship Required
EOE M/F/Vet/Disability

EXPAND YOUR MIND

You don't have to stop reading here.
The conversation continues on the blog.

Design: Shannon O'Brien

Here you will find more Berkeley news, opinions, and the latest science.

berkeleysciencereview.com
@BerkeleySciRev

We want your perspectives and voices.

Are you itching to try your hand at writing, designing, and science communication?

Get in touch!