The Adolph C. and Mary Sprague

Miller Institute

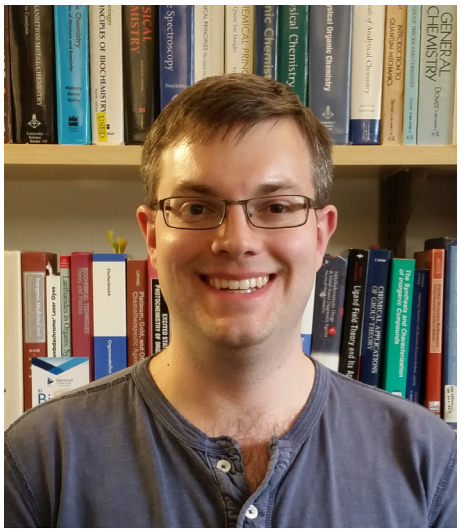
for Basic Research in Science

Newsletter
Fall 2018

Metabolite Sensors for Early Cancer Detection

Miller Fellow Focus: Christopher Lemon

Cancer is a deeply personal disease. We all know someone who has suffered through this insidious disease, fighting to survive. I have lost several important people to cancer, including my grandmother and my undergraduate research advisor. After decades of research, why does cancer remain an unsolved problem? The simple answer is that cancer is a complex, multifaceted disease that adapts to survive. Much is known about the genetics and biochemistry of cancer, but often the underlying causes of these observations remain elusive. Understanding why and how tumorigenic transitions occur are the keys to unlocking the secrets of the disease. Nevertheless, many amazing advancements have been made. We live in an age where cancer is not an automatic death sentence. New drugs have been developed that extend the lives of patients and improve their quality of life. One burgeoning area of research seeks to understand how cancer cells conceal themselves from the immune system. New drugs called immunotherapeutics turn on the innate immune response and enable it to recognize and attack cancer cells, obviating the need for toxic chemotherapeutics. While biologists perform the bulk of cancer research, chemists make valuable contributions



in the areas of therapeutics and diagnostics. As a Miller Fellow, I am using my background in synthetic chemistry and optical spectroscopy to develop sensors for early cancer detection.

Our knowledge of tumor metabolism has significantly advanced since Otto Warburg's initial 1924 observation that cancer cells consume abnormally high amounts of glucose. A new paradigm in oncology has emerged that focuses on identifying metabolites associated with specific tumorigenic transformations or "oncometabolites". Tracking metabolic changes represents an opportunity to identify malignant phenotypes at an early stage. For example, glutamine metabolism is altered in pancreatic

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Deadline: September 10, 2018

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For more information on all our programs:
miller.berkeley.edu

"Beyond my interest in Physics of biological systems my visit was very much enriched by the regular Miller luncheons and the exceptionally nice dinners and special events, where I was able to meet very interesting colleagues and got exposed to a very diverse range of topics. It was very stimulating to learn about areas, which are so far from my field and I was very positively impressed by the quality of the talks and the stimulating discussions thereafter."

Andreas Bausch
Chair, Cellular Biophysics
Technische Universitat Munchen, Germany
Visiting Miller Professor 2015

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cancer and thus presents an opportunity to identify differences in cellular glutamine levels for early diagnosis.

Pancreatic cancer is a slowly progressing form of cancer that develops over the course of decades. However, the progression of the disease is largely asymptomatic and a diagnosis is not usually reached until the disease has significantly advanced to nearly incurable levels. Most patients will die within five years of diagnosis, largely from extensive metastases to surrounding organs. Surgery is an option, but only a small percentage of newly diagnosed patients are candidates for the procedure. Currently, there are no clinically validated screening methods for pancreatic cancer in the early stages of the disease. However, pancreatic cancer, as well as certain other types of cancer, exhibits altered metabolism of the amino acid glutamine. While glutamine is non-essential in normal cells, certain cancer cells become dependent on, or "addicted" to, glutamine, resulting in higher intracellular concentrations of glutamine than normal cells. Thus, quantitative glutamine sensors can differentiate normal cells from cancerous ones, thereby serving as an early diagnostic for the disease.

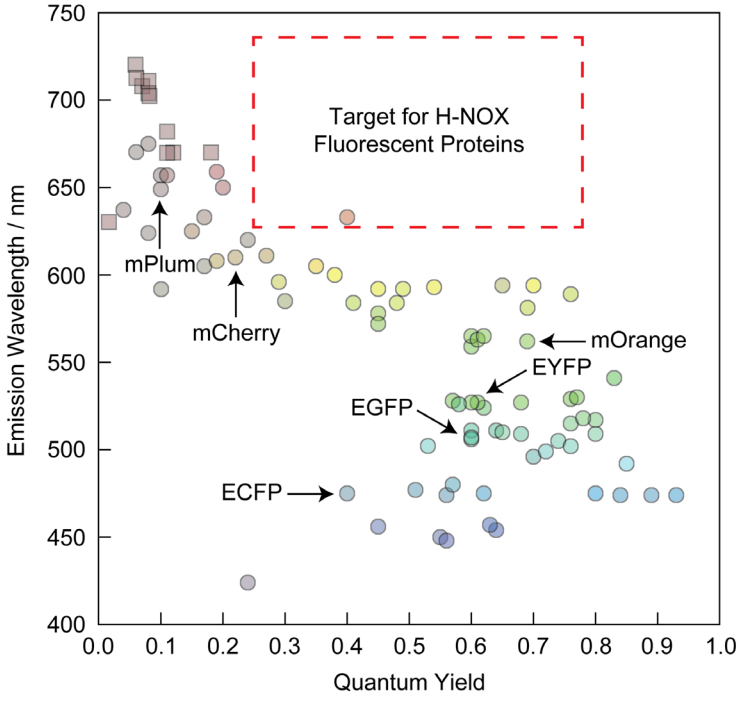

Figure 1. A comparison of the emission wavelength and fluorescence quantum yield of traditional fluorescent proteins. The color of each point is an approximation of the emission color. Well-known examples are highlighted and contrasted with the targeted properties of fluorescent H-NOX proteins.

I am using fluorescent proteins as a compact, biocompatible platform for metabolite sensing. For biological applications, red or near-infrared (NIR) light should be used because tissue is transparent to these wavelengths. This is easily demonstrated by holding your hand over a flashlight; you observe red light because your hand acts a filter, absorbing the other, shorter wavelengths. Unfortunately, traditional red fluorescence proteins exhibit weak fluorescence with low quantum yields (**Figure 1**), limiting their utility for biological imaging. The quantum yield is defined as the fraction of absorbed photons that are subsequently emitted as fluorescence.

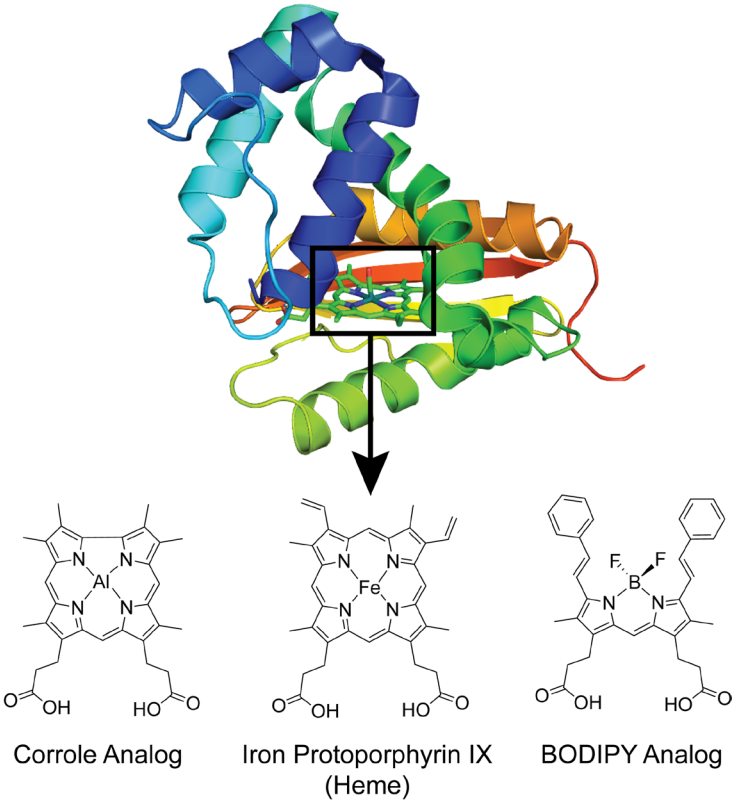

Figure 2. The structure of the H-NOX protein, highlighting the heme binding pocket. A comparison of the molecular structures of the native porphyrin cofactor, as well as structurally similar corrole and BODIPY analogs that are bright, red-emitting fluorophores.

To overcome this, I am incorporating bright, red-emitting cofactors into a stable protein: the heme nitric oxide/oxygen (H-NOX) binding protein from the thermophilic bacterium *Caldanaerobacter subterraneous* (**Figure 2**). Bacteria use H-NOX proteins to sense nitric oxide (NO) and/or oxygen in their environment and subsequently respond to these stimuli. The H-NOX protein is robust and thermostable, is readily expressed in *E. coli*, is easily modified, and readily binds unnatural heme cofactors. Additionally, the Marletta

> CONTINUED FROM PAGE 2 [Miller Fellow Focus]

lab has previously developed H-NOX derivatives for oxygen sensing and MRI imaging applications. Together, these factors make H-NOX an ideal scaffold for protein-based metabolite sensors.

To convert H-NOX into a fluorescent protein, I am incorporating red fluorescent molecules that are structurally similar to the native iron porphyrin (heme) cofactor (**Figure 2**). One family of molecules closely related to porphyrin is corrole, which has one less carbon atom in the cyclic skeleton of the molecule. This results in properties that are distinct from porphyrins. Corrole complexes containing gallium, phosphorous, and aluminum are highly fluorescent in the red region of the spectrum with high quantum yields (25–75%). Additionally, I am synthesizing boron dipyrrin fluorophores, also known as BODIPY dyes. The optical properties of BODIPY can easily be tuned by modifying the structure of the molecule, accessing a variety of emission colors (**Figure 3**). By incorporating these fluorophores into the H-NOX protein, new derivatives with superior optical properties to traditional fluorescent proteins will be obtained.

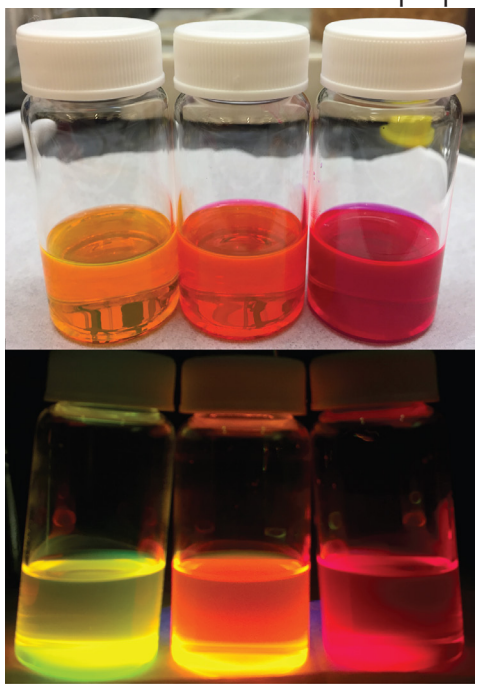

Figure 3. Solutions of a series of BODIPY fluorophores under visible light (top) and ultraviolet light (bottom), demonstrating that the fluorescence can be tuned to any color.

The fluorescent H-NOX protein on its own is not a sensor. It must be combined with a receptor molecule that binds the metabolite of interest. For glutamine sensing, glutamine binding protein (QBP) loaded with a fluorescent glutamine analog will be tethered to the fluorescent H-NOX (**Figure 4**). This sensor relies on Förster resonance energy transfer (FRET) for signal transduction. In the absence of glutamine, H-NOX emission is quenched and the absorbed energy is transferred to the fluorescent glutamine analog, resulting in its emission.

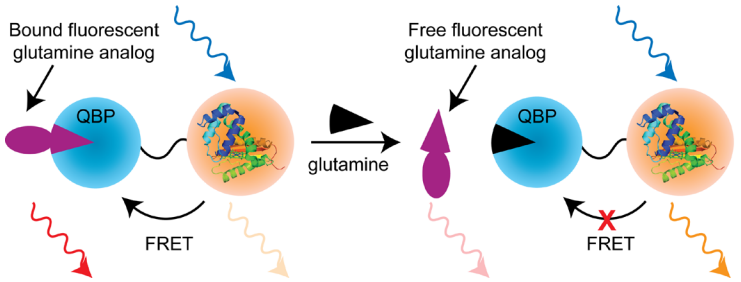

Figure 4. Schematic representation of the H-NOX-based glutamine sensor. In the absence of glutamine, the energy absorbed by H-NOX is transferred to the fluorescent glutamine analog bound to QBP, which subsequently emits. When glutamine binds, the glutamine analog is displaced and H-NOX emission increases, while emission from the glutamine analog decreases. The emission intensity ratio of the two components is a quantitative measure of glutamine concentration.

When glutamine binds to QPB, the glutamine analog is displaced, resulting in an enhancement of H-NOX emission and a decrease in emission of the glutamine analog. Since the H-NOX and the fluorescent glutamine analog emit different colors of light, the intensity ratio of the two wavelengths serves as a quantitative measure of glutamine concentration. This is known as ratiometric sensing: a robust methodology that is independent of sensor concentration and is functional in scattering media, such as cells and tissue. The glutamine sensor will then be used to measure glutamine levels in pancreatic cells, differentiating healthy cells from cancerous ones. Using this approach, I am developing metabolite sensors that can detect the changes in cell metabolism associated with cancer. Researchers and clinicians can then use these sensors to answer fundamental questions about the metabolic biochemistry of cancer and develop clinical assays for early diagnosis.

Chris Lemon was born and raised outside of Pittsburgh, Pennsylvania. He studied chemistry, physics, and statistics at Ohio Northern University. He spent a year abroad as a Fulbright scholar at the University of Auckland in New Zealand, working with Professor Penelope Brothers. In 2010, he began his PhD studies at MIT and then Harvard University under the supervision of Professor Daniel Nocera, where he developed quantum dot-based oxygen sensors. In 2016, he began postdoctoral studies at UC Berkeley in the laboratory of Professor Michael Marletta as a Miller Fellow. He enjoys listening to music by Arcade Fire, reading the *Song of Ice and Fire* series, and watching *Bob's Burgers*.

Contact: clemon@berkeley.edu

From the Executive Director

Marla Feller, Miller Institute Executive Director & Professor of Neurobiology

What a thrill it has been for me to return to the Miller program as the Executive Director. I had not been associated with the group since I was a Miller Fellow in 1994-1997. At that time, the Miller Fellowship helped make it possible for me to transition from a Ph. D. in nonlinear optics and condensed matter physics to an independent research career in neurobiology. During the intervening 21 years, I have become quite focused in neurobiology research, losing touch with the vastly interesting research going on in other disciplines, including my old field of physics. Luckily, under the stewardship of Kathy, the Miller Institute has persisted in its mission of fostering basic research. Spending a year with the Miller group has been a wonderful opportunity to learn more about the research in a vast number of other fields. It has reawakened my fascination with science across disciplines. I thought I would take this opportunity to update you on changes in leadership and reflect on the scientific highlights from this year.

First the changes in the leadership. In addition to my taking over the helm from Jasper Rine, the rest of the Executive Committee -- Stephen Leone from Chemistry/Physics, Yun Song from Math/Statistics, and Roland Burgmann from Earth and Planetary Science -- has remained constant. We also welcomed some changes to the Institute's Advisory Board. Steve Block, (Stanford) renewed his appointment and Feryal Ozel (University of Arizona), Luis Caffarelli (University of Texas – Austin) and Tim Stearns (Stanford) joined the Board for their first term. We are grateful for the wise advice they provide to our program.

The year started with the Fall Dinner, which we like to think of as "Evenings of Conversation" – a great way to encourage discussions among the scientists sponsored by the Institute. Our guest speaker was John Holdren, a former UC Berkeley professor who is currently the Teresa and John Heinz Professor of Environmental Policy at the Harvard Kennedy School Belfer Center for Science and International Affairs. Dr. Holdren accepted the 1995 Nobel Peace Prize on behalf of the Pugwash Conferences on Science and World Affairs, which worked to diminish the role of nuclear arms in international politics. He also served as President Obama's Science Advisor and Director of the White House Office of Science and Technology Policy from 2009 - 2017. He highlighted the dramatic change in the role that science plays in policy making with a change in administration and encouraged all of us to continue to influence science policy through public engagement. This was a personal thrill for me since I remember very clearly as a graduate student going to lectures held by the Energy Resource Group, a graduate degree program that he co-founded here at UC Berkeley.

Once again, our Spring Symposium was a thrill. Under beautiful blue skies at the Marconi Center in Tomales Bay, we heard fascinating lectures on a variety of topics ranging from deep insights into Deep Learning from Richard Baraniuk (Rice University), the origin of the moon from Sarah Stewart (UC Davis), the reason that chili peppers taste hot from David Julius (UCSF), and an absolutely thrilling lecture by Nergis Mavalvala (MIT) about the first detection of gravitational waves. Lior Pachter (Caltech), Paula Hammond (MIT) and Danna Freedman (Northwestern) rounded out this star panel of speakers. It was also great to meet the "alumni" Miller class – a somewhat new tradition (when space allows) for the Symposium. This year Miller Fellows from the Miller 2010 and 2011 cohorts joined us.

The year was also filled by highly entertaining weekly lunches by Fellows, Miller Visiting Professors and Miller Professors. It is also striking the incredible successes of the members of our institute, which are highlighted on the Miller website (http://miller.berkeley.edu). Every week I am reminded what a privilege it is to be a scientist and to be associated with the Miller Institute.

Don't miss an issue!

Do you wish to receive the Miller Institute newsletter at your home address? Please email millerinstitute@berkeley.edu with your updated address information so as not to miss a single issue.

Call For Nominations: Miller Research Competitions

Miller Research Fellowship 2019-2022
Online Nomination Deadline: September 10, 2018

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. 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 on the Berkeley campus. 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**. 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, 2019. 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: http://**miller.berkeley.edu**

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 $65,000 with annual increases on subsequent anniversary dates and an annual research fund of $10,000, for total initial compensation of $75,000. 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, 2019 and ending July 31, 2022. 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 2019 - 2020
Online Application Deadline: September 13, 2018

The Miller Professorship program is pleased to announce the call for applications for terms in 2019-2020. The goal is to accommodate a greater range of Berkeley campus faculty to participate in the vibrant Miller community. The objective of the Miller Professorship program is to provide opportunities for faculty to pursue new research directions on the Berkeley campus. For some, this may best be enabled by taking time off from teaching. For others, the teaching obligations are critical to maintaining campus academic programs. Thus the option for Miller Professors to continue campus service and teaching. Funds will be distributed differently depending upon the choice selected. Details of the terms and the application procedure are posted on the Miller Institute website. The primary purpose of the Miller Professorship program and the evaluation criteria continues to be research excellence. Applicants are encouraged to describe their interest in participating in the Miller Institute community.

Applications from UC Berkeley faculty for Miller Research Professorship terms in the 2019-20 academic year are being accepted online now. Appointees are encouraged to follow promising leads that may develop in the course of their research.

Applications are judged competitively and are due by Thursday, September 13, 2018. It is anticipated that between five to eight awards will be made.

Visiting Miller Research Professorship AY 2019
Online Nomination Deadline: September 14, 2018

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 2019 or Spring 2020. 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 are in residence at Berkeley during their appointment term. Faculty members or research scientists from any place in the world are eligible to be considered for sponsorship. Non-US citizens must be eligible for J-1 Scholar visa status. 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 the invitation to the nominee after advising the nominator of its selection.

Nomination & Application details: miller.berkeley.edu

Questions? Kathryn Day: 510-642-4088 | millerinstitute@berkeley.edu

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In the News

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

Jennifer Doudna (Miller Senior Fellow 2017) was awarded the **2018 Kavli Prize in Nanoscience** for the pioneering work in the development of the powerful nanoscale tool CRISPR-Cas9 to edit DNA. The Kavli Prize in Nanoscience, given every other year by the Norwegian Academy of Science and Letters and the Kavli Foundaion to "laureates who represent truly pioneering science, the kind of science which will benefit humanity in a profound way."

Dan Stamper-Kurn (Miller Professor 2009 - 2010, 2018-2019) has been named a **Distinguished Scholar of the Max Planck Institute of Quantum Optics (MPQ)** "in appreciation of his groundbreaking contributions to the field of Ultracold Quantum Gases and Quantum Optics."

Miller Members named winners of the **2018 Royal Society of Chemistry Awards:**

- **Christopher Chang** (Miller Professor 2011-2012) was honored with the **Jeremy Knowles Award** for the inter-disciplinary research between chemistry and the life sciences.
- **John Hartwig** (Visiting Miller Professor 2009) was honored with the **Centenary Prize** for inventing new chemical reactions that are used to make molecules with multiple applications, including the discovery of new pharmaceuticals. The Centenary Prize is awarded to outstanding chemists, who are also exceptional communicators from overseas, to give lectures in the British Isles.
- **Daniel Neumark** (Miller Professor 1999-2000) was recognized with the **Bourke Award** for developing novel experiments in chemical reaction dynamics that probe the breaking and making of chemical bonds. The Bourke Award enables distinguished scientists from overseas to lecture in the UK in the field of physical chemistry or chemical physics.
- **Dean Toste** (Miller Professor 2014) was presented with the **Catalysis in Organic Chemistry Award** for the development and mechanistic understanding of novel catalytic concepts in organic chemistry.

Maryam Modjaz (Miller Fellow 2007-2010) was a recipient of the **Humboldt Research Fellowship in Astronomy.**

Christophe Copéret (Somorjai Visiting Miller Professor 2015), a co-author of the international team of chemists that found a method to accelerate the development of new catalysts. Using NMR spectroscopy together with computational chemisty, they can evaluate whether or not molecules can enable reactions.

Maciej Zworski (Miller Professor 2015) will receive the title of **Doctor Honoris Causa of Université Paris-Sud** at a ceremony in October 2018.

Richard Henderson (Visiting Miller Professor 1993) honored with a **RSE Royal Medal** for his work in the field of electron microscopy that resulted in new treatments for several serious diseases and saving lives.

Bin Yu (Miller Professor 2004, 2016-2017) received a prestigious **Scott Award** for her dedication and commitment to diversity, equity, and inclusion in the statistics field and for her mentorship of women students, as well as for her scientific contributions to statistical and machine learning methodology.

Ray Jayawardhana (Miller Fellow 2000-2002), distinguished astrophysicist, renowned science writer and accomplished academic leader **has been named the 22nd dean of Cornel's College of Arts and Sciences.**

Meredith Hughes (Miller Fellow 2010 - 2013) has been named as one of the **2018 Cottrell Scholars** for her innovative research proposal and education program, , The Last Gasp of Planet Formation: Gas and Dust in Debris Disks.

Mikhail Shapiro (Miller Fellow 2011 - 2013) is one of 13 scholars recognized with **2018 Camille Dreyfus Teacher-Scholar Award** for his frontier accomplishments in research of molecular engineering for noninvasive imaging and control of cellular function.

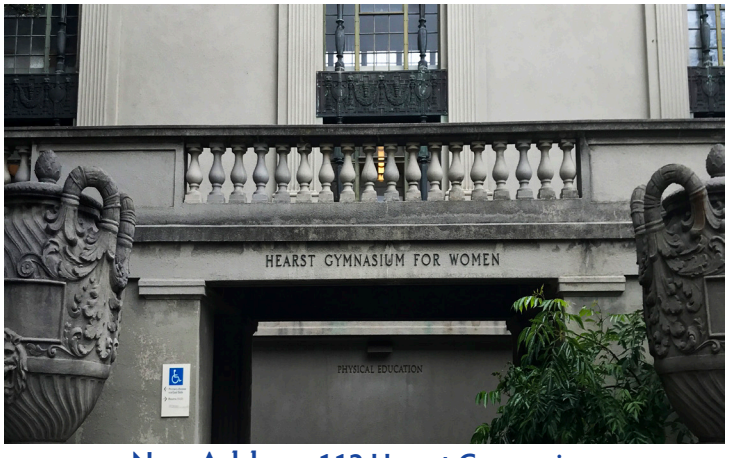
Four Miller Members have been awarded **2018 Guggenheim Fellowships:**

- **Arup K. Chakraborty** (Miller Professor 2006) is honored for his research of induction of broadly neutralizing antibodies against highly mutable pathogens.
- **Will Dichtel** (Visiting Miller Professor 2016) is recognized for development of structurally precise organic materials.
- **Shri Kulkarni** (Visiting Miller Professor 1995) is honored for his contributions to the studies of exotic cosmological explosions.
- **Lisa Randall** (Visiting Miller Professor 2012) is recognized for distinguished contributions to the studies of black hole mergers and their environment.

Selected from a pool of exceptional colleagues, **Britt Glaunsinger** (Miller Professor 2015) and **Marla Feller** (Executive Director2017- present, Miller Fellow 1994-96), were honored as the **2018 Graduate Division's Distinguished Faculty Mentor Awards Recipients.**

We welcome news contributions from our former members.
Please email news to: miller_adm@berkeley.edu

We've Moved!

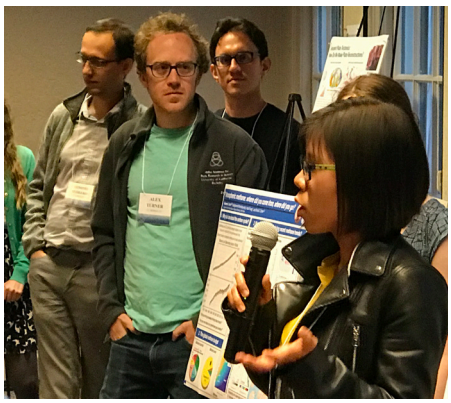


New Address:112 Hearst Gymnasium
Berkeley CA 94720-5190

22nd Annual Interdisciplinary Symposium

Miller Fellow Alumni Mikhail Shapiro, Claude-André Faucher-Giguère & Matt Good

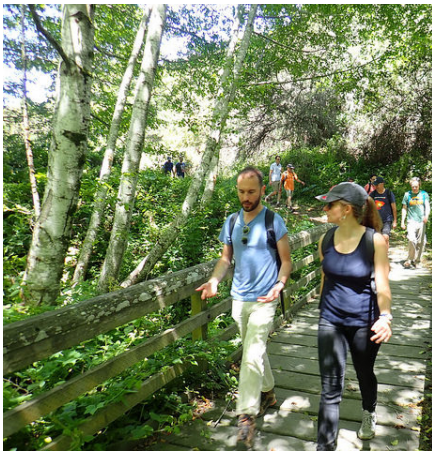
Symposium speaker Paula Hammond and Visiting Miller Professor Talat Rahman

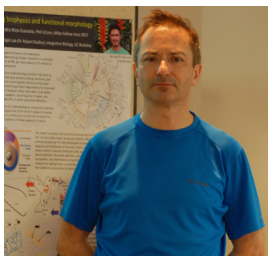


Miller Fellows Kelly Nguyen, Alex Turner, Simone Ferraro & Jeff Martell

Miller Senior Fellow Barbara Meyer, Kathy Day, Executive Director Marla Feller, Miller Fellows Sarah Slotznick, Cara Brook & Becky Jensen-Clem

Pre-Symposium Hikers





Speakers: Richard Baraniuk, Danna Freedman, Paula Hammond, David Julius, Nergis Mavalvala, Lior Pachter and Sarah Stewart

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Miller Institute News - Fall 2018
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Birth Announcements

Chris Martin (Miller Fellow 2013-2015) & his wife, Erica Morehouse, announced the birth of daughter, Cassandra (Cassie) Annagail Morehouse Martin, born in May 2018.

Eric King (Miller Fellow 2010-2013) & his wife, Natalie, welcomed their son, Milo McGrath King, born in April 2018.

Next Steps

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

Simone Ferraro (Physics Postdoc @ UC Berkeley)

Shirshendu Ganguly (Assistant Professor @ UC Berkeley)

Doug Hemingway (Carnegie Postdoctoral Fellow, Department of Terrestrial Magnetism at the Carnegie Institution for Science in Washington, DC)

Peter Hintz (Assistant Professor @ MIT - starting 2019)

Jeff Martell (Assistant Professor @ University of Wisconsin - Madison starting 2019)

Andrew Moeller (Assistant Professor @ Cornell)

Jessica Ray (Assistant Professor @ University of Washington - starting 2019)

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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. Visit our **"Make a Gift"** page at: *miller.berkeley.edu/***gift**

The Miller Institute is "dedicated to the encouragement of creative thought and the conduct of research and investigation in the field of pure science and investigation in the field of applied science in so far as such research and investigation are deemed by the Advisory Board to offer a promising approach to fundamental problems."

For More Information:
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