Berkeley College of Letters & Science

WINTER 2019

# DIVISION OF BIOLOGICAL SCIENCES

# Letter from the Dean

Dear Friend,

I am delighted to share with you exciting developments in our division from the past year. We find ourselves on the cusp of a new era, one of renewed discovery, insight and appreciation for what has made Berkeley one of the greatest teaching and research institutions in the world. You'll find a few examples of the stellar work being done represented here with many more to come in the near future.

Berkeley's division of biological sciences represents a wide array of scientific inquiry, from the amazing work being done by Eric Betzig and Gokul Upadhyayula in our Advanced Bioimaging Lab, a global leader in high-resolution microscopy, to Helen Bateup's work with organoids, and how these models further important research into the human brain. From Jim Allison's breakthrough in immunotherapy during his time here, to our new SEED Scholars initiative to foster diversity in the sciences, the one constant that can always be found is that we are striving to attain excellence.

The huge increase we are currently seeing in STEM majors is a great example of the impact being felt here. As dean, I am always looking for better ways to provide core courses to our students, with the most relevant curricula, and most valuable research experiences. I am proud of the efforts we have made to date but there is always room for improvement. Through the creation of more mentoring and undergraduate research programs, state-of-the-art lab facilities, and funding to expand our recruitment of new faculty – we are working to make our 21st century classrooms available to everyone.

Our division is an environment that cultivates rigorous and congenial intellectual exchange. Our success depends upon how we support the faculty, graduate students, and undergraduates that make a difference every day in our labs and classrooms. I am continually amazed at how far we have come, but understand that it is prologue to major achievements yet to be imagined. In the meantime, our responsibility is to ensure Berkeley continues to be a destination for undergraduates who want to learn and work with some of the world's leading scientific minds, as evidenced in these pages. I hope you enjoy reading about our work.

Thank you for your support!

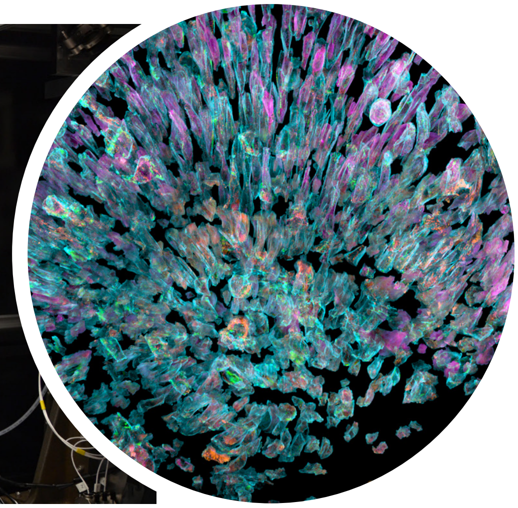
Warmest Regards,

Michael Botchan, Ph.D.
Dean of Biological Sciences

Cover photo: This metallic Blue Beetle belongs to the Cerambycidae family (Sphingnotus insignis)

# Seeing Is Believing: Berkeley's Advanced Bioimaging Center

Scientific director Gokul Upadhyayula and instrumentation scientist Valentina Ferro discuss an image produced by the ABC's next-generation adaptive optical multi-functional lattice light sheet microscope. Photo: Ben Ailes.



This floral-like image shows cells, which have been computationally separated for better viewing, across the eye of a zebrafish embryo.

In 2014, Eric Betzig won the Nobel Prize in Chemistry for developing a microscope that surpassed the limitations of optical light. His technology produced an image with sharper detail than any light microscope had ever created. He did this by utilizing fluorescent molecules, then combining images in which different molecules were activated. This method, known as super-resolution fluorescent microscopy, revolutionized bioimaging by illuminating the complex processes within living cells.

Now at the Berkeley campus, Betzig and a multidisciplinary team of researchers are taking these images even further into the nanodimension. On the third floor of Barker Hall, this team comprises the Advanced Bioimaging Center (ABC), a global leader in the field that continually develops pre-commercial microscopy technologies to unveil the super-small in vivid and beautiful detail.

The ABC utilizes the lattice light sheet microscope with adaptive optics, technology that Betzig and his colleagues developed which uses a thin plane of laser light. The concentrated light is fast and gentle enough to illuminate living cells without cooking their light-sensitive innards, while also preserving applied fluorescent dyes used to label structures within the cell.

Gokul Upadhyayula, scientific director of the ABC, and his extended team leverage a combination of artificial intelligence tools and multimodal imaging systems to obtain their super-detailed data. Their most advanced microscopes are able to do adaptive image correction with ten different modes of imaging squeezed into one.

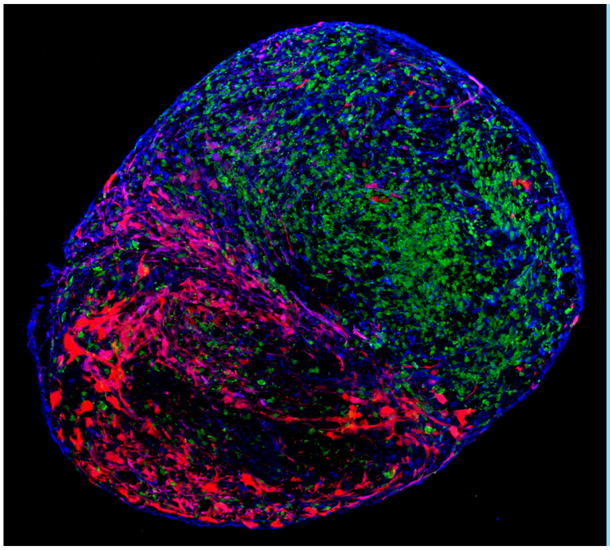
"What we're doing is five dimensional imaging," Gokul explains. "We're combining the x-y-z axis, temporal resolution, and the light wavelength of each fluorescent color. You add adaptive optics, and you have a very powerful tool."

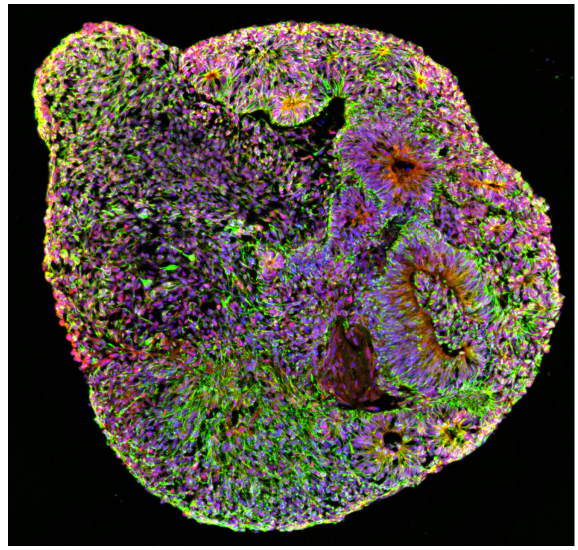
Adaptive optics, originally developed by astronomers to better observe distant stars, involve taking a powerful laser and placing it adjacent to the microscope lens. By shooting a laser "guide star" into a specimen, the ABC team are then able to track and de- mess the microscope-light's bends and twists as it moves through living tissues.

The ABC's highly advanced microscopes produce explosive quantities of immensely complex data. Thankfully, the ABC team is comprised of engineers and computer scientists to help biologists decipher the data and apply it to their research. The lab also hosts a computer cluster that processes the data at 10 gigabit connections.

"Most biologists don't have the computing resources to analyze and assemble these images," Gokul says. "The ABC provides researchers with powerful visualizing tools to see their subjects in an entirely new light."

# Organoids:
# A Dynamic New Model for Discovery





Pictured above are organoids, tiny self-organized three-dimensional tissue cultures that are derived from stem cells.

Brain organoids, three-dimensional man-made structures grown from pluripotent stem cells to resemble the embryonic human brain, sound like something out of a science fiction movie. That is, until you speak with Assistant Professor of Neurobiology Helen Bateup, who uses this new type of lab model to investigate Tubular Sclerosis Complex (TSC), a developmental disorder that causes cortical malformations in the brain.

"Patients with TSC have a high prevalence of a severe form of epilepsy that can start in infancy, and often becomes intractable," Bateup says. "By creating organoid models with different cell types, we can study how these gene malformations impact human cortical development, and ultimately lead to TSC."

The specific genes she studies are TSC1 and TSC2. She looks at their effect on deregulating the mTOR pathway into being chronically active, thus affecting neurodevelopment. The cortical tubers associated with TSC are a human-brain-specific phenomenon and don't form in mouse models of the disease. Enter organoids, which can be genetically modified to emulate human cortical development. Unlike mouse models, organoids grow at the same rate of a developing human brain, approximately nine months. But they are worth the wait, in that they can survive for years, and lend themselves to an infinite variety of genomic engineering.

"Organoids can continue to mature and differentiate on roughly the same time frame as a developing human brain," Bateup says. "So far, they are proving a valuable tool to understanding TSC, and there are a lot of other disorders that share similar mechanisms in their biology that we hope to learn about as well."

In the near future Dr. Bateup, who recently came to Berkeley after doing post-doctoral work at Harvard Medical School in Boston, hopes to be able to create even more complex organoid models. These models could one day lead to groundbreaking discoveries in targeting and treating disorders like TSC.

"There's questions you can ask using these organoids that would just not be possible with more traditional (cell) culture systems," Dr. Bateup says. "Also, the cells stay alive much longer and can mature and develop over years, which is pretty cool."

These living, growing brain models could provide us with answers to scores of questions about neurological diseases, and offer an exciting glimpse at where advanced lab models are headed in the future. Pretty cool indeed.

# Berkeley Essig Museum at SFO

Xerces blue butterflies from the Essig collection on display at SFO.

It took over a year to plan, transport, and install 20 glass cases of Berkeley's most beautiful insect specimens for "The Intriguing World of Insects" display at the International Terminal of San Francisco International Airport. Essig Museum of Entomology curator Pete Oboyski calls them Berkeley's "Oh My" displays. The cases are filled with the most eye-catching specimens normally found scattered throughout the 5 million plus specimens in the museum's holdings.

Oboyski, an entomologist who identified seven new species of moth for his dissertation, knows those holdings better than anyone. He's been curator of the Essig Museum for the last eight years and possesses a fine eye when it comes to highlighting the collection's stand-out specimens. Approximately 20 million international travelers and visitors are expected to pass by the special exhibit, which will be on display until January 5, 2020. From electric blue butterflies to scarabs, these creatures are sure to stop many travelers in their tracks just before the security gates with their beautiful, shimmering, and sometimes unnerving ability to blend into their environment.

The exhibit highlights uniquely Northern Californian insects, such as the Xerces blue butterfly, first discovered in 1852 on the sand dunes of San Francisco's shoreline, and now extinct as a result of urban development. Many other Bay Area species with dangerously low population levels have habitats similarly threatened. Climate change is a factor threatening species of insect both known and yet to be discovered with extinction, in California and around the world. Oboyski is hoping his displays will give people a deeper appreciation for these special inhabitants of earth – and their relationship to the environment we all share.

Oboyski was first approached by Nicole Mullen, previously an Education Specialist at Phoebe A. Hearst Museum of Anthropology on the UC Berkeley campus, and now curator of exhibitions at SFO Museum. Mullen knew the Essig Museum had incredible holdings and worked with Oboyski and his small team on the curated SFO exhibit to showcase insects from California and the tropics. They set about organizing the menagerie of insects by taxonomic grouping, ecology, and genetics as well as themes including camouflage, mimicry, and structural color. Also included is artwork inspired by insects, brass bookplates for color inserts to an early textbook on entomology found in Wellman Hall, and a giant paper mache model of a Cockchafer beetle (*Melolontha melolontha*) circa 1881, found in a storage cabinet on campus.

"I am incredibly excited to share some of UC Berkeley's most diverse and spectacular natural history collections that span over 100 years of change in California," Oboyski says. "My hope is that more people will appreciate the delicate beauty and ecological importance that these insects represent."

# The Innovative Genomics Institute: Entering a New Era of CRISPR-led Discovery

The Innovative Genomics Institute (IGI) has experienced incredible growth over the last several years. Over 50 IGI Fellows and almost as many collaborating scientists and affiliate labs have joined the ranks of the IGI brain trust. In 2019 alone, over 21 research articles have been published by IGI investigators in top journals, covering all IGI program areas – Agriculture, Biomedicine, Microbiology, Technology, and Society. Projects are as diverse as cloning rice seeds, a major food crop whose DNA rearrange and can lose desirable traits with each generation, to EvolvR, an inventive new system that lets scientists "shake" DNA letters in a gene until they find the variation that is just right.

## New Center

In conjunction with these important new discoveries, the opening of the new Center for Translational Genomics (CTG) is empowering the IGI to make a profound impact on human health throughout the world. The first-of- its-kind facility is dedicated to improving global food stability and accelerating clinical trials for experimental CRISPR- based medicines.. The new center, which includes a CRISPR-Cas-centered wet lab and computational facility, will enable the IGI to accelerate the path to finding new cures for diseases plaguing humans, and discovering new traits to resist disease in crops.

## New Science

Recently, DARPA, the United States Defense Advanced Research Projects Agency, made a $25 million commitment to the IGI to develop a CRISPR-based therapeutic intervention to reduce the toxic side-effects of radiation therapy for cancer patients. Intended to be used in a clinical setting, these interventions will also hold the promise of protecting soldiers and civilian populations from exposure to nuclear radiation in a war setting. And since radiation is an effective treatment for several types of cancer, CRISPR-based interventions will be groundbreaking in the treatment and ultimate curing of patients afflicted with this deadly disease. The four-year funding will enable the IGI to develop and submit an investigational new therapy drug to the FDA, the first step in initiating a clinical trial.

## New Leadership

No amount of funding or facilities can take the place of stellar leadership at the IGI, in the form of new faculty and staff. Fyodor Urnov is the new Scientific Director of Technology and Translation at the IGI. Previously the Deputy Director of the Altius Institute for Biomedical Sciences, Urnov is a Professor of Genetics, Genomics, and Development in the Molecular and Cell Biology Department. He joins Scientific Directors Alex Marson, Brian Staskawicz, and Jill Banfield to manage over 50 innovative, genome-editing research projects. Urnov's first priority will be overseeing IGI's efforts to develop a CRISPR based treatment for sickle cell disease, radiation injury, and brain/nerve diseases.

## New Patent

Earlier this year on September 24, 2019, the U.S. Patent and Trademark Office (USPTO) granted a new CRISPR-Cas9 patent to the University of California and its partners, the University of Vienna and Emmanuelle Charpentier, co-inventor of the CRISPR-Cas9 gene-editing tool along with Jennifer Doudna, executive director of the IGI. The new patent covers compositions of certain DNA-targeting RNAs that contain RNA of defined lengths that bind with Cas9, a protein, and target a desired DNA sequence. It is the 15th U.S. patent to be awarded to UC and its partners since Doudna and Charpentier submitted their priority application. International patent offices have also recognized the pioneering innovations of the Doudna-Charpentier team, and will continue to enrich the IGI's efforts to provide CRISPR patented technologies, including CRISPR-Cas9, for the betterment of humankind.

# Where Integrative Biology Happens

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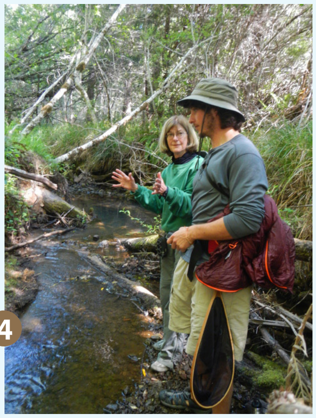

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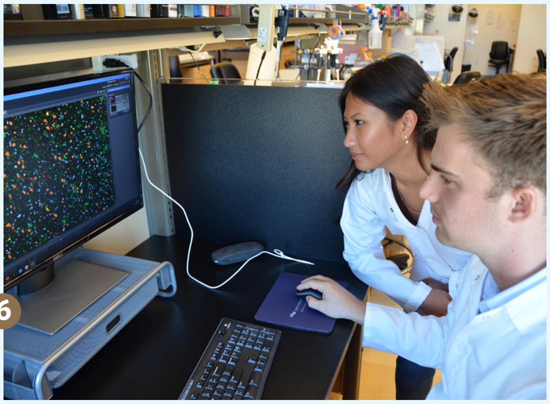
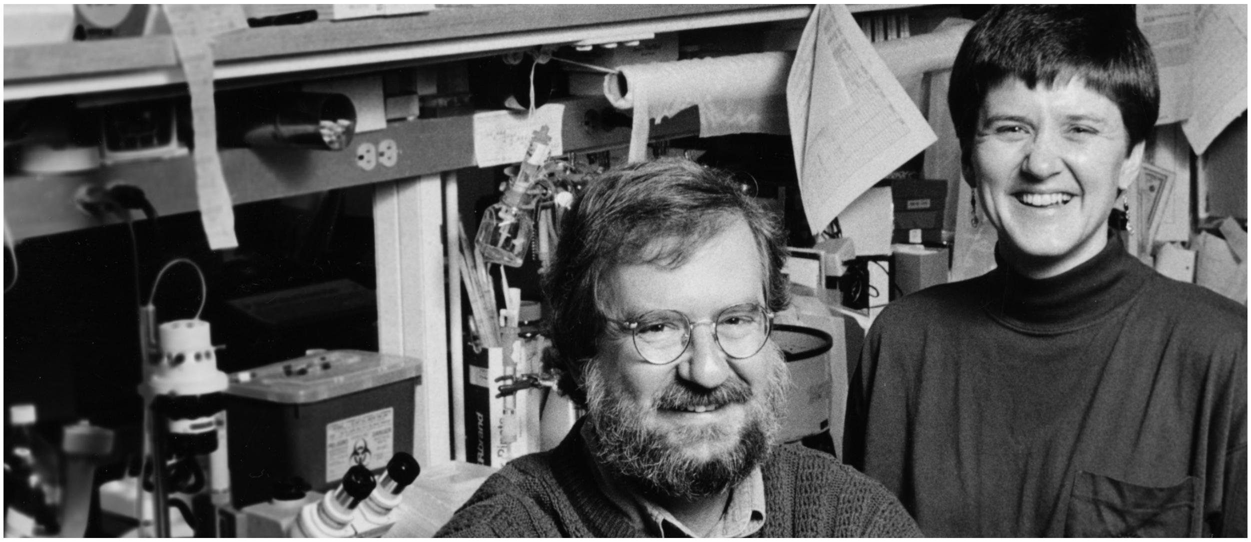


1 Professor Noah Whiteman examines genetically modified fruit flies in his lab. His lab uses CRISPR-Cas9 gene editing to engineer normal fruit flies to resist the toxicity of milkweed when eating it, just as the monarch butterfly does. They created these "monarch flies" to firmly establish which genetic changes were needed in the butterfly genome to allow them to safely eat milkweed. 2 Robert Full Lab members Lawrence Wang and Ruby Ruopp acclimate campus fox squirrels to their adjustable rod setup so that they'll feel safe jumping from rod to rod. They record high speed video of the squirrels' jumps and use that data to inform robotic foot and leg design. 3 Museum of Vertebrate Zoology students Kwasi Wrensford and Sarah Banker examine an Antilocapra americana, or Pronghorn, skull in the museum's collection. 4 Professor Mary Power and graduate student Phil Georgakakos in Redwood Creek, a tributary of the South Fork Eel River near the Angelo Coast Range Reserve, one of UC Berkeley's five natural history field stations. Power's group studies food webs, or what eats what, in rivers and their watersheds, and how species interactions change under different environmental regimes. Photo: Pat Higgins. 5 This photo was taken during Professor Rasmus Nielson's research on the Bajau people of Southeast Asia who live and work at sea, diving deep underwater to hunt. They have developed spleens that are 50% larger than their land-based neighbors, which could provide extra oxygenated blood needed for long breathless dives. Photo: Melissa Ilordo.
6 Ph.D. student Alexander Ehrenberg and lab manager Dominique Cajanding review microscopy images from a Daniela Kaufer Lab study on blood brain barrier dysfunction in Alzheimer's Disease.

All photos unless otherwise attributed courtesy Ben Ailes.

# JIM ALLISON: A BREAKTHROUGH IN BERKELEY



Jim Allison in his Berkley lab with his colleague Sarah Townsend. Photo: Lynn Scherr, 1993.

The atmosphere was electric in the packed theater at BAMPFA for the Berkeley premiere of the Jim Allison: Breakthrough documentary on August 6, 2019. With a panel moderated by Julia Schaletzky, Ph.D. and including immunologist James Allison, Ph.D. himself, the evening explored the 71 year old Nobel Prize winner's journey with cancer. He lost his mother, uncles, and an older brother to the disease, all before receiving a prostate cancer diagnosis himself. Now cancer-free, Allison's heroic struggle to bring immunology to the forefront of treatment for advanced disease is an intensely personal one, and fully engaged the crowd at the campus where he spent a critical juncture of that journey.

Allison was awarded the 2018 Nobel Prize in Physiology or Medicine jointly with Japanese immunologist Tasuku Honjo, M.D., Ph.D., for the discovery of cancer therapies that stimulate the immune system to attack tumor cells. Treatments developed from Allison's work have extended the lives of thousands of people with advanced disease. But when Allison left Texas for Berkeley in late 1984 he didn't regard himself as a cancer researcher, and had never explored medical treatments. That all changed in 1988, when Allison's Berkeley Lab discovered that an immune cell, or T cell, had a molecular gas pedal on its surface called CD28.

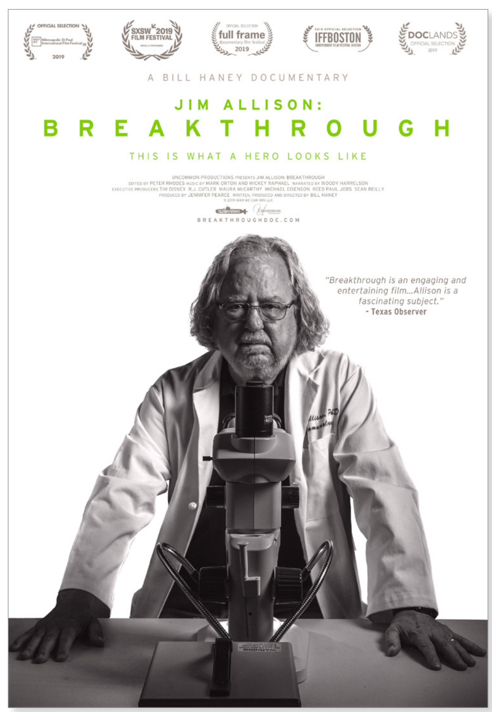
CD28 was a major discovery. But an even greater one lay just around the corner. Max Krummel, a graduate student in Allison's lab, began to study a molecule called cytotoxic T-lymphocyte-associated protein 4, or CTLA-4. But before Krummel could figure out what CTLA-4 did, another lab beat him to it. Peter Linsley, a scientist at Bristol Myers Squibb, published a paper showing that CTLA-4 was a co-stimulatory molecule with CD28. Undeterred, Allison and Krummel continued their CTLA-4 experiments and as data piled up, they came to a shocking realization: CTLA-4 wasn't a gas pedal at all. It was a brake.

More research led to confirmation of their discovery. Allison hypothesized that tumors had evolved to activate CTLA-4, essentially stopping T cells from seeing them as hostile. To prove it, Allison devised a plan to inject Krummel's antibody into tumor-stricken mice and assigned the experiment to Dana Leach, a postdoc in his lab. When Leach showed Allison the initial results in late November 1994, Allison was dumbstruck. "I thought we would slow the tumors down, but we completely cured the mice," he remembers.

Allison insisted on repeating the experiment immediately, this time in a blind study with a control group. For the first two weeks, the tumors in all the mice grew, and Allison suspected

Julia Schaletzky, Ph.D. (left) moderates a panel discussion between Alan Korman, Ph.D., Rachel Humphrey, M.D., Jim Allison, Ph.D., Padmanee Sharma, M.D., Ph.D., and David Raulet, Ph.D. following a screening of the film “Jim Allison: Breakthrough” at the Berkeley Art Museum and Pacific Film Archive on August 6, 2019. Photo: Marcus Edwards.

Leach bungled the experiment. But then the tumors in the treated mice began to regress dramatically. By showing T cells could eradicate tumors so effectively, Allison and his Berkeley team had made a breakthrough that would alter the fields of immunology and cancer treatment forever.




It would be another twelve years before ipilimumab, the drug developed from Allison’s breakthrough Berkeley research would enter phase I clinical trials in June 2000 and show incredible results in treating human cancers. And another eleven years before the FDA approved the drug in March 2011. Allison would leave Berkeley for New York City and Memorial Sloan Kettering Cancer Center in 2004, but he credits his time here with validating his immunotherapy research for the first time, the greatest time of his life.

Berkeley is working hard to advance and expand on Allison’s foundational discovery. At the Immunotherapeutics and Vaccine Research Initiative (IVRI), UC Berkeley cancer immunologists team with colleagues working on infectious disease to understand the immune system’s biochemical tools and how it recognizes invaders. Fueled by funding from founding partner Aduro Biotech, a leading immunotherapy company focused on the commercialization of transformative treatments for disease, the IVRI is working to discover new ways to selectively target and control many human diseases.

# The SEED Scholars Program: STEM Excellence through Equity and Diversity

From left to right: Ira Young, Ed.D., director of the SEED Scholars Program, third-year environmental engineering Ph.D. student Adrian Davie, second-year chemical engineering student Daniel Ocasio, and first-year chemistry Ph.D. student Kristen Gardner.

Today, nearly one-third of the U.S. population is African American or Latinx. By 2045, the nation's population is projected to be a "majority minority." But these numbers are not currently reflected in STEM (Science, Technology, Engineering, and Math) jobs, where African American and Latinx workers continue to be underrepresented at just 9% and 7%, respectively, according to the Pew Research Center.

The SEED Scholars Program starting at Berkeley in Summer 2020 hopes to capitalize on the fact Silicon Valley companies hire more students out of UC Berkeley than any other institution in the U.S. The goal is to build upon Berkeley's enrollment of underrepresented students in STEM majors, approximately 23 percent in 2016, and begin to level the playing field. Modeled off the successful Meyerhoff Scholars Program from the University of Maryland, Baltimore County (UCMB), the program was made possible through a $6.9 million, 5-year grant from the Chan Zuckerberg Initiative for Berkeley and UC San Diego. Both UC campuses are hoping to replicate UCMB's proven track record of outreach and recruitment of underrepresented participants, who were 5.3 times more likely to go on to graduate programs in STEM than students who were invited to participate but decided to go to a different college.

## A Strength-Based Approach

Co-directed by Oscar Dubón, Vice-Chancellor for Equity and Inclusion, and Michael Botchan, Dean of Biological Sciences, as well as the Deans of Math & Physical Sciences, Chemistry and Engineering, the goal is to develop a more diverse and inclusive culture across the strengths of the STEM academy at Berkeley. Leaders from Berkeley and UCSD visited the UCMB campus this summer to learn how their leadership conduct the Meyerhoff Scholars Program, which includes a four-year merit scholarship and access to a mentor, advisers, and counselors.

Here at Berkeley, between 100 – 120 students will be awarded the five-year STEM Scholarship. They'll be required to attend a six-week summer bridge program, and live in the same dorm their freshman year. The model is intended to position students with a passion for science every possible opportunity to prepare for a career in STEM once they graduate. Over the course of the five-year grant, UC Berkeley and UCSD will conduct research to assess how the program impacts students' retention, graduation, and STEM career outcomes.

> "This is about enabling a group of super-talented undergraduates to bond and work together to become the leaders in the STEM fields of tomorrow."
>
> — Michael Botchan
> Dean of Biological Sciences , College of Letters & Sciences

# Student Standouts


### Ifechukwu Okeke, MCB ‘21

Having joined the Bautista Lab in 2018, Ifechukwa studies the molecular mechanisms of acute and chronic pain and itch. There is a lot of work to be done to understand the pathways and genes associated with chronic pain. Ifechukwu hopes that in the future, her work in the lab will help to develop therapies for those suffering chronic pain and itch, without them experiencing off-target effects that impair central nervous system and brain function. Ifechukwu is also the undergraduate STEM coordinator at Underrepresented Researchers of Color (UROC), one of four coordinators who provide information and programming materials to nearly 800 students, in an effort to build a community of researchers of color here at Berkeley.

### Peter Kloess, Ph.D., IB ‘21

Peter grew up in the Bay Area, but he never thought that his reason to return to Berkeley would be to study turtles. But now that his Ph.D. research is focused on functional morphology in the feeding apparatus of turtles, it’s safe to say he’s fallen in love with them. Using the extensive collection in the University of California Museum of Paleontology on Berkeley campus, Peter CT-scans hundreds of turtle beaks and has found, much like Darwin’s finches, the turtle’s diet and habitat have over thousands of years developed fine ridges and bumps on the palate to assist them in processing food. It’s a line of scientific inquiry Peter is passionate about, and why turtles have found a place in his heart.

### Jenna T. B. Ekwealor, IB ‘21

Jenna is no stranger to remote locations. Her research focuses on extremophiles, organisms that are able to survive in extreme conditions. Recently, Jenna was in the Mojave Desert, studying dryland mosses that can ‘live’ for hundreds of years in spite of intense heat and little water. The trick to their survival? Their ability to go completely dormant, or quiescent. In a recent experiment, Jenna reduced the level of UV radiation on individual mosses over the course of a year. To her amazement, initial data indicated the moss was adversely impacted by the lack of radiation. Jenna hopes to one day uncover how these life forms survive and thrive in conditions commonly thought to be extremely difficult for life itself.

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# The Biological Sciences Division's Physical Education Program teaches 5,000 students annually in 190 courses.

Photos: Ben Ailes.

This year, we've added courses in social dance, specifically Ballroom, Salsa, and African Dance, to enhance the variety of experiences for our students. We've also added a new course in distance running. That course reached its maximum enrollment on the second day of registration, and provides a safe and inclusive environment for campus runners.

Each semester we have over 1,100 students on the wait-list to enroll in our courses. We hope to continue to add to our course catalogue and teach Berkeley students to practice lifelong wellness.

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