Understanding the Evolution of Signaling Systems

Miller Fellow Focus: Antoine Koehl

Cells are the fundamental building blocks of all living organisms. At their core, cells are isolated compartments full of biomolecules, such as nucleic acids and proteins, that allow them to carry out fundamental behaviors—including reproduction and programmed response to changes in the environment—that we associate with the concept of 'life.' As the functional products of genes, proteins are the workhorses of cells and the fundamental unit of evolution. Proteins are polymer chains comprised of 20 different types of amino acids; these chains adopt a particular three-dimensional shape, or "fold", in order to carry out their various functions. As organisms have evolved to live in increasingly varied environments, their protein repertoires have also expanded through gene duplication and diversification events, leading to large families of proteins that share a common fold, but exhibit subtle differences in the types of chemical matter they can work with. These protein families work together to drive the majority of cellular processes and are essential to all aspects of animal physiology. GPCRs are expressed at the surfaces of cells and are responsible for modifying cellular behavior in response to the presence of a specific hormone on the outside of the cell. As examples of two fundamental biological pathways that rely on GPCR signaling, consider the opposing roles of adrenergic receptors in activation of the stress response and muscarinic receptors in regulation of the body at rest. Adrenergic receptors in the heart detect (i.e. by physically bind-
Call for Visiting Miller Professor Nominations
Online Nomination Deadline: September 6, 2022

Visiting Miller Research Professorship AY 2023-2024

The Advisory Board of the Miller Institute for Basic Research in Science invites Berkeley faculty to submit online departmental nominations for Visiting Miller Research Professorships and the Gabor A. and Judith K. Somorjai Visiting Miller Professorship Award for terms in Fall 2023 or Spring 2024. The purpose of these Visiting Miller Professorships is to bring promising or eminent scientists to the Berkeley campus on a short-term basis for collaborative research interactions. It is required that awardees be in residence at Berkeley during their appointment term. Faculty members or research scientists from around the world are eligible to be considered for sponsorship. Non-US citizens must be eligible for J-1 Scholar visa status in order to be awarded. Faculty members at other UC campuses are eligible to be nominated for this program. The Miller Institute, as the sponsor and administrative department, will extend an invitation after advising the department of its selection.

Beginning in May 2022, nominations will be accepted from UC Berkeley faculty for Visiting Professorship candidates for the 2023-2024 academic year. Nominations are judged competitively and are due by September 6, 2022. It is anticipated that between four and ten awards will be made.

For more information, and to access the nomination form, visit miller.berkeley.edu/visiting-professorship.

Call for Miller Professor Applications
Online Applications Deadline: September 16, 2022

Miller Research Professorship AY 2023-2024

The Miller Professorship program is looking with a view to the future in announcing the call for applications for terms in the academic year 2023-2024. The objective of the Miller Professorship program is to provide opportunities for faculty to pursue new research directions on the Berkeley campus and to participate in the vibrant Miller Institute interdisciplinary scientific community. Appointees are encouraged to follow promising leads that may develop in the course of their research. In order to accommodate a range of faculty members, the Miller Professorship program offers appointees, in consultation with their Departmental Chair, the option of taking teaching relief or continuing to teach during their Miller Professorship term. Funds will be distributed differently depending upon the choice selected.

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.

Beginning in May 2022, applications will be accepted from UC Berkeley faculty for terms in the 2023-2024 academic year. Applications are judged competitively and are due by September 16, 2022. It is anticipated that between four and ten awards will be made.

For more information, and to access the application, visit miller.berkeley.edu/professorship.

:: Nomination & Application details: miller.berkeley.edu
:: Questions? millerinstitute@berkeley.edu
The Miller Institute for Basic Research in Science

Call for Nominations: Miller Research Fellowship
2023-2026 Term

Nomination Deadline: September 12, 2022

The Miller Institute for Basic Research in Science invites department chairs, faculty advisors, professors and research scientists at institutions around the world to submit nominations for Miller Research Fellowships in the basic sciences. Through this program, 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. 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 administrative home department for each Miller Fellow who is hosted by an academic department on the Berkeley campus. A list of current and former Miller Research Fellows can be found at: https://miller.berkeley.edu/fellowship/members/all-mf-by-name.

The Miller Institute also welcomes nominations for the Kathryn A. Day Miller Postdoctoral Fellowship award for the 2023-2026 Fellowship cohort. Named in honor of the Institute’s retired Chief Administrative Officer Kathy Day, this award is intended for an early career scientist who, in addition to excelling in their pursuit of basic science research, also engages in outreach in support of science.

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. Miller Fellows are expected to begin their Fellowship shortly after being awarded their Ph.D. A short period as a postdoctoral fellow elsewhere does not exclude eligibility, but applicants who have already completed more than two years of postdoctoral experience are not eligible for nomination. 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 extend into February 2023. Nominees who are non-US citizens must show eligibility for obtaining J-1 Scholar visa status for the duration of the Miller Fellowship. Non-US citizens will be required to prove English language proficiency prior to award. The Miller Institute does not support H1B visa status. Eligible nominees will be invited by email by the Institute to apply for the Fellowship after the nomination has been reviewed. Direct applications and self-nominations are not accepted. All nominations must be submitted using the online nomination system at: miller.berkeley.edu/fellowship.

Nominations 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 that will be valid through March 2023, and 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 (saved in PDF format). 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 $68,000 with annual 2% increases and an annual research fund of $10,000, for total initial compensation of $78,000. There is provision for travel to Berkeley for incoming 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, 2023 and ending July 31, 2026. 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.

We are grateful for your thoughtful participation in this process and the contribution you are making in the careers of distinguished early-career researchers.

:: Nomination & Application details: miller.berkeley.edu
:: Questions? millerinstitute@berkeley.edu
The Miller Institute is pleased to introduce the 2022-2025 Miller Research Fellows. Each year, the Miller Research Fellowship program seeks to discover individuals of outstanding talent and to bring young scholars of great promise to the Berkeley campus. The Fellows will be working with Berkeley faculty hosts for a three-year term beginning in the 2022 academic year. A full list of all past and present Miller Fellows is available on our website.

**ANNOUNCING THE INSTITUTE’S FIRST KATHY DAY FELLOW!**

This year, the Institute named the first Kathryn A. Day Miller Postdoctoral Fellow, incoming 2022-2025 Fellow Raul Ramos! This award was established in 2019 through a major pledge to the Institute by Professor Randy Schekman and Professor Sabeeha Merchant in honor of Kathy’s dedicated service to the Institute over a 30-year career. In addition to demonstrating great promise in research, Raul was chosen for his work in outreach and communication in science. We’re thrilled to welcome Raul and celebrate Kathy’s legacy at the Institute through this special Fellowship award!

**Raul Ramos**
Kathy Day Award
Ph.D. - Brandeis University
Berkeley Dept. - MCB
Faculty Hosts: Diana Bautista, Ellen Lumpkin

My long-term research goal is to uncover novel molecular, cellular, and circuit mechanisms underlying sensory processing disorders (SPD’s). I am especially interested in identifying the cellular underpinnings of tactile hypersensitivity and ways to treat this SPD. My research as a Miller Fellow will explore the therapeutic potential of psychedelics in the context of tactile hypersensitivity and the peripheral nervous system function.

**Lijie Chen**
Ph.D. - MIT
Berkeley Dept. - EECS
Faculty Host: Avi Shay Tal

I have a broad interest in theoretical computer science. My current focus is on proving unconditional lower bounds against specific restricted models of computation and studying how to remove randomness in algorithms while paying little overhead.

**Boryana Hadzhiyska**
Ph.D. - Harvard University
Berkeley Dept. - Physics
Faculty Host: Martin White

My work blends the distinct fields of cosmology, galaxy formation, particle physics, and statistics to probe some of the most puzzling enigmas of our Universe: dark matter, dark energy, and neutrinos. In particular, I compare predictions from powerful numerical simulations with observations from cutting-edge galaxy experiments, jointly analyze early Universe probes and galaxy observations, and develop analytical approaches, in an effort to provide competitive constraints on galaxy formation and cosmology.

**Kelian Dascher-Cousineau**
Ph.D. - UC Santa Cruz
Berkeley Dept. - EPS
Faculty Host: Roland Burgmann

I study earthquakes physics and tectonic geomorphology. As a primary tool, I leverage the statistical laws and patterns of seismicity to diagnose the physical processes that control nucleation and interactions. This research aims to reveal how stresses in the earth’s crust evolve over time and, in some cases, culminate in catastrophic earthquakes. I also study the lasting influence of earthquakes in the landscape. Over thousands of years, the faults that host earthquakes leave a geomorphic imprint. This interplay is a natural laboratory to better understand the earthquake cycle and landscape evolution over tens of thousands of years.

**Chadi Saad-Roy**
Ph.D. - Princeton University
Berkeley Dept. - IB
Faculty Host: Michael Boots

Infectious diseases exert significant burden across the world, and understanding their dynamics is thus crucial for proper mitigation and control. In my research, I use mathematical and theoretical approaches to study the cross-scale eco-evolutionary dynamics of pathogens. Additionally, I am interested in determining the impacts of host characteristics on pathogen dynamics and the subsequent implications for control.
Carly Schissel  
Ph.D. - MIT  
Berkeley Dept. - Chemistry  
Faculty Host: Alanna Schepartz

Nature is an expert in synthesizing biopolymers with defined sequences and structures using a defined pool of monomers. However, the ability to expand the chemical and structural possibilities of these biopolymers would have a great impact on materials and medicines. My PhD research focused on the design and chemical synthesis of unnatural peptides that are able to deliver macromolecular cargo to a cell’s nucleus. My postdoctoral work will shift towards new methods to synthesize unnatural peptides and proteins using nature’s machinery. Specifically, I aim to engineer a recently discovered tailoring enzyme to modify the amide backbone of ribosomally-synthesized proteins in order to change their physical properties.

Georgios Varnavides  
Ph.D. - MIT  
Berkeley Dept. - MSE/Physics  
Faculty Hosts: Mary Scott, Joel Moore

Recent advances in transport measurements have revealed that electrons in materials can flow collectively, exhibiting fluid phenomena such as vortices. Unlike everyday fluids however, preferred directions in crystals imply electron fluids exhibit anisotropic and non-dissipative viscous contributions, giving rise to novel phenomena. As a Miller Fellow, I will image these anisotropic electron fluids with high spatial resolution (<5 nm) using a transmission electron microscopy computational imaging technique. Correlating non-uniform current densities with the underlying structure would open the door to investigating the role of structure and defects in designing near-dissipation-less electronics, inviting questions like “does current flow around defects in materials similar to how rivers flow past pebbles? If so, can we engineer them to minimize thermal dissipation?”.

Mengshan Ye  
Ph.D. - MIT  
Berkeley Dept. - Chemistry  
Faculty Host: Jeffrey R. Long

Quantum information science and technologies have brought advances in computing, sensing and communication. In particular, optically addressable quantum sensors harness sensitivities to external disturbances to accurately trace environmental fluctuations. At Berkeley, I will develop atomically tailorable, spatially accessible, and optically active molecular qubits and illustrate their advantages in magnetic field sensing.

Elena Zavala  
Ph.D. - University of Leipzig  
Berkeley Dept. - MCB  
Faculty Host: Priya Moorjani

My interests are centered on method development for working with low amounts of degraded DNA for applications in both ancient DNA and forensic genetics. During my PhD I utilized ancient DNA methods to reconstruct human and faunal occupational histories from Pleistocene sediment DNA and demonstrated that the integration of these methods into forensic workflows increases success rates for DNA profiling of unidentified historical remains. My research will focus on the development of new workflows for individualizing unidentified forensic and historical remains and increasing our understanding of the accuracy of genealogical searching methods for highly degraded samples.

Lingfu Zhang  
Ph.D. - Princeton University  
Berkeley Dept. - Statistics  
Faculty Host: Shirshendu Ganguly

I study probability theory and use it to mathematically analyze real-world problems in theoretical physics, computer science, and statistics. Examples of specific topics include localization of waves in a disordered medium, random processes on large social networks, and random growth modeling bacterial colonies or molecular condensation. A central objective is to understand universality, the phenomenon where different random systems produce the same big-scale behavior, regardless of the microscopic structures.

Recent Publications by Miller Members

Yu He (Miller Fellow 2019-2022) & Dung-Hai Lee (Miller Professor Spring 1999) are co-authors of the paper “Unconventional spectral signature of Tc in a pure d-wave superconductor” published in Nature.

Yao Yang (Miller Fellow 2021-2024) is a co-author of the paper “A completely precious metal-free alkaline fuel cell with enhanced performance using a carbon-coated nickel anode” published in PNAS.

Emily Davis (Miller Fellow 2020-2023) is a co-author of the paper “Programmable interactions and emergent geometry in an array of atom clouds” published in Nature.

Jeffrey Townsend (Miller Fellow 2002-2005) is a co-author of the paper “Environmental and sex-specific molecular signatures of glioma causation” published in Neuro-Oncology.

Jill Banfield (Miller Professor 2006-2007) is a co-author of the paper “Petabase-scale sequence alignment catalyses viral discovery” published in Nature.
ing) adrenaline molecules, which are secreted in response to a fear stimulus, and trigger an increase in heart rate in response. Muscarinic receptors, in turn, detect acetylcholine molecules, which are released at a later time to slow the heart back down, thereby facilitating a return to a "resting" state. The critical nature of GPCRs in homeostasis and disease is reflected in the fact that approximately 35% of FDA-approved drugs directly target this particular protein family. However, their therapeutic potential is still relatively under-developed: only ~25% of receptors have an approved therapeutic; these represent the systems that have historically been well-studied. Furthermore, of the ~400 hormone-binding GPCRs identified in the human genome, there still remain ~80 for which the endogenous (natural) ligand is not known. Included amongst these so-called "orphans" are receptors whose function in regulating brain development is so important that they have remained virtually unchanged across organisms spanning hundreds of million years of evolution. The ability to "de-orphanize" even a single signaling system has historically been transformative, opening both new therapeutic avenues to treat diseases as well as opening new lines of biological inquiry.

In an effort to better understand the roles of these orphan receptors, I am working to develop models of how a protein’s presence in a given signaling pathway influences its evolutionary trajectory in order to better leverage existing information from other proteins with known function. A unifying feature of hormone systems is their underlying architecture. For a given hormone, its production and degradation are regulated by a set of enzymes; if it is made inside of the cell, its transport out of the cell is mediated by a transporter, and finally it signals by binding to its native receptor on its target cell (Figure 1-left). What is remarkable is that these various proteins have evolved to recognize the same molecule, despite having completely unrelated folds and evolutionary origins. What instead unites these proteins is the requirement that they form a core set of locally similar interactions with their natural ligand; this involves placing amino acids with similar properties in a similar geometric arrangement. Since a deficiency in any one of these proteins would lead to dysfunction of the entire pathway, it is expected that this group of genes has coevolved in order to maintain its function.

As a Miller Fellow, I have begun to use novel machine-learning algorithms to better reconcile sequences, structures and functions of proteins. Existing methods leverage the fact that protein structures are uniquely determined by their amino acid sequences, and that proteins must adopt their canonical fold in order to carry out their functions. In particular, this need to maintain a particular fold imposes constraints on the evolution of sequences within a protein family, and extracting at patterns of co-evolution amongst positions in sequences from different organisms is at the core of models that predict protein structures from their sequences. This recently culminated in the development of AlphaFold 2, which has revolutionized the field of protein structure prediction. However, attempts at detecting indirect signals of coevolution amongst proteins that interact at a distance via a shared ligand have been much less successful. At the core of this challenge is the need to disentangle the relative contributions of evolution that act on different time and length scales. As each protein in a given signaling pathway has evolved, it has faced constraints
to not only maintain its fold so that it may carry out its general function (e.g. transporting molecules across cell membranes) but also to retain the set of local interactions that give it specificity for a particular chemical ligand. Delineation of these contributions requires balancing information from proteins that share the same fold (family) with information from the other members of the same signaling pathway that instead share a need to recognize the same molecule (Figure 1- Right). A particular challenge comes from the fact that the coevolution signal from these respective sources are of vastly different magnitudes, as proteins from the same family will inherently show much greater similarity with each other than with proteins from other families despite large differences in their specificity for different chemical matter. I believe that consideration of protein sequences in their correct evolutionary and structural contexts will ultimately lead to more accurate models of protein function.

B eing able to place a receptor in its functional milieu not only provides mechanistic insights about a particular signaling process: knowledge of its endogenous hormone enables the rational design of novel molecules that can act as tools to better interrogate its underlying biology. More generally, this approach should help to provide functional annotations for other protein families involved in multi-protein signaling processes.

Antoine Koehl was born in Strasbourg, France but has lived in California since the age of 5. He received his B.S in Molecular, Cell and Developmental Biology from UCLA and returned to Northern California to do his PhD in Structural Biology at Stanford University in the lab of Brian Kobilka, where he became interested in GPCR signaling. Antoine has been a Miller Fellow since 2020, having made a transition to computational biology in the lab of Yun S. Song. He lives with his partner and their two cats.

Contact: akoehl@berkeley.edu
twitter: @antoinekoehl

ANNUAL SPRING DINNER 2022

IN THE NEWS

Chung-Pei Ma (Miller Professor 2010, 2019-2020, Executive Committee 2021) & Imke de Pater (Miller Professor Spring 1993, 2003-2004) were named 2022 Fellows of the American Astronomical Society for their extraordinary achievements and service.

Miller Members elected to the AAAS in 2021 in recognition of their distinguished and continuing achievements in original research:
- Philip Buckbaum (Visiting Miller Professor Spring 1996)
- Roberto Car (Visiting Miller Professor Spring 1994)
- J. Seamus Davis (Miller Professor 2000-2001)
- Matthew Fisher (Visiting Miller Professor Spring 1991)
- Mark Hauber (Miller Fellow 2002-2005)
- Michael Hochberg (Visiting Miller Professor Spring 2009)
- Stephen Mayo (Miller Fellow 1987-1989)
- Axel Meyer (Visiting Miller Professor Spring 1996)
- Hitoshi Murayama (Miller Professor Spring 2006)
- Dustin Rubenstein (Miller Fellow 2006-2009)
- Jennifer Schomaker (Somorjai Visiting Miller Professor Fall 2019)

Dmitry Budker (Miller Professor 2002-2003, Fall 2012) was a recipient of the 2021 Norman F. Ramsey Prize in Atomic, Molecular and Optical Physics, and in Precision Tests of Fundamental Laws and Symmetries "for seminal work studying complex atoms, testing fundamental symmetries of nature, measuring electromagnetic fields, searching for exotic interactions, probing the nature of dark matter, and measuring nuclear magnetic resonance in ultralow fields."

Alex Filippenko (Miller Senior Fellow 2017-2021, Miller Professor 2005, Miller Professor 1996, Miller Fellow 1984-1986) was awarded the American Astronomical Society 2022 Education Prize "for his passionate and wildly popular teaching of non-science majors; his mentoring of hundreds of teaching assistants and undergraduate research students; his dedication to public education through lectures, TV documentaries, and video courses; his textbook and other popular writings; and his leadership in saving Lick Observatory, a prominent California observatory that faced defunding in 2014."

UC Berkeley will be home to a new Kavli Center for Ethics, Science, and the Public, which will connect scientists, ethicists, social scientists, science communicators and the public in necessary and intentional discussions about the potential impacts of scientific discoveries. Stuart Russell (Miller Professor Fall 1996) will direct the new center. In addition to Russell, the Kavli Center leaders include Nobel laureate Saul Perlmutter (Miller Senior Fellow 2010-2015), who provided some of the first evidence that the expansion of the universe is accelerating, and Nobel and Kavli Prize laureate Jennifer Doudna (Miller Senior Fellow 2017), known for her discovery of the gene-editing tool CRISPR, among others.

Ekta Patel (Miller Fellow 2019-2022) was featured in the Scientific American article "Women Are Creating a New Culture for Astronomy".

The inaugural VinFuture Special Prize, dedicated to "Innovators with Outstanding Achievements in Emerging Fields" was awarded to Omar Yaghi (Visiting Miller Professor Fall 2009) for his work on discovering metal-organic frameworks.

Sebastian Höhna (Miller Fellow 2014-2017) was one of the recipients of the prestigious European Research Council (ERC) Starting Grants Award.
ANNUAL SPRING DINNER 2022

Invited speaker Professor Hitoshi Murayama with guest Natsuko Murayama & Executive Committee Member Chung-Pei Ma

Visiting Miller Professor Astrid Kiendler-Scharr with guest Hanno Scharr, former Institute Executive Director Raymond Jeanloz, Visiting Miller Professors Adrian Buganza Tepole, Tanja Bosak & Zeljko Ivezic

Miller Fellows Ekta Patel & Grayson Chadwick, former Miller Fellow Yong Zheng with guest Michael Blonski & Miller Fellow Allie Gaudner

Miller Fellows Iwnetim Abate & Alfred Zong

Executive Committee Member Yun Song & Executive Director Marla Feller