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

Newsletter
Fall 2023

Using structure to decipher function

Miller Fellow Focus: Aaron Joiner

Close your eyes and imagine that you are a Formula One race car driver. Your team of engineers has guaranteed you that they will build the best vehicle on the track and now they have invited you to their garage to unveil the vehicle that you'll be racing in at the next competition. Before they lift the curtain, take a second to envision what this vehicle will look like.

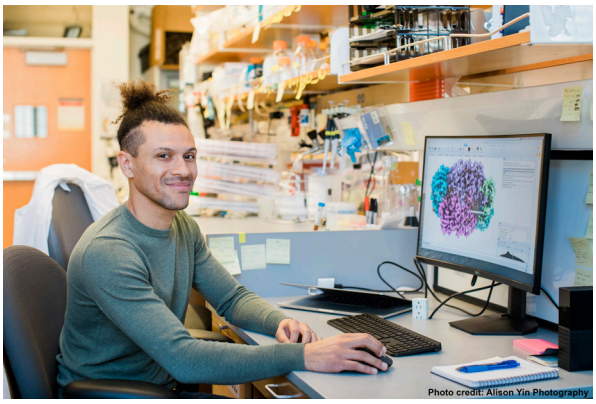
Photo credit: Alison Yin Photography

You are likely picturing something low to the ground and highly aerodynamic, with four wheels, a large engine, a single seat on the interior for the driver, and effective protection against a high-speed crash. You would be shocked and disappointed if instead they revealed a school bus. The reason why is that school buses and race cars are designed for two completely different purposes.

The principle that design is linked to purpose, or in other words, that structure is linked to function, surrounds us at every scale of size, from buildings and vehicles to furniture and tools. Importantly, we can often infer the purpose (function) of something by observing its design (structure). This paradigm also traverses the microscopic world, even holding true for the cells in our bodies and their building blocks.

Proteins are one of a cell's molecular building blocks and the main set of biomolecules that perform the various cellular functions required to support life. Since the Human Genome Project of the early 2000s, we have had a sense of the identities of each protein in a human cell, but our knowledge of each protein's structure and function within a cell has trailed behind due to the arduous tasks associated with direct experimental investigation. As a structural and cell biologist, I am particularly interested in illuminating the three-dimensional structures of proteins and using that information to understand its role within the cell.

During graduate school, I became fascinated with a class of proteins

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Call for Nominations

Visiting Miller Professorship Departmental Nominations
Deadline: September 8, 2023

Miller Research Fellowship Nominations
Deadline: September 13, 2023

Miller Research Professorship Applications
Deadline: September 18, 2023

See page 5 for more details on all our programs.

"The Miller Professorship allowed me to build a team and plan the execution of a project that has broad applications across both fundamental physics and nuclear non-proliferation. The effects of this position will continue to reverberate through both this effort and, via its impact more broadly, on the field of particle astrophysics."

Gabriel Orebi Gann
Associate Professor, Physics
University of California, Berkeley
Miller Professor 2021-2022

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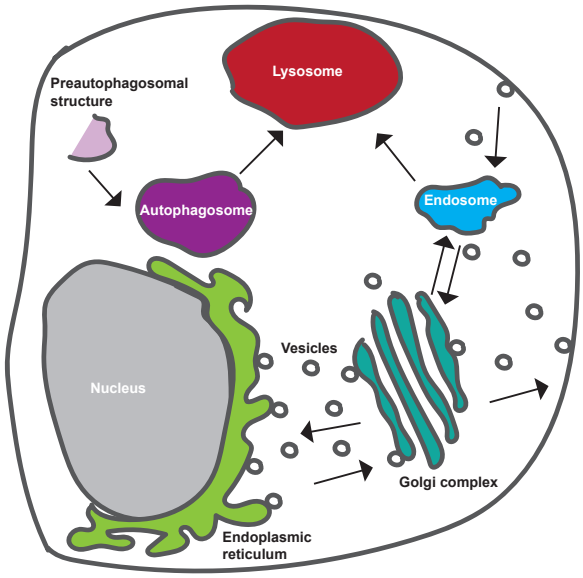


Figure 1. A cartoon depiction of a cell's system of organelles, with vesicles shuttling between them.

called Arf/Rab guanine nucleotide exchange factors (Arf/RabGEFs, for short). The function of Arf/RabGEFs is to activate a set of secondary proteins called Arf/Rab, in order to enable a cellular process named "vesicular trafficking". All animal and plant cells use this process to transport various cellular materials between their distinct internal compartments (also known as organelles) and their environments to maintain homeostasis (**see Figure 1**). In essence, a donor organelle creates a "vesicle" by pinching off a small piece of itself. This vesicle, and all of the material contained inside, is then physically directed to another location inside of the cell where it fuses with a recipient organelle. A number of diseases and cancers can arise when these transport events do not happen correctly, thus their implementation involves a complex series of steps that must be highly spatially and temporally regulated.

Arf/Rab proteins play a central role in orchestrating each stage of vesicular trafficking pathways by switching between "on" and "off" states. Notably, Arf/Rab proteins do not alternate between these two states on their own, and instead require the assistance of Arf/RabGEFs to be switched "on". If we had a comprehensive understanding of vesicular trafficking pathways, we could wield that information towards combatting numerous diseases and cancers. The first step towards this goal is to identify each Arf/RabGEF and its associated target Arf/Rab. In addition, there are other crucial questions: How does the Arf/RabGEF enzyme recognize its target Arf/Rab? What mechanism does the Arf/RabGEF use to switch the Arf/Rab "on"? What allows the Arf/RabGEF to localize to the proper organelle and orient itself correctly for the activation reaction? We can begin to answer these questions and more, by illuminating the three-dimensional structure of these proteins!

For my PHD, I studied two Arf/RabGEFs that are responsible for controlling vesicular traffic between the endoplasmic reticulum and the Golgi complex: Sec12 and the TRAPPIII complex. Using a combination of X-ray crystallography and cryogenic electron microscopy, I elucidated the structures of Sec12 bound to its target Sar1, and TRAPPIII bound to its target Rab1 (see **Figure 2**). By viewing these Arf/RabGEFs in the process of activating their target Arf/Rab, we uncovered a critical snapshot in each of their enzymatic processes. We learned how a rigid feature of Sec12, called the K-loop, engages the active site of Sar1 to switch it on. We found a groove along the center of TRAPPIII which enables recognition of its target Rab1. We also discovered a cluster of positively charged amino acids on the surface of Sec12 and on TRAPPIII, as well as an additional membrane-binding helix in TRAPPIII, which we think allude to a mechanism for how Sec12 and TRAPPIII position themselves correctly on the surface of organelles for activation of their targets. Importantly, these structures presented valuable insights that when combined with other experiments provided clear models for nucleotide exchange by Arf/RabGEFs at the surface of an organelle.

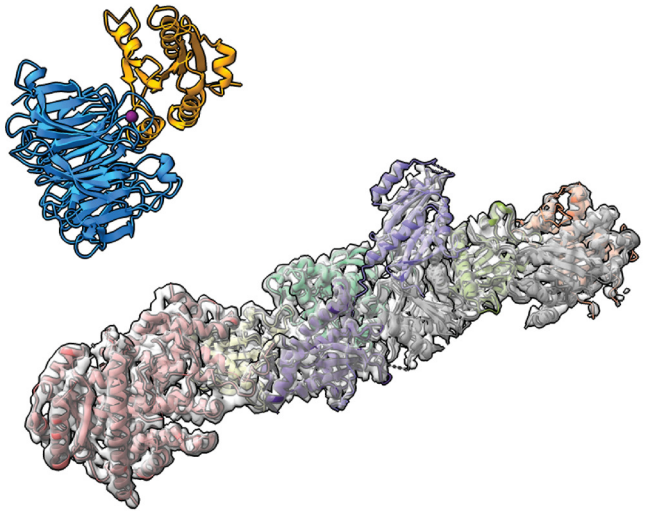


Figure 2. Top: X-ray crystallography structure of GEF Sec12 (blue) bound to its target Sar1 (orange). **Bottom:** Cryogenic electron microscopy structure of GEF TRAPPIII complex bound to its target Rab1, multi-colored to distinguish the various proteins within the complex and outlined by the cryoEM density in transparent gray.

As a postdoctoral scholar, I wanted to focus on another class of protein enzymes called Arf/RabGAPs which work, in opposition to Arf/RabGEFs, by controlling the "off" side of the process for Arf/Rab proteins. I decided that Berkeley, with its storied history in research on vesicular trafficking, for which Randy Schekman was awarded the 2013 Nobel Prize in Medicine, would be a fantastic environment to do this. In the laboratory of my host James Hurley, my research is now centered on the C9orf72 protein. C9orf72 has been implicated in the onset of two debilitating neurodegenerative diseases: amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) and frontotemporal degeneration (or FTD). A three-dimensional structure of C9orf72 was recently revealed, leading to its identification as an Arf/RabGAP, however the identity of its target Arf/Rab is still elusive. I am currently working to find its target and answer other key questions about its function as an Arf/RabGAP, with the hopes that deepening our understanding of its cellular function will lead to insights for counteracting neurodegeneration.

Aaron Joiner is a third-year Miller Fellow in Molecular and Cell Biology, hosted by James Hurley. Dr. Joiner earned his Ph.D. from Cornell University in structural biology and biochemistry under the skillful tutelage of former Miller Fellow Chris Fromme. His work illuminated the mechanism of enzyme-mediated nucleotide exchange for small GTPases in vesicular transport pathways using structural approaches. Prior to graduate school, he earned a B.S. in biochemistry from Beloit College and performed research at the Smithsonian Tropical Research Institute in Panama.

Contact: amj85@berkeley.edu

In the News

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

The U.S. National Science Foundation has selected **Susan Marqusee** (Miller Professor 2016-2017, Miller Senior Fellow 2019-present) to **head the Directorate for Biological Sciences.** *"Susan Marqusee's vast experience will be a monumental benefit to NSF and our effort to tackle some of the most complex societal challenges."*

Yao Yang's (Miller Fellow 2021-2024) recent discovery, **"Catalyst Chemistry Could Turn Emissions into Green Fuels,"** was highlighted by the Kavli Foundation.

Iwnetim Abate (Miller Fellow 2021-2022) was selected to be part of the **Talented 12** by the American Chemical Society.

Luis Caffarelli (Advisory Board Member 2017-2022) was announced as the winner of the **Abel Prize**, given by the Norwegian Academy of Sciences and Letters and considered the "Nobel of mathematics."

Meredith Hughes (Miller Fellow 2010-2013) was recognized by Wesleyan University as one of the recipients of the **Binswanger Prizes for Excellence in Teaching.**

Next Steps

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

Grayson Chadwick
Postdoc @ Nayak lab
Molecular & Cell Biology
UC Berkeley

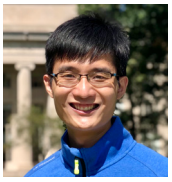
Emily Davis
Postdoc @ Yao lab, Harvard
In January 2024: Assistant Professor
Physics Department, NYU

Vayu Maini Rekdal
Postdoc @ Keasling lab
Chemical & Biomolecular Engineering
UC Berkeley

Michael P. Kim
In January 2024: Assistant Professor
Computer Science Department
Cornell University

Antoine Koehl
Postdoc @ Song lab
Electrical Engineering & Computer Sciences
UC Berkeley

Nayeli A. Rodriguez Briones
Postdoc @ Whaley lab, UC Berkeley
In January 2024: Postdoc
Physics Department, Atominstitut
Technische Universität Wien
Vienna, Austria



Alfred Zong
Postdoc @ Zuerch lab, UC Berkeley
In Fall 2024: Assistant Professor
Physics and Applied Physics Departments
Stanford

Recent Publications

Alfred Zong (Miller Fellow 2020-2023) is a co-author of the paper, "Probing lithium mobility at a solid electrolyte surface," published in *Nature Materials.*

Omar Yaghi (Visiting Miller Professor 2009), the inventor of a metal-organic framework (MOF), led the study on MOF-powered water harvesters that was published in *Nature Water.*

From the Executive Director

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

I am thrilled to be given the chance to lead the Miller Institute into its 67th year. I have experienced the intellectual vitality of this community from various angles over the past 20 plus years — as a Miller Professor, a host to Miller Fellows and Visiting Miller Professors, a speaker at two Symposia, and a member of the Executive Committee. In this new role as Executive Director, in addition to deepening my appreciation of the Institute, I look forward to upholding the excellence while broadening the representation of the Institute amidst the competition from a rising number of other prestigious postdoctoral fellowships.

As you read this newsletter, we are enjoying catching up with one another after much summer traveling and getting to know the new members of the Institute. Our ten new Miller Fellows come from as close as across the San Francisco Bay, and as far away as Nigeria. Our ten Visiting Miller Professors are arriving throughout the year, half of them from institutions outside the U.S. And we're delighted to welcome three new Miller Professors to our interdisciplinary community. As they complete their terms, our stellar outgoing Miller Fellows will be joining the ranks of our distinguished alums around the world. We look forward to nominations and applications for the 2024-2027 Miller Fellowship, 2024-2025 Miller Professorship and Visiting Miller Professorship programs. I ask for your participation in identifying outstanding candidates from diverse backgrounds, to nominate them and/or encourage them to apply.

On behalf of the Miller community, I offer my deepest gratitude to outgoing Executive Director Marla Feller for her six years of outstanding leadership. This was no ordinary term; it demanded extraordinary efforts in managing unforeseen circumstances due to the pandemic and other challenges. Our thanks also to outgoing Executive Committee member Yun Song for his tireless service, and to outgoing Advisory Board members Feryal Özel and Tim Stearns for their insightful advice.

Moving forward, I am excited to welcome new Executive Committee members Nicole King and Alistair Sinclair. Together with Jeffrey Long, we have already had productive meetings and are ready for a stimulating 2023-2024. I am also delighted that Eliot Quataert (Princeton) and Linda Hsieh-Wilson (Caltech) have accepted our invitation to join the Advisory Board, along with Anna Gilbert (Yale) and Scott Edward (Harvard). With Senior Miller Fellows Susan Marqusee and Ken Ribet, we have a team of ten faculty members covering a broad spectrum of research expertise and advising, mentoring, and administrative experiences to guide the Institute forward.

But of course, nothing would happen without our wonderful staff Emily Birman, Clara Duman, Donata Hubert, and Vrinda Khanna under the baton of Chief Administrative Officer Hilary Jacobsen! Cheers to another exciting year at the Institute, with more science talks, lunches, happy hours and many more opportunities to learn from each other!

We are excited to welcome Chung-Pei Ma as the Miller Institute's new Executive Director as of July 2023. An Executive Committee member of the Institute since 2021, Chung-Pei is an astrophysicist who enjoys using luminous matter to study dark components in the universe: dark matter, dark energy, and black holes. Her research group uses both theoretical and observational tools to investigate the cosmic assembly of black holes and galaxies. Chung-Pei looks forward to deepening her involvement with the Miller community and leading the Institute in this new capacity in the years to come.

Participants in the 2023 pre-Symposium hike

Call For Nominations: Miller Research Competitions

Miller Research Fellowship 2024-2027
Online Nomination Deadline: September 13, 2023

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. Applicants who have already completed substantial postdoctoral training are unlikely to be successful except in unusual circumstances. **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 2024.** Nominees who are non-US citizens must be eligible for obtaining 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, 2024. 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: **https://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 $75,000 with annual increases and an annual research fund of $10,000, for total initial compensation of $85,000. 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, 2024 and ending July 31, 2027. 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 2024-2025
Online Application Deadline: September 18, 2023

The Miller Professorship program announces the call for applications for terms in AY 2024-2025. 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 Friday, September 18, 2023. Applications are available on our website: **https://miller.berkeley.edu/professorship.**

Visiting Miller Research Professorship AY 2024-2025
Online Nomination Deadline: September 8, 2023

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 2024 or Spring 2025. 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 sponsorship. Nominations can be made through our portal on our website: **https://miller.berkeley.edu/visiting-professorship**. For questions about our programs or competitions, please contact millerinstitute@berkeley.edu

THANK YOU TO OUR OUTGOING EXECUTIVE COMMITTEE MEMBERS

Marla Feller, the Miller Institute's Executive Director and Professor of Neurobiology at UC Berkeley, completed her tenure as the Institute's Executive Director in June 2023. She was previously a Miller Fellow from 1994-1996 in Molecular & Cell Biology and Neurobiology and became the Institute's Director in 2017.

Marla says, "'May you have a strong foundation when the winds of changes shift.' This quote from Bob Dylan resonates with my experience of being the Executive Director of the Miller Institute. In my 6 years, I have witnessed many changes (Kathy -> Hilary!) and challenges (pandemic!), but the community remained together. It has been such a privilege to work alongside passionate and talented scientists, and I am grateful for the opportunity to have played a part in the launching of so many exciting careers and the start of so many collaborations. Given the dedicated staff and leadership, I am confident that the Miller Institute will continue to be a shining example of excellence and collaboration in the UC Berkeley scientific community."

We are grateful for Marla's leadership over the past six years and she looks forward to staying connected with the Institute following her tenure.

Our deepest gratitude and thanks to outgoing Executive Committee member **Yun Song** (2016-2023) for his wise counsel and leadership at the Institute.

Yun says, "It has been a tremendous privilege to be part of the Miller Institute's vibrant intellectual community for the past six years. I feel honored to have contributed to the Institute's mission of fostering great scientists, and I have much enjoyed learning about their cutting-edge research. The weekly Tuesday lunch talks and interactions with colleagues have been a highlight of my time at the Institute, and I will undoubtedly miss the stimulating conversations. Overall, my experience at the Miller Institute has been a profound and enriching one, and I am grateful for the chance to have been part of such a remarkable community."

THANK YOU TO OUR OUTGOING ADVISORY BOARD MEMBERS

Our thanks to the outgoing **Advisory Board members Feryal Özel** (2017-2023) (**L**) and **Tim Stearns** (2017-2023) (**R**) for their wise counsel and leadership at the Institute. Their commitment to the Institute, and especially their interest in enhancing the "Fellow experience," have proven valuable beyond measure.

WELCOME NEW EXECUTIVE COMMITTEE MEMBERS

Nicole King first became fascinated with the natural world as a young girl, when she spent weekends collecting sharks' tooth fossils from her neighborhood creek in Gainesville, Florida. While her research in college and grad school focused on genetics and biochemistry, she never lost her interest in evolution. In her current research, she and members of her laboratory use approaches from genomics, biochemistry, and cell biology to investigate the origin of animals.

She is a professor at the University of California, Berkeley, an Investigator in the Howard Hughes Medical Institute, and a MacArthur Fellow. Nicole was elected to the Académie des Sciences (French Academy of Sciences) in 2021 and the National Academy of Sciences in 2022. Nicole was a Miller Professor from 2018-2019.

Alistair Sinclair received his BA in Mathematics from Cambridge in 1982, and his PhD in Computer Science from Edinburgh in 1988. He moved to UC Berkeley in 1994, where he is now the Ogawa Professor of Computer Science and Professor of Statistics. From 2012 to 2017 Sinclair was Founding Associate Director of the Simons Institute at Berkeley. His major honors include the 1996 Gödel Prize and the 2006 Fulkerson Prize.

His research interests focus on randomized algorithms, as well as on topics at the intersection of computer science and statistical physics.

WELCOME NEW ADVISORY BOARD MEMBERS

Linda Hsieh-Wilson is currently the Milton and Rosalind Chang Professor of Chemistry at the California Institute of Technology. She received her Ph.D. in chemistry from the University of California at Berkeley, where she was a National Science Foundation predoctoral fellow in the laboratory of Professor Peter Schultz. Hsieh-Wilson joined the faculty as an Assistant Professor of Chemistry at the California Institute of Technology in 2000 and was an investigator of the Howard Hughes Medical Institute from 2005-2014. She has pioneered the application of organic chemistry to understand the roles of carbohydrates and protein glycosylation in the brain. She was elected to the American Academy of Arts and Sciences in 2015 and the National Academy of Sciences in 2022.

Eliot Quataert is a Professor of Astrophysical Sciences and the Charles A. Young Professor of Astronomy at Princeton University. Quataert is an astrophysics theorist who works on a wide range of problems, including stars and black holes, plasma astrophysics, and how galaxies form. He is a Simons Investigator in Physics and an elected member of the American Academy of Arts and Sciences and the National Academy of Sciences. Quataert is also a highly regarded teacher and public lecturer.

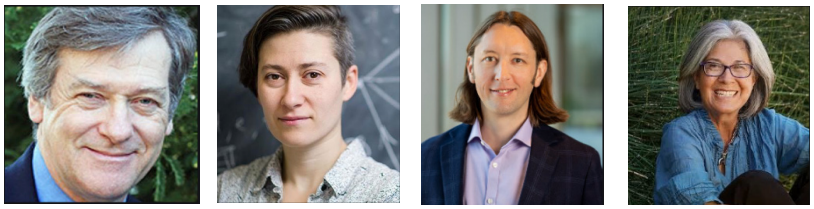
Eliot was a Miller Professor from 2009-2010 and served on the Executive Committee from 2012-2013. Eliot is looking forward to interacting with the broad science community present in the Miller Institute, particularly the amazing group of Miller Postdoctoral Fellows.

25th Annual Interdisciplinary Symposium

Miller Institute Executive Director Chung-Pei Ma, former Miller Institute Executive Director Marla Feller and former Executive Committee member Yun Song

2023 Symposium participants

Miller Fellows James Santangelo, Kelian Dascher-Cousineau, Yanni Kipouros, Carly Schissel, former Miller Fellow Allie Gaudinier & Miller Fellow Elena Zavala



Speakers: Roger Blandford, Moon Duchin, Julius Lucks, Isabel Montañez, Piali Sengupta, Nicola Spaldin & William Tarpeh

Miller Senior Fellow Susan Marqusee, Miller Fellow Aaron Joiner and former Miller Senior Fellow Randy Schekman

Symposium Committee Chair Michael Manga & Kathryn A. Day Miller Postdoctoral Fellow Raul Ramos

Miller Senior Fellow Ken Ribet and Miller Fellow Georgios Varnavides

Miller Institute Executive Director Chung-Pei Ma and Symposium Speakers Isabel Montañez & Nicola Spaldin

Former Miller Senior Fellow Raymond Jeanloz, campus journalist Bob Sanders & Miller Fellow Yao Yang

Miller Fellow Michael Celentano & former Executive Committee member Yun Song

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Miller Institute News - Fall 2023
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miller_adm@berkeley.edu

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News & Recent Publications

Ray Jayawardhana (Miller Fellow 2000-2002) was named as **Johns Hopkins University's 16th provost**.

Alanna Schepartz (Miller Professor 2022-2023) is a co-author of the papers, appearing in the journals *Nature Chemistry and ACS Central Science*, that are the beginning of a playbook for reengineering the cellular synthetic machinery to produce never-before-seen polymers, including bio-polymers and circular polymers, which are called peptide macrocycles, with predetermined or completely unforeseen applications.

Jeremy Thorner (Miller Professor, 1984-1985 & 1999-2000) has written two comprehensive review articles describing the structure, function and biogenesis of TORC2, a multi-subunit protein kinase that is one of the master regulators of eukaryotic cell growth, one in the *Biochemical Journal* (2022) and the other in *Annual Review of Cell and Developmental Biology* (2023).

Elena Zavala (Miller Fellow 2022-2025) is a co-author of the paper, "Ancient human DNA recovered from a Palaeolithic pendant," published in *Nature*.

Lijie Chen (Miller Fellow 2022-2025) and others helped develop a new algorithm that uses randomness and determinism to quickly produce reliable large prime numbers.

Alfred Zong (Miller Fellow 2020-2023) was recently interviewed at the CLEO Conference in San Jose organized by Optica (formerly known as the Optical Society of America), where he shared his experience as a Miller Postdoc Fellow.

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