The Adolph C. and Mary Sprague

MILLER INSTITUTE

Seeing Is Believing: Understanding Biology Through Structures Miller Fellow Focus: Kelly Nguyen

Il living organisms are made up of small building blocks called cells. Each living cell is a fascinating pool of tiny molecular machines that work in an orchestrated fashion to perform all processes within it. Molecular machines are generally made up of proteins, nucleic acids, sugars and lipids. Malfunction of certain molecular machines or the action of viruses or bacteria, which use their own molecular machines to disrupt cellular processes of their hosts, could lead to diseases. Thus, many drugs work by binding to these machines and affecting their functions. Despite the advancement of modern biology, it is difficult to study cells as a whole at the level of detail required to understand the mechanisms of molecular processes. Often we focus on a particular cellular process and the molecular machines involved in it, just like solving pieces of a puzzle. The functions of molecular machines are closely related to their three-dimensional (3D) structures or shapes. One approach to understand the function is to determine these 3D structures at an atomic level. This atomic visualization allows us to gain a molecular understanding of the machine/process of interest, to dissect the molecular pathology of diseases and to advance the search for a cure.



am a second year Miller Fellow working in the laboratories of Professors Eva Nogales and Kathleen Collins in the Department of Molecular and Cell Biology and focusing on regions of our genome called telomeres. What are telomeres and why are they important?

DNA encodes the genetic information that instructs all cellular processes. It forms a double helix structure with two complementary strands. During cell division, DNA has to be duplicated by copying each strand back into a complementary duplex in a process called DNA replication. Each daughter cell will inherit an identical copy of DNA from the parent cell. The approximate length of our DNA,

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Newsletter Fall 2017

Call for Nominations:

Miller Research Fellowship Nominations Deadline: Sunday, September 10, 2017

Miller Research Professorship Applications Deadline: Thursday, September 14, 2017

Visiting Miller Professorship Departmental Nominations Deadline: Friday, September 15, 2017

See page 5 for more details.

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

"The model for this Institute is both unique and effective. A mix of scientists... brought together in a spirit of collegiality and scholarship in a number of interesting venues...from lunchtime talks to formal dinners to cocktail hours. I found all of this to be an excellent mechanism that brings younger scientists into casual contact with seasoned professionals in a way that fosters free exchange of ideas, anecdotes, and friendship. Altogether, this is a class act."

Mark Johnson Arthur T. Kemp Professor of Chemistry, Yale University, Miller Visiting Professor 2017





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if stretched out, would be about 2 meters long, while cells are only micrometers in size. Therefore, DNA is packaged into compact protein-DNA structures called "chromosomes", which not only conserve space but also provide additional protection and regulation. Most of us have seen the characteristic shape of highly compacted chromosomes in high school biology textbooks with a constriction point in the center, termed centromere, flanked by two arms and capped with telomeres at the end (Figure 1A). Telomeres play crucial roles in protecting our chromosomes from degradation and interchromosomal fusion. However, telomere length is progressively shortened with each cell division due to the inability of the molecular machine that performs DNA replication to copy the end of the chromosome. Cells with critically short telomeres undergo proliferative senescence - meaning they can no longer divide - or suffer cell death (Figure 1A). Telomere length is thus often regarded as an "aging clock", determining the lifespan of a cell or an organism.



Figure 1. Telomeres and telomerase. (A) Telomere shortening problem in normal cells. As cells age, their telomeres are shortened over time and when telomeres are critically short, cell growth is halted. (B) Telomerase replenishes telomeres in cancer cells, allowing them to maintain a stable telomere length and thus immortalize.

Besides aging, telomeres also have important implications in cancer. Shortened telomeres can be replenished by a specialized molecular machine, called telomerase. The discovery of telomerase was made here at Cal in the 80s by Elizabeth Blackburn and Carol Greider and earned them the Nobel Prize in Medicine in 2009. Telomerase activity is undetectable in somatic cells (most of the cells in our body) while it is upregulated in cancer cells, allowing them to immortalize (Figure 1B). In addition, a number of human diseases such as dyskeratosis congenita, aplastic anemia and pulmonary fibrosis are caused by mutations in telomerase components or dysregulation of telomerase activity. Despite its medical significance, little is known about the 3D structure of telomerase. My aim is to elucidate the 3D structure of the human telomerase to high resolution and use it as a framework to answer questions about this enzyme. What is its composition? How do its components assemble to form an active molecular machine? What does its structure tell us about its function and action at telomeres? How can it be used for designing drugs that target telomerase?

o accomplish this goal, we are planning to use cryoelectron microscopy (cryo-EM). Why cryo-EM? For many centuries, visualization of biological specimens has been a powerful means to understand biology (Figure 2). Light microscopy has been employed to reveal the overall shapes and architectures of mammalian cells, bacteria, and large organelles within cells. For biomolecules or molecular machines, which are much smaller in size (Figure 2), more specialized techniques, such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy and cryo-EM, have been developed to determining their 3D structure at resolution where atomic details are discernible (generally 3 Å or below). X-ray crystallography is the most commonly used and well-developed method to-date. However, it is limited to samples that can form well-ordered crystals. NMR is a useful tool to study structures and dynamics of biomolecules in solution, but is ill-suited for structure determination of large biomolecules. Until about 4 years ago, cryo-EM was still a low-resolution technique compared to the other two methods and often used to obtain the overall architecture and shape of very large molecules that do not form well-ordered crystals. Available high-resolution X-ray or NMR structures of components would then be fitted into the resulting EM 3D reconstruction. Recently, there have been technical advances in the EM field that have led to a quantum leap in the resolution achieved with this technique. This improvement opened new opportunities for structure determination of molecular machines, such as telomerase, that are large in size, flexible and of low abundance, and thus out of the reach of X-ray crystallography or NMR. Given that EM covers a much



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wider range of molecule sizes and requires smaller amounts of sample that does not even need to be completely pure, the structural biology field has entered at an exciting new era.

w do we approach telomerase? Human telomerase is a large multi-subunit protein-RNA complex (ribonucleoprotein, RNP). One hurdle faced when studying telomerase structure is its extremely low abundance in cells. In normal cells, telomerase is almost absent. Even in cancer cells with the highest telomerase levels, there are generally only 20-50 telomerase



Figure 3. Three-dimensional (3D) structure determination of biological machines by cryo-EM. **(A)** An illustration of the sample preparation process. The molecular machine of interest is purified from cells and applied on an EM grid where it is embedded in a thin layer of vitrified (glassy) ice. **(B)** Major steps involved in EM image processing where noisy two-dimensional images of the biological machines in all random orientations are classified in 2D and 3D to reconstruct a 3D volume of the machine.

molecules per cell, making it one of the rarest enzymes in the cell. In order to obtain even a microgram of this enzyme, one would need a large quantity of cancer cells, on the order of a few hundreds of liters. My first task has been to develop an efficient protocol to purify minute amounts of telomerase from a large amount of cells. In biochemistry, we often introduce "tags" into our molecule of interest, which binds specifically to microbeads. This tag allow us to selectively isolate our target molecule from the myriads of different molecules in the cell (**Figure 3A**). Multiple of such isolation steps may be required

to achieve high purity. Subsequently, the purified sample is characterized by a number of methods before being used for 3D structure determination by cryo-EM.

ryo-EM involves a process called "vitrification" where a very thin layer of sample is flash-cooled at liquid nitrogen temperature on a copper grid (about 1.5 mm in size) so that it forms "glassy ice", i.e. without the formation of ice crystals (Figure 3A). The biological molecules of interest embedded in this thin layer of vitrified water are visualized at tens of thousands of times magnification in an electron microscope. We collect thousands of these electron micrographs, which contain noisy 2D projections of the molecules, in ideal cases, in many different random orientations (Figure 3B). Hundreds of thousands



Introducing New Miller Institute Leadership



Marla Feller, Miller Institute Executive Director & Professor of Neurobiology

The Miller Institute warmly welcomes new members to the leadership of the Institute.

Professor Marla Feller, of the Neurobiology Division of Molecular and Cell Biology, joins the Executive Committee as the Executive Director. Marla has a distinguished career as a neurobiologist with many discoveries to her credit on how our retinas translate the visual world into an electrical language that the brain can understand.

Marla has deep roots at Berkeley. She received both her B.A. and her Ph.D. in our Physics Department. She left briefly for a postdoctoral position at Bell Labs in the laboratory of David Tank, and then returned as a Miller Fellow in the Laboratory of Carla Shatz, then head of the Neurobiology Division of MCB.

Her first independent position was as an investigator at NIH in the National Institute of Neurological Disorders and Stroke. She was recruited back to California to a faculty position at UCSD and then came to Berkeley in 2007 as an Associate Professor. Following a sabbatical at the Institut Pasteur in 2011, she was promoted to Full Professor in 2012. In addition to her research prowess, she is serving as head of the Neurobiology Division and on the Executive Committee of the Helen Wills Neuroscience Institute. We are very pleased that she has nevertheless made time in her hyper-committed schedule to join us in what we hope will be her favorite job on campus.



A lso new to the Executive Committee is Yun Song, Professor of EECS, Statistics and Integrative Biology. Following a brief leave at the University of Pennsylvania, Yun returns to Berkeley this fall. Yun received his Ph.D. at Stanford University and then spent a year at the Mathematical Institute at the University of Oxford before moving to UC Davis as a postdoc. He has been at Berkeley since 2007. Among his many

honors, Yun was recently awarded a Chan Zuckerberg Biohub investigator honor to derive novel mathematical formulas and new analytical techniques for inferring demographic history from population genetic data and for increasing the power of genome-wide natural selection scans.

Professors Roland Bürgmann, EPS and Stephen Leone, Chemistry and Physics continue their terms on the Committee.

We have three new members joining Steve Block, Stanford University, on the Advisory Board: Feryal Özel, University of Arizona; Tim Stearns, Stanford University; and Luis Caffarelli, University of Texas – Austin.



Luis Caffarelli is a Professor of Mathematics. He received his Ph.D. from the University of Buenos Aires in 1972. He has held positions at the University of Minnesota, the University of Chicago, the Courant Institute of NYU and the IAS at Princeton University. He is currently the Sid Richardson Chair at the University of Texas at Austin. He has been considered one of the world's leading

experts in free boundary problems and nonlinear partial differential equations. He developed several regularity results for fully nonlinear elliptic equations including the Monge-Ampere equation. He is also famous for his contributions to homogenization.



Feryal Özel is a Professor of Astronomy and Astrophysics. She has made pioneering contributions to the physics of neutron stars and black holes, as well as to the co-evolution of black holes and galaxies in the early Universe. Born in Istanbul, Turkey, she moved to the US for her higher education, receiving her Ph.D. from Harvard in 2002. Dr. Ozel is a Fellow of the American Physical Society and

a member of the Science Academy of Turkey. Ózel received the Maria Goeppert Mayer award from the American Physical Society, the Radcliffe Institute for Advanced Study Fellowship, the Miller Institute Visiting Professorship from the University of California in Berkeley, and the Bart J. Bok Prize from Harvard University.



Tim Stearns received his Ph.D. from MIT and has been a faculty member in the Department of Biology at Stanford University since 1993. His major research accomplishments include the identification and characterization of new members of the tubulin superfamily of proteins critical for understanding the function of the centrosome and cilium, organelles in cells

that mediate many processes and whose dysfunction is the basis of several human diseases. He also has appointments in the Department of Genetics, the Cancer Center in the Stanford Medical School, and is an HHMI Professor.

The Miller Institute is eternally grateful to the dedicated service and wise counsel of Jasper Rine and Craig Evans who have served on the Executive Committee and to Roger Blandford and David Botstein who ably served on the Advisory Board. Their leadership and guidance over the years have been appreciated beyond measure.



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Call For Nominations: Miller Research Competitions

Miller Research Fellowship 2018-2021 Online Nomination Deadline: Sunday, Sept. 10, 2017

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, 2018. Eligible nominees will be invited by the Institute to apply for the Fellowship. Direct applications and self-nominations are not accepted.

Miller Research Professorship 2018 - 2019 Online Application Deadline: Thursday, Sept. 14, 2017

The Miller Professorship program is pleased to announce the call for applications for terms in 2018-2019. 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 2018-19 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 14, 2017. It is anticipated that between five to eight awards will be made. *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, 2018 and ending July 31, 2021. 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.

Visiting Miller Research Professorship AY 2018 Online Nomination Deadline: Friday, Sept. 15, 2017

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 2018 or Spring 2019. 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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of images of individual particles extracted from these micrographs are classified in 2D and averaged to obtain high signalto- noise ratio 2D class averages of different views of the molecule. Selected particles from 2D classification are subjected to 3D classification to further reduce compositional and conformational heterogeneity (Figure 3B). A subset of particles with sufficient homogeneity resulting from these classification steps is used for the final 3D reconstruction of the molecule of interest.

have been working in the Collins lab on the biochemical aspects of human telomerase from cancer cells and performing EM imaging in the Nogales lab. We have been able to obtain a preliminary EM reconstruction of human telomerase and are currently working on improving its resolution. In many biological fields, the availability of a first high-resolution structure of the molecular machines involved has been the turning point for the field. We hope that these collaborative efforts at Berkeley will shed light onto the long-awaited molecular structure of the human telomerase and inspire further biochemical and functional studies on this machine to unravel the secrets of the molecular causes of cancer and aging.

Kelly (Thi Hoang Duong) Nguyen grew up in Quang Ngai province, in the central coast of Vietnam. She completed a Ph.B (Honours) degree in Chemistry at the Australian National University, having spent the last couple of years of her high school education in Wellington, New Zealand. She moved to the UK for her PhD in Molecular Biology at the University of Cambridge. Her PhD work was performed at the MRC-Laboratory of Molecular Biology. When she is not doing science, she enjoys baking, playing badminton and going to fitness classes.

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Where in the World Is Your Fleece?

Please share a photo of you wearing your Miller Institute fleece at places around the world. We will post these photos on our website sharing the world wide reach of the Miller Institute!



Peter Hintz, Cassandra Hunt and Jacqueline Cherfils don their Miller gear at Tahoe!

In the News

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

Hitoshi Murayama (Miller Professor 2006) has been named a Genius Contributor for a project celebrating the 100th anniversary of the publication of Einstein's General Theory of Relativity.

Daniel Rabosky (Miller Fellow 2009 - 2012) was selected to receive the **Henry Russel Award** that is one of the University of Michigan's highest honors for junior faculty members for his research about the evolutionary drivers responsible for the unequal composition and distribution of Earth's biodiversity.

Cédric Villani (Visiting Miller Professor 2004), a prize-winning mathematician who was awarded the Fields Medal in 2010, won a Seat in 2017 France's Parliamentary Elections.

Robert Coleman (Miller Professor 1995) was one of the 20th century's most influential number theorists. This special collection has been assembled in his memory.

Angel Rubio (Visiting Miller Professor 2014) receives the highest award of the Royal Spanish Society of Physics for his research work in simulation of materials and as the creator of a software tool widely used by hundreds of research groups around the world.

Omar Yaghi (Visiting Miller Professor 2009) is the Royal Society of Chemistry Spiers Memorial Award winner for 2017 in recognition of an outstanding contribution to the chemical sciences. The award also recognises the importance of teamwork across the chemical sciences and the abilities of individuals to develop successful collaborations.

Robert Zucker (Miller Professor 1999) received the **2017 Sir Bernard Katz Prize** awarded annually by the Biophysical Society for excellence in research on exocytosis and endocytosis, for his groundbreaking studies on short-term synaptic plasticity and the role of calcium in triggering transmitter release.

Alan Perelson (Visiting Miller Professor 2004) is a recipient of the American Physical Society's 2017 Max Delbruck Prize in Biological Physics "for profound contributions to theoretical immunology, which bring insight and save lives."

Ahmet Yildiz (Miller Professor 2016 - 2017), faculty scientist in Molecular Biophysics and Integrated Bioimaging, was awarded Vilcek Prize for Creative Promise in Biomedical Science.

Claude-André Faucher-Giguère (Miller Fellow 2010 - 2013) receives the NSF Faculty Early Career Development Program (CAREER) Award from National Science Foundation's Division of Astronomical Sciences to create the next generation of galaxy formation simulations. He also will develop summer research opportunities for undergraduate students and interactive visualizations for public outreach. The foundation's most prestigious honor for junior faculty members supports both research and education initiatives.

Chris Chang (Miller Professor 2011 - 2012) has been elected to the American Academy of Arts and Sciences for his research in bioinorganic chemistry, molecular and chemical biology.



21st Annual Interdisciplinary Symposium



Miller Fellows Benjamin Good & Jeff Martell



Miller Fellow Elaine Angelino & Shizue Matsubara



Miller Fellow Lian Xue





Miller Fellow Da Yang & former Miller Fellow Chang Liu Miller Fellow Chris Lemon



Speakers: Paul Corkum, Gil Holder & Christos Papadimitriou





Executive Committee member Roland Bürgmann & former Miller Fellow Pascal Audet



Former Miller Fellow Brooke Gardner & Miller Senior Fellow Raymond Jeanloz

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Miller Fellow Alejandro Rico-Guevara



Speakers: Michael Nachman, Lauren Meyers, Laura Keissling & Mike Brown



Miller Fellows: Carson Bruns, Doug Hemingway, Andrew Moeller and Ryan Trainor



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Miller Institute News - Fall 2017

Please send address corrections to: miller_adm@berkeley.edu

Birth Announcements

Alex Engstrom (Miller Fellow 2009-2012) announced the birth of daughter, Emma Isabella Eva Engstrom, born in April 2017.

Chen Li (Miller Fellow 2012-2015) & his wife, Jin Liao, announced the birth of their daughter, Jasmine Mo Li, born in June 2017.

Next Steps

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

Carson Bruns (Assistant Professor @ University of Colorado, Boulder) Kęstutis Česnavičius (Wissenschaftlicher Mitarbeiter @ University of Bonn, Germany. Charge de Recherche CNRS @ Universite Paris Sud, Orsay) Sebastian Höhna (Research Group Leader @ University Munich, Germany) Julian Shun (Assistant Professor @ MIT) Ryan Trainor (Assistant Professor @ Franklin & Marshall)

Da Yang (Assistant Professor @ UC Davis)

Norman Yao (Assistant Professor @ UC Berkeley)

Rachel Zucker (Senior Research Scientist @ Kernel)

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. 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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