The Adolph C. and Mary Sprague
Miller Institute
for Basic Research in Science

Newsletter
Fall 2024

Adding more building blocks to Nature's toolbox

Miller Fellow Focus: Carly Schissel

Life is built from basic building blocks. Imagine a fully functional airplane built from just 20 different sizes of Lego pieces. Each Lego piece is simple, and yet their assembly can lead to an amazing machine. Proteins are the machines of life, responsible for digesting our food, sensing touch, and transporting oxygen and nutrients in our bodies. Knowing this, it is astounding that the diversity of proteins is encoded by just 20 naturally occurring amino acids. These building blocks are different only in their "side chain," stemming off from the "backbone" of the protein string. Protein backbones are all built from α-amino acids, carefully installed one after the other by nature's most advanced machine: the ribosome (**Figure 1**.)

If this level of structural and functional complexity is encoded by just 20 amino acids, what could we build with an even more diverse set of building blocks? Specifically, I am interested in peptides, which are like small proteins, that contain unnatural building blocks and can act as therapeutics or diagnostics. A specific example that has become widely known is Ozempic (semaglutide) and other glucagon-like peptide-1 (GLP-1) analogs. This peptide, composed of 30-40 α-amino acids, contains one

unusual backbone structure with two side chains sticking out instead of one (called di-substituted). Because this building block is foreign to Nature, our enzymes cannot digest the peptide at that position, extending its lifetime in our bodies. Metabolic stability is just one example of a unique function that a non-α amino acid can lend to a peptide or protein.

My interest in unnatural peptides started during my PhD with Prof. Bradley Pentelute at MIT. I developed tools to design cell-penetrating peptides, which can help carry large drug molecules across the cell membrane and into the cell to perform their function. I specifically worked with an antisense oligonucleotide, called PMO (phosphorodiamidate morpholino), which is the type of molecule

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Call for Nominations

Miller Research Fellowship Nominations
Deadline: September 12, 2024

Miller Research Professorship Applications
Deadline: September 16, 2024

Visiting Miller Professorship Departmental Nominations
Deadline: September 16, 2024

(See page 5 for more details on all our programs.)

"The Visiting Miller Professorship provided me with excellent research opportunities and professional interactions. I have developed long standing collaborations with colleagues at Berkeley and expanded my research projects to areas where I would have thought I would get to work in some distant future."

Mihaela Ifrim
Associate Professor
Mathematics
University of Wisconsin - Madison
VMP Fall 2023

> CONTINUED FROM PAGE 1 [Miller Fellow Focus]

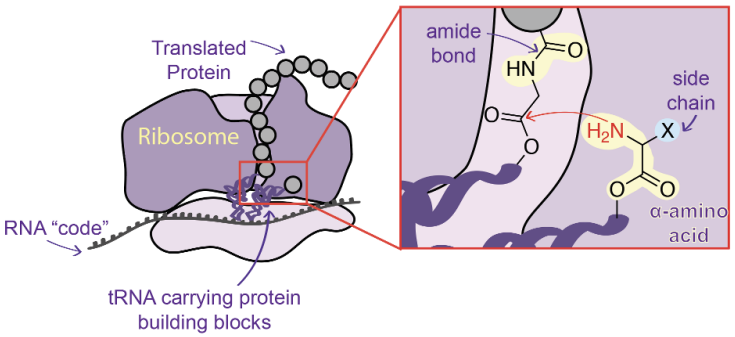


Figure 1. The ribosome translates RNA code into protein using α-amino acid building blocks, delivered by tRNA (left). α-amino acids have chemical diversity on their side chain, and are strung along in a protein via an amide bond backbone.

approved for the treatment of Duchenne muscular dystrophy. Improving the activity of the drug as a whole would mean that a lower dose would be required, thus reducing side effects and lower treatment costs, making therapies more accessible to patients. In collaboration with Prof. Rafael Gomez-Bombarelli, an expert in artificial intelligence tools, we found that machine learning was invaluable in predicting and optimizing active peptide sequences.

While most of the building blocks in our designed peptides were natural amino acids, the machine learning model indicated that the few building blocks with extended carbon-chain backbones were important for activity. This prediction turned out to be true when I made these peptides and tested them in a cellular assay. Even more, changing that unnatural monomer to one with a longer backbone chain (11 carbons) boosted the sequence's activity even further.

At the end of my PhD, I was fascinated by the potential that unnatural building blocks could have on therapeutic peptides. While synthetic chemistry allows for the synthesis of these unnatural peptides, scaling up this process is costly and environmentally taxing. My interest shifted towards the next question: can living cells install these unnatural building blocks? Cellular synthesis of unusual peptides and proteins offers a more efficient and eco-friendly alternative. Therefore, I pursued postdoctoral studies in a lab that uses cells to make unnatural protein products using genetic code expansion. I joined Prof. Alanna Schepartz's lab as a Miller Fellow, as she is the director of the NSF Center for Genetically Encoded Materials (C-GEM).

Nature's protein factory, the ribosome, is a massive biochemical machine that decodes RNA templates into protein strings. While 20 α-amino acids are standard, we've known for a few decades that the ribosome can install "unnatural" α-amino acids into proteins. These building blocks have a natural backbone, but have unusual side chains. There have been a few examples of building blocks with unnatural backbones installed by the ribosome—but they have been few and far between. I am fascinated by these non-α-amino acids, because their unconventional structures hold great promise for therapeutic applications and could be synthesized more efficiently and sustainably within live cells.

As a postdoctoral fellow, I wanted to develop strategies to force the natural ribosome to produce unnatural peptides. Unsurprisingly, the ribosome has evolved over billions of years to efficiently make one type of bond, between carbon and nitrogen to yield a so-called amide bond. Researchers have long asked a fundamental question: can the ribosome form a bond between two carbon atoms to make a ketone instead? Ketones are a unique and highly reactive group, distinct from amide or ester bonds that the ribosome has built previously. There is currently no general way to put ketones in protein backbones in Nature, and purely synthetic methods are tedious and limited. I've designed a unique monomer that is able to accomplish this feat, and look forward to sharing this story soon.

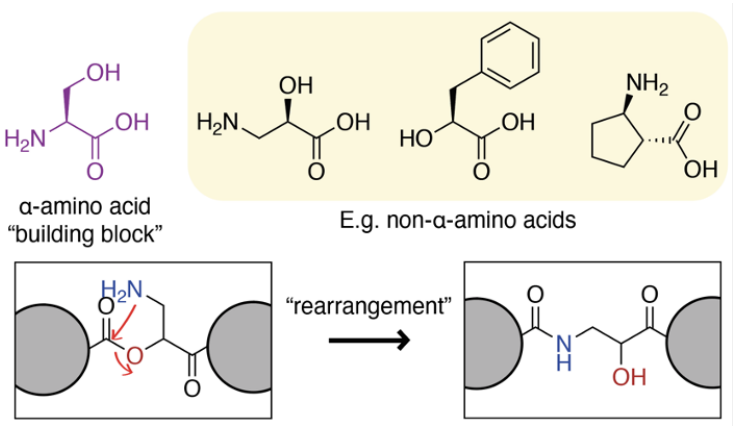


Figure 2. Unnatural α-amino acids have side chains that are different from the natural 20 amino acids. Non-α-amino acids that have distinct backbones are much more challenging to install into peptides and proteins using the ribosome (top). We recently reported a method that uses "rearrangement" to transform an α-ester linkage into a more stable, yet unnatural β-amide backbone (bottom).

I've also contributed to work that makes proteins containing β-amino acids. The method uses rearrangement to "trick" the ribosome into incorporating unusual backbones into peptides (**Figure 2**.) A building block with an oxygen in place of nitrogen was installed, forming an ester instead

of an amide. The ester, which is less stable than an amide, is only allowed to "relax" into a β-amide form after protein translation. I demonstrated this phenomenon in synthetic peptide standards, where the rearrangement can be observed directly by mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy. We then showed this could be done in proteins made by the ribosome. These advancements pave the way for creating proteins with unique structures and functions, synthesized directly within live cells.

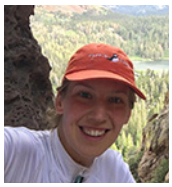
The field of chemical and synthetic biology is evolving rapidly, with the potential to create proteins and peptides with novel properties that impact human health and the environment. I've witnessed how combining experimental chemistry with machine learning can push the boundaries of what we know about bioactive peptides. Looking forward, I am interested in specific structures and functions bestowed upon unnatural peptides by unique non-α amino acid building blocks. In my own research group, I will aim to use chemical synthesis, molecular biology, and machine learning to tackle problems related to signaling processes in disease.

Carly Schissel is a third-year Miller Fellow in Chemistry, hosted by Prof. Alanna Schepartz. Dr. Schissel earned her PhD from the Massachusetts Institute of Technology in Chemistry under the guidance of Prof. Bradley Pentelute. Her work led to the discovery and design of peptides that enhanced the delivery of therapeutic molecules to the nucleus of cells. Prior to graduate school, she earned a B.A. in chemistry from Williams College and performed research with Prof. Thomas Smith in the total synthesis of polyketides.

Contact: schissel@berkeley.edu
LinkedIn: carly-schissel-2021
X: CarlySchissel
Google Scholar: scholar.google.com/citations?user=Hup3CZQAAAAJ&hl=en&oi=ao

Next Steps

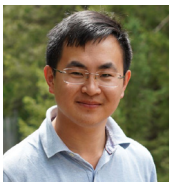
The Miller Institute congratulates these Miller Fellows on their next endeavors:



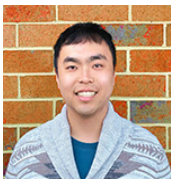
Anna Barth
Chief Scientist
Strabo Engineering

Dimitrios Fraggedakis
Assistant Professor
Department of Chemical and Biological Engineering
Princeton University

Andrew Rosen
Assistant Professor
Department of Chemical and Biological Engineering
Princeton University



Yao Yang
Assistant Professor
Department of Chemistry and Chemical Biology
Cornell University



Lingfu Zhang
Assistant Professor
Division of Physics, Mathematics and Astronomy
Caltech

Recent Publications

Chadi Saad-Roy (Miller Fellow 2022-2025) is a co-author of the paper "Unlock the potential of vaccines in food-producing animals," published in *Science*.

Nicolas Mathevon (Visiting Miller Professor 2008, 2024) is a co-author of the article "Puppy whines mediate maternal behavior in domestic dogs," published in *PNAS*. He is a co-author of another article "Is plant acoustic communication fact or fiction?" published in *New Phytologist*.

Holger Müller (Miller Professor 2020-2021) is a co-author of the paper "Coherence limits in lattice atom interferometry at the one-minute scale," published in *Nature Physics*.

Melissa Wilson (Miller Fellow 2011-2014) led the team that fully sequenced the genome of Gila monsters for the first time. She is a co-author of the article "Lack of Dosage Balance and Incomplete Dosage Compensation in the ZZ/ZW Gila Monster (Heloderma suspectum) Revealed by De Novo Genome Assembly," published in *Genome Biology and Evolution*.

In a new study in the journal *Proceedings of the National Academy of Sciences*, the researchers, led by study senior author **Steven Beissinger** (Miller Professor 2020-2021), present nearly 30 years of observations revealing what drives parrotlets to either care for - or kill - one another's babies.

From the Executive Director

Chung-Pei Ma, Miller Institute Executive Director & Judy Chandler Webb Professor in Physical Sciences, Professor of Astronomy, Professor of Physics

Welcome to the 68th year of the Miller Institute. As you read this newsletter, our new cohort of Miller Fellows is just settling in and will share their research discoveries and outlooks at the one-day New Fellow Retreat in September. We have sent off departing Fellows with our best wishes. Some are continuing their exciting research on campus, some have joined industry, and several have taken on new roles at other universities, e.g., as Assistant Professor at Caltech, Cornell, and Princeton. Learn more about their next steps on page 3.

The Institute is energized by this year's nine Miller Professors, one of the largest cohorts in our history. Their year-long participation at the Institute will bring invaluable intellectual vitality to the Tuesday lunches and other gatherings. Complementing their presence are the shorter visits of our eleven Visiting Miller Professors, seven of whom are from institutions outside the U.S. As I greet the Miller community each week at the Faculty Club, I am always amused by how relaxed our MPs and VMPs are in comparison to my haggard colleagues (and myself). Enjoy this precious time!

We are now accepting nominations and applications for the 2025-2028 Miller Fellowship, 2025-2026 Miller Professorship and Visiting Miller Professorship programs. I ask for your participation in identifying outstanding candidates from a diverse background and nominate them or encourage them to apply. Learn more about how to nominate and apply on page 5.

On behalf of the Institute, I offer my deepest gratitude to outgoing Miller Senior Fellow Susan Marqusee for her five years of outstanding contributions to the Institute. I am thrilled to welcome new Senior Fellow Hitoshi Murayama and look forward to many stimulating discussions in the coming years.

Last but not least, our dedicated administrative team, Hilary Jacobsen, Emily Birman, Clara Duman, Donata Hubert, and Vrinda Khanna, has found a new home in the spiffy Stanley Hall after 5 years in Donner Lab. They are now within arm's reach of a sparkling kitchen and instant caffeine injections at Kiklo Café downstairs.

Cheers to another exhilarating year at the Miller Institute!

Welcome New Miller Senior Fellow

The Miller Institute is pleased to announce the appointment of Professor Hitoshi Murayama as a Miller Senior Fellow! Professor Murayama is a theoretical physicist who seeks to understand the connection between the small (elementary particles) and the large (the universe). He has been a professor at UC Berkeley since 2000, was a Miller Professor in Spring 2006, and is also the founding director of the Kavli Institute for the Physics and Mathematics of the Universe (Kavli IPMU) at the University of Tokyo, serving from 2007 to 2018.

In his research, Professor Murayama develops new techniques to solve difficult theoretical problems, both in particle and condensed matter physics, and also delves into galaxy surveys and neutrino experiments. He was elected to be a fellow of the American Physical Society, American Academy of Arts and Sciences, and American Association for the Advancement of Science. He has also delivered a speech at the UN headquarters about how science unites the world. We are thrilled to welcome Professor Murayama back to the Institute in this role as Miller Senior Fellow!

He shares, "I was a Miller Professor back in 2006 and it was a special experience. Even though I love teaching, freedom away from it allowed me to concentrate on my research and travel to meetings and conferences. I also enjoyed weekly lunches with amazing Miller fellows across disciplines and the broader Miller community. It truly expanded my horizon as a scientist, which I still benefit from years later. Now, as a Senior Miller Fellow, I very much look forward to an even better experience with more interdisciplinary interactions. See you all in the fall!"

Make a Gift

Private donations are becoming an increasingly significant resource for the Miller Institute. Your personal investment in support of the future of the Miller Institute will be greatly appreciated.

Join Miller friends and alumni in contributing to this important endeavor by logging on to ***miller.berkeley.edu/gift*** to help support the independent research of the Miller Institute members.

Call For Nominations and Applications: Miller Research Competitions

Miller Research Fellowship 2025-2028
Online Nomination Deadline: September 12, 2024

The Miller Institute for Basic Research in Science invites department chairs, faculty advisors, professors and research scientists at institutions around the world to submit online nominations for Miller Research Fellowships in the basic sciences. The Miller Institute seeks to discover and encourage individuals of outstanding talent, and to provide them with the opportunity to pursue their research on the Berkeley campus. The Institute also welcomes nominations for the **Kathryn A. Day Postdoctoral Fellowship** for outstanding candidates who demonstrate a commitment to outreach in support of science. Fellows are selected on the basis of their academic achievement and the promise of their scientific research. Miller Fellows also have a keen curiosity about all science and share an appreciation for an interdisciplinary experience. The Miller Institute is the sponsor and the administrative home department for each Miller Fellow who is hosted by an academic department. All research is performed in the facilities provided by the host UC Berkeley academic department(s). A list of current and former Miller Research Fellows is available on our website.

Miller Research Fellowships are intended for exceptional young scientists of great promise who have recently been awarded, or who are about to be awarded, the doctoral degree. Normally, Miller Fellows are expected to begin their Fellowship shortly after being awarded their Ph.D. Their PhD must be received between 1/1/2023 and 8/31/2025. **A nominee cannot hold a paid or unpaid position on the Berkeley campus at the time of nomination or throughout the competition and award cycle which may last through the end of February 2025.** Nominees who are non-US citizens must be eligible to obtain J-1 Scholar visa status for the duration of the Miller Fellowship. The Miller Institute does not support H1B visa status. The Fellowship term must commence between July 1 and September 1, 2025. Eligible nominees will be invited by the Institute to apply for the Fellowship.

Direct applications and self-nominations are not accepted. *All nominations must be submitted using the online nomination system at: **miller.berkeley.edu/fellowship.**

Nominators will need the following required information to complete the online nomination process:
+ Nominee's complete full and legal name (do not use nicknames)
+ Nominee's current institution
+ Nominee's complete, current, and active E-mail address, current mailing address with postal code and telephone number
+ Nominee's Ph.D. Institution and (expected) Date of Ph.D. (month & year required)
+ Letter of recommendation and judgment of nominee's promise by the nominator. Letter must be specific to the Miller Fellowship, have a current date, and be on institutional letterhead. The Executive Committee finds it helpful in the recommendation letter to have the candidate compared with others at a similar stage in their development.
+ Nominator's current active E-mail address, title, and professional mailing address (include zip code/campus mail code)

The Institute provides a stipend of $85,000 with annual increases and an annual research fund of $10,000, for a total initial package of $95,000. There is provision for travel to Berkeley for Miller Fellows and their immediate families and a maximum allowance of $3,000 for moving personal belongings. Benefits, including medical, dental, vision and life insurance, are provided with a modest contribution from the Miller Fellow. All University of California postdocs are represented by the UAW. Fellowships are awarded for three years, generally beginning August 1, 2025 and ending July 31, 2028. Approximately eight to ten Fellowships are awarded each year. Candidates will be notified of the results of the competition starting in mid-December, and a general announcement of the awards will be made in the spring.

Miller Research Professorship AY 2025-2026
Online Application Deadline: September 16, 2024

The Miller Professorship program announces the call for applications for terms in AY 2025-2026. The objective of the program is to provide opportunities for UC Berkeley faculty to pursue new research directions on the Berkeley campus and to participate in the vibrant Miller Institute interdisciplinary scientific community. Only UC Berkeley faculty are eligible to apply.

The primary evaluation criteria will continue to be research excellence. Proposals to write books are not viewed as competitive. Applicants are also encouraged to describe their interest in participating in the Miller Institute community and providing mentorship to the Miller Research Fellows.

Applications are judged competitively and are due by September 16, 2024. Applications are available on our website: **miller.berkeley.edu/professorship.**

Visiting Miller Research Professorship AY 2025-2026
Online Nomination Deadline: September 16, 2024

The Advisory Board of the Miller Institute for Basic Research in Science invites Berkeley faculty to submit online nominations for Visiting Miller Research Professorships and the Gabor A. and Judith K. Somorjai Visiting Miller Professorship Award for terms in Fall 2025 or Spring 2026. These Visiting Miller Professorships are intended to bring promising or eminent scientists to the Berkeley campus on a short-term basis for collaborative research interactions. It is required that awardees are in residence at Berkeley during their appointment term.

Faculty members or research scientists from anywhere in the world are eligible to be considered for nomination by UCB faculty. Nominations can be made through our portal on our website: **miller.berkeley.edu/visiting-professorship**. For questions about our programs or competitions, please contact millerinstitute@berkeley.edu.

Miller Institute Special Events

The Miller Institute hosted a Women in Miller event at the Berkeley Art Museum and Pacific Film Archive (BAMPFA)

Miller members participated in a walk around the UC Botanical Gardens. Pictured (left to right): Miller Fellow Olatubosun Fasipe, Miller Professor David Eisenbud, Miller Fellow Matt Kustra, and Miller Fellow Mengshan Ye.

Miller Fellows Olatubosun Fasipe, Mengshan Ye, Carly Schissel and Molly McFadden presented their research through engaging demonstrations to Biology classes at Middle College High School, inspiring and educating the next generation of scientists.

In the News

(see more past & current Miller Institute News: miller.berkeley.edu)

Chuan He (Somorjai Visiting Miller Professor Spring 2017), **Vivek Malhotra** (Visiting Miller Professor Fall 2016) and **Elchanan Mossel** (Miller Fellow 2002-2005) have been elected to the **American Academy of Arts & Sciences** *"for their accomplishments and for the curiosity, creativity, and courage required to reach new heights."*

UC Berkeley's College of Chemistry celebrated the groundbreaking of its new research and teaching facility, Heathcock Hall, named for **Clayton Heathcock** who was a Miller Professor (1982-1983 and Fall 1992).

The following Miller members were among the **newly elected NAS members: Juan Ignacio Cirac** (Visiting Miller Professor Spring 2014), **Abby Dernburg** (Miller Professor 2020-2021), **Stephen Hedrick** (Visiting Miller Professor Fall 1999), **Raymond B. Huey** (Miller Fellow 1975-1977), **Jonas Peters** (Miller Fellow 1998-1999), **Ashvin Vishwanath** (Miller Professor Fall 2009) & **Peter Wolczanski** (Visiting Miller Professor Spring 1995) in recognition of their distinguished and continuing achievements in original research.

NASA recently selected 4 proposals for Phase A of the Earth System Explorer program. **Alex Turner** (Miller Fellow 2017-2020) is on the science team for two of the missions (STRIVE and Carbon-I).

Omar Yaghi (Visiting Miller Professor Fall 2009) won the **Tang Prize for Sustainable Development** in recognition of his groundbreaking efforts founding and advancing the field of reticular chemistry.

The Norwegian Academy of Science and Letters named **Paul Alivisatos** (Miller Professor 2001-2002) a **winner of 2024 Kavli Prize** in the field of nanoscience, shared with two scientists — Robert Langer of MIT and Chad Mirkin of Northwestern University in Evanston, Illinois — for engineering nanoscale materials that have improved therapeutics, vaccines, bioimaging and medical diagnostics.

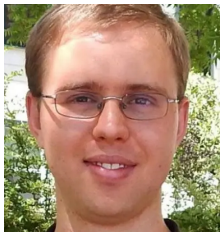
In May, the Institute hosted a special **Kathryn A. Day Fellowship** luncheon with presentations by the two Kathryn Day fellows, Raul Ramos (2022-2025) and Molly McFadden (2023-2026), pictured in the center. Major supporters of the Fellowship fund Professor Randy Schekman and Professor Sabeeha Merchant attended (right) and Kathy herself (left) joined in.

26th Annual Interdisciplinary Symposium

Miller Fellows (2011-2014) cohort: Eric Neuscamman & Rachel Pepper were guest speakers, Melissa Wilson, Mikhail Shapiro, a guest speaker, Joshua Ruderman & Justin Brown

2024 Symposium participants at the Lodge at Marconi on Tomales Bay

Miller Fellow Anna Barth, Kathy Day Miller Fellow Molly McFadden, Miller Fellows James Santangelo & Georgios Varnavides



Speakers (Top): Harmit Malik, Eric Neuscamman, Dianne Newman
(Bottom): Rachel Pepper, Jonas Peters, Mikhail Shapiro & Nicholas Swanson-Hysell

Counter-clockwise from bottom left: Former Miller Fellow Alfred Zong, Miller Fellows Kelian Dascher-Cousineau & Sherry Zhang, former Miller Fellows Yi Zhang & Antoine Koehl, Miller fellow Anna Barth & former Miller fellow Grayson Chadwick

Symposium Chair Michael Manga speaks to the audience

Poster session presentations by Miller Fellows

Miller Institute Executive Director Chung-Pei Ma & Miller Fellows Yao Yang and Sherry Zhang

University of California, Berkeley
206B Stanley Hall
Berkeley, CA 94720-5190
510.642.4088
miller.berkeley.edu

Miller Institute News - Fall 2024
Please send address corrections to:
miller_adm@berkeley.edu

We are excited to announce that the Miller Institute Administrative Offices have moved!
We are now located on the 2nd floor of Stanley Hall, room 206B.
Please reach out to Hilary at millerinstitute@berkeley.edu if you would like to see our new space!

For More Information:
Staff: Hilary Jacobsen, Emily Birman, Clara Duman, Donata Hubert & Vrinda Khanna.

Miller members and guests enjoyed an evening of star gazing with Astronomy Professor and Miller Senior Fellow Alex Filippenko (center).

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