

Deciphering the role of bats as reservoirs for emerging human disease

Miller Fellow Focus: Cara Brook

Over three-quarters of emerging human diseases are classified as 'zoonotic,' meaning sourced from a wildlife reservoir. Celebrated examples of zoonotic infections include bubonic plague, which is regularly transmitted from rodent reservoirs to human 'spillover' hosts through flea vectors, and HIV, which is believed to have first jumped from wild primates to humans via blood-borne contact during bushmeat preparation but has since become independently established in human populations. For many zoonoses, emergence into the human population represents a dead-end to the transmission chain, while for others, spillover can perpetuate into sustained disease (**Figure 1**). What factors contribute to successful zoonosis? Can understanding infection dynamics in the wildlife reservoir help us predict and prevent future spillover events? As a second-year Miller Fellow based jointly in the labs of Mike Boots in the Department of Integrative Biology and Britt Glaunsinger in the Department of Plant and Microbiology, I am studying the drivers and dynamics of zoonotic emergence, with a particular focus on viral infections in Madagascar fruit bats.

Bats (Order: Chiroptera) have received increasing attention in recent years for their roles as reservoir hosts for some of the world's most virulent zoonoses, including Hendra and Nipah henipaviruses, SARS coronavirus, and Ebola and Marburg



filoviruses. Bats appear to host these pathogens, which cause extreme disease in other mammals, without experiencing any obvious morbidity or mortality, leading researchers to question, "Are bats somehow 'special' in their capacity as pathogen hosts?"

As the only volant, or flying, mammal, bats are inherently unique. Flight is one of the most physiologically expensive activities known to any mammalian taxon: a bat in flight can elevate its metabolic rate up to 15- or 16-times higher than baseline, compared to a 7-fold increase in a running rodent. Typically, high metabolic rates yield tradeoffs of reduced longevity, but bats are, on average, among the longest-lived for their body size of any mammalian order. Indeed,

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"I interacted with various Miller Fellows during my Miller Professorship and found them to be engaged, inquisitive, interested in a broad range of topics, and respectful of different perspectives on science. Additionally, their spot-on constructive criticisms of my lunch talk really helped improve it. I learned a lot during my term and the program challenged me to think outside of my comfort zone!"

- Richmond Sarpong

Miller Professor 2017-2018, Professor, Department of Chemistry, University of California, Berkeley

the oldest known bat, the Brandt's bat, has been recorded living over 40 years in the wild! In recent years, different bat species have been shown to host a variety of unique molecular pathways to mitigate oxidative damage and reduce inflammation, which researchers hypothesize may have evolved to facilitate flight but resulted in cascading consequences promoting bat longevity and viral tolerance. In bats, these unique metabolic pathways include loss

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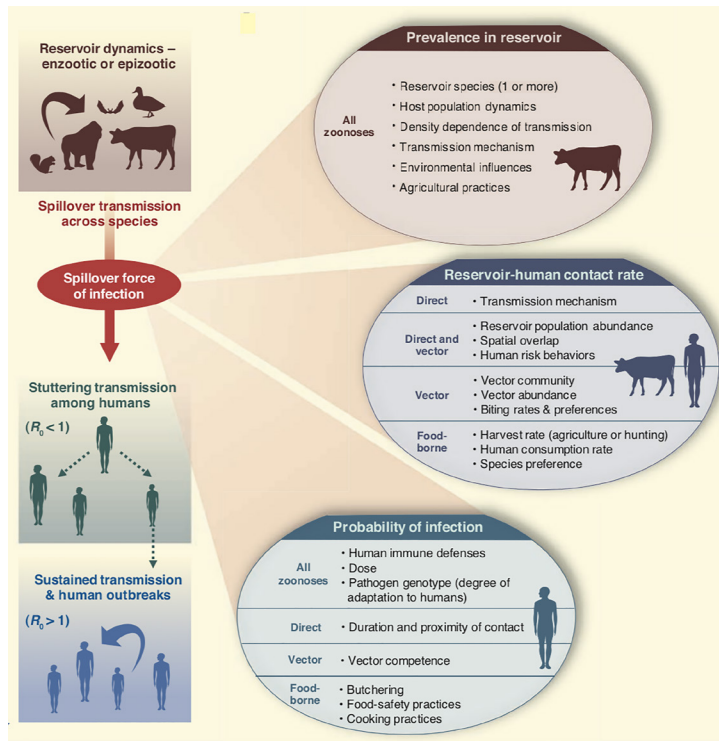


Figure 1. Epidemic dynamics at the human-animal interface. Zoonotic pathogens circulate in animal reservoir hosts, either enzootically (sustaining continuous transmission chains) or epizootically (in periodic, cyclic epidemics) and spillover to humans probabilistically based on the combined inputs of (1) prevalence in the reservoir population, (2) contact rate with the human spillover host, and (3) human susceptibility to infection. Once in a human population, zoonoses may stutter out if their basic reproduction number is below replacement ($R_0 < 1$) or establish chains of human-to-human transmission ($R_0 > 1$). Figure adapted from Lloyd-Smith et al 2009. *Science*. 326(5958)1362-7.

of the inflammasome-forming PYHIN gene family in certain species, down-regulation of the DNA damage recognition STING pathway in other species, and expansion of the immune inhibitory KLRC/KLRD pathways in other species still.

As a Miller Fellow, I am exploring bats' unique viral tolerance at both population-level and within-host scales. The bulk of my population-level studies are focused in the island-nation of Madagascar where three endemic fruit bat species, *Pteropus rufus*, *Eidolon dupreanum*, and *Rousettus madagascariensis*, are hunted heavily for human food. During my PhD in the Department of Ecology and Evolutionary Biology at Princeton University, I initiated a long-term population study in collaboration with Institut Pasteur de Madagascar (IPM), through which I began tracking viral- and immune-dynamics in fruit bat populations infected with Hendra-and-Nipah-related henipaviruses and Ebola-related filoviruses (Figure 2). Monthly, my Madagascar-based field team captures bats at longitudinally-monitored roost sites and collects biological samples for pathogen assay in IPM's laboratories in

Madagascar's capitol city of Antananarivo. Back at Berkeley, I build epidemiological models testing various hypotheses of the transmission mechanisms which wild bat populations employ to maintain these circulating viruses. In human hosts, bat-associated henipaviruses and filoviruses demonstrate classic epidemiological dynamics: hosts are born susceptible to infection, become exposed and infected at different rates based on risk categories and contact rates, then either die from infection or survive while maintaining a protective antibody response which endures across the host's remaining lifespan. Theory predicts that highly virulent, fast-replicating pathogens like henipaviruses and filoviruses will only persist in large host populations with high birth rates which constantly resupply epidemics with new susceptible hosts—akin to perpetually adding foliage to an intensely burning forest fire.



Figure 2. Field work studying the dynamics of viruses infecting three endemic Madagascar fruit bats: (a) *Eidolon dupreanum*, (b) *Pteropus rufus*, (c) *Rousettus madagascariensis*. (d) Field lab with Dr. Cara Brook and Dr. Christian Ranaivoson of Institut Pasteur de Madagascar.

Contrary to theoretical predictions, bats appear capable of maintaining fast-replicating pathogens in small, isolated populations, which reproduce in discrete annual birth pulses, leading researchers to question whether traditional epidemiological paradigms need to be reconsidered. Rather than hosting henipaviruses and filoviruses as other mammals do—as transient infections yielding high mortality or sustained immunity—could bats instead host these pathogens as persistent, long-term infections with periodic transmissions?



My population-level studies in Madagascar seek to build the longitudinal datasets needed to differentiate between epidemiological hypotheses of population-level transmission and within-host persistence. Increasingly, my models and data are converging on support for the latter.

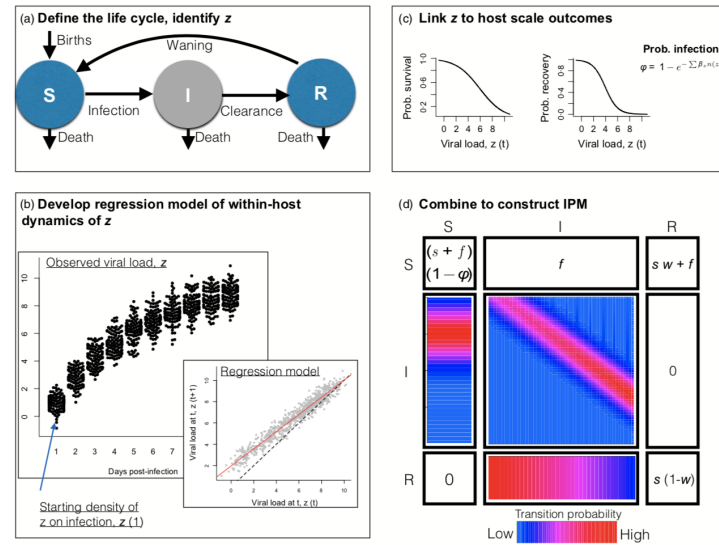


Figure 3. Conceptual integral project framework for linking within-host and population-level scales in modeling the dynamics of infection. (a) Define the state variables and processes relevant to the infection in question (here, S = susceptible, I = infectious; R = recovered). (b) conduct within-host *in vitro* and *in vivo* experiments to build datasets of within-host dynamics of viral load, antibody titer, gene expression, etc. and fit appropriate regression models. (c) Link within-host variables to population-level probabilities. (d) link in an integral projection model (IPM) framework. Adapted from Metcalf et al 2016. *J Animal Ecology*. 85(2): 343-355.

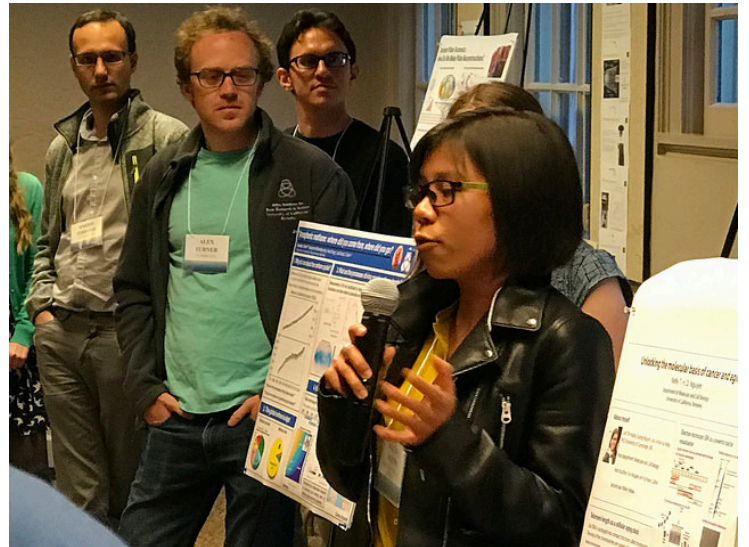
If the persistent-infection hypothesis proves to be correct, how then are bats able to maintain health while infected with pathogens that are lethal in most mammalian hosts? The crux of my research as a Miller Fellow focuses on this within-host question. Already, we know that bats utilize a variety of unique molecular mechanisms to help mitigate damage induced by viral infection; in addition, recent work indicates that bats also employ a variety of resistance mechanisms to help control pathogen loads to tolerable levels. In particular, researchers recognize several bat-virus species-specific incompatibilities at the receptor level which limit cell entry for certain pathogens in certain hosts. Additionally, some bat species have been shown to constitutively express antiviral signaling molecules known as cytokines, making them perpetually primed to fight viral infections. In a series of theoretical and simulation models constructed in the Boots lab, joint with tissue culture studies of viral infection in bat cells, sponsored by the Glaunsinger lab, I am exploring how such constitutive immune defenses might enable viral persistence in damage-tolerant bat hosts but could lead to the evolution of faster replicating viruses which demonstrate extraordinary

virulence upon spillover into secondary hosts lacking bats' unique immune pathways. Ultimately, I am working to bridge these scales in an integral projection modeling framework (Figure 3), with the goal of translating the consequences of viral defense within-host to population-level probabilities for transmission and zoonotic emergence.

Cara Brook was born and raised in beautiful Sonoma County, California and received her bachelor's degree in Earth Systems from Stanford University. Post-graduation, Cara communicated science for World Wildlife Fund in Madagascar, deciphered rodent-borne disease for the Smithsonian in Kenya, and tracked predator-prey dynamics of wolves and deer for the USGS in Minnesota. Between 2012-2017, Cara completed her M.Sc. and Ph.D. in the Department of Ecology and Evolutionary Biology at Princeton University, advised by Professor Andy Dobson, and pioneered the studies in fruit bat viral dynamics which she continues to pursue today. She came to Berkeley in fall 2017 as a Miller Fellow, advised jointly by Professor Mike Boots in the Department of Integrative Biology and Professor Britt Glaunsinger in the Department of Plant Biology. When not chasing bats in Africa, Cara enjoys hiking and running throughout the North American West.

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Miller Fellows Video Presentations

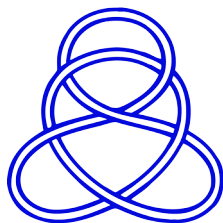


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Miller Institute Announces 2019 Miller Senior Fellowships



The Miller Institute is pleased to introduce two new Miller Senior Fellows, Susan Marqusee and Michael Jordan, who will join the Institute in 2019.

The Miller Senior Fellowship was started in 2008 to recognize the special achievement of select Berkeley faculty and to create an opportunity for Miller Fellows to gain insights from them via informal interactions.

Susan Marqusee holds the Warren C. Eveland Chair as a Professor in both Molecular & Cell Biology and Chemistry Departments. Professor Marqusee is the Director of California Institute for Quantitative Biosciences on the Berkeley campus (QB3-Berkeley). She is a fellow of the American Academy of Sciences and the National Academy of Sciences.



Susan Marqusee

Professor Marqusee's research is focused on the structure and function of proteins. Proteins are comprised of linear sequences of small organic compounds called amino acids. Despite this seemingly simple organization, proteins fold into complicated three-dimensional shapes and it is these shapes that are key to understanding their biological function. Indeed, small changes in folding of a protein can lead to dramatic changes in function. For example, misfolding of proteins can lead to aggregation such as observed in prion-based diseases such as Creutzfeldt-Jakob or amyloid-based diseases like Alzheimer's. The Marqusee lab is focused on using a combination of biophysical, structural, and computational approaches to understand the dynamical processes that underlie protein dynamics, folding, and misfolding.

Michael I. Jordan is the Pehong Chen Distinguished Professor in the Department of Electrical Engineering and Computer Sciences and the Department of Statistics. He is a leader in several interdisciplinary groups on campus including the Center for Computational Biology, the Simons Institute for the Theory of Computing, and the Berkeley Artificial Intelligence Research Lab (BAIR). Professor Jordan is a member of the National Academy of Sciences, a member of the National Academy of Engineering and a member of the American Academy of Arts and Sciences.

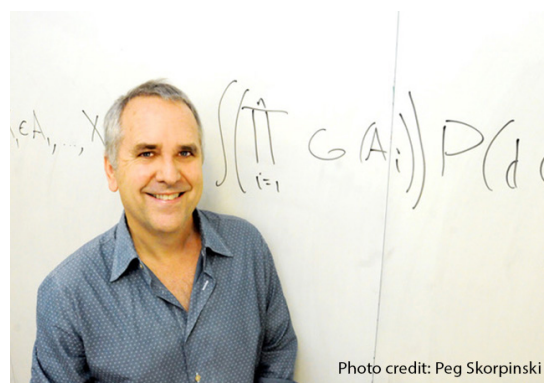


Photo credit: Peg Skorpinski

Michael Jordan

His research interests bridge the computational, statistical, cognitive and biological sciences, and have focused in recent years on Bayesian nonparametric analysis, optimization theory, probabilistic graphical models, diffusion processes and applications to problems in distributed computing systems, natural language processing, signal processing and statistical genetics. His work has contributed to the theoretical foundations of statistical machine learning and has yielded algorithmic innovations that have had significant impact on applied problems in industry and science.



Miller Research Competitions: Awards

The Advisory Board

On December 3, 2018, the Advisory Board of the Miller Institute met to select next year's Professorship awards. The Board is comprised of four advisors external to UCB: Steven Block (Physics, Stanford University), Luis Caffarelli (Mathematics, University of Texas, Austin), Feryal Özel (Astronomy & Physics, University of Arizona) and Tim Stearns (Biology, Stanford University); and four internal Executive Committee members: Executive Director Marla Feller (Molecular & Cell Biology), Stephen Leone (Chemistry/Physics), Roland Burgmann (Earth & Planetary Science) and Yun Song (EECS/Statistics/IB). The Board is chaired by Chancellor Carol Christ.

The Miller Institute is proud to announce the awards for Professorship terms during the Academic Year 2019-2020. These outstanding scientists pursue their research, following promising leads as they develop. The Visiting Miller Professors join faculty hosts on the Berkeley campus for collaborative research interactions.

Miller Professorship Awards

Daniel Fletcher

Bioengineering

Rosemary Gillespie

Environmental Science, Policy and Management

Hartmut Haeffner

Physics

Iswar Hariharan

Molecular and Cell Biology

Chung-Pei Ma

Astronomy

Linda Wilbrecht

Psychology

Visiting Miller Professorship Awards

Laura Baudis

Physics

Host: Yury Kolomensky

Home Institution: University of Zurich

Nuh Gedik

Physics

Host: Joe Orenstein

Home Institution: MIT

Simonetta Gribaldo

ESPM

Host: Jill Banfield

Home Institution: Pasteur Institute

Yann Klinger

Earth & Planetary Science

Host: Barbara Romanowicz

Home Institution: Institute de Physique du Globe de Paris, France

Vyacheslav Krushkal

Mathematics

Host: Ian Agol

Home Institution: University of Virginia

Dong Lai

Astronomy

Host: Eliot Quataert

Home Institution: Cornell University

Jeremiah Ostriker

Astronomy

Host: Chris McKee

Home Institution: Columbia University

Graca Raposo

Molecular & Cell Biology

Host: James Hurley

Home Institution: CNRS/Institute Curie

Jochen Roeper

Helen Wills Neuroscience Institute

Host: Stephan Lamme

Home Institution: Goethe University

Jennifer Schomaker

Somorjai Visiting Miller Professor

Chemistry

Host: Robert Bergman

Home Institution: University of Wisconsin-Madison

JoAnne Stubbe

Chemistry

Host: Michelle Chan

Home Institution: MIT

Dmitri Talapin

Chemistry

Host: Eran Rabani

Home Institution: University of Chicago

Michael Turner

Physics

Host: Bernard Sadoulet

Home Institution: Kavli Institute for Cosmological Physics

In the News

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

Paul Alivisatos (Miller Professor 2001-2002) has been awarded the **2018 Wilhelm Exner Medal** for his pioneering research in nanoscience.

Barbara Meyer (Miller Senior Fellow 2013-2018) has been honored with the **ASCB's highest scientific honor** — the **E.B. Wilson Medal**. "Barbara's contribution stands far apart because it is the product of a sustained brilliance...."

Jennifer Doudna (Miller Senior Fellow 2017) is awarded the **Medal of Honor from American Cancer Society** for her valuable contributions in the fight against cancer through basic research, clinical research and cancer control. Doudna's discoveries allowed her to tweak the bacterial systems to create CRISPR-Cas9.

Barbara Meyer (Miller Senior Fellow 2013-2018) is one of only a few NAS members **elected to the National Academy of Medicine (NAM)** for her "groundbreaking work on chromosome dynamics that impact gene expression, development, and heredity using the nematode as a model organism."

Dan Nicolau (Miller Fellow 2008-2011) has been named an **ARC Future Fellow** for his project, "Scalable biocomputing on networks: design and mathematical foundations."

Chang Liu (Miller Fellow 2009-2012), **senior author of the innovative research project** published in *Cell* that details a new method for simplifying and accelerating directed evolution experiments in labs. "*The technique will stimulate new applications and new avenues of investigation which will continue to expand our ability to compose new DNA.*" - Frances Arnold.

Jeremy Thorner (Miller Professor 1984 - 1985, 1999 - 2000) was named a winner of the **ASBMB Herbert Tabor Research Award for excellence in biological chemistry**, molecular biology and contributions to the community of scientists.

Three Miller members are among the **2018 AAAS Fellows**:

- **Allen Goldstein** (Miller Professor 2011) was recognized for his "*distinguished contributions to the field of chemistry and emissions of natural and anthropogenic trace gases and aerosols in the atmosphere.*"
- **Corrie Moreau** (Miller Fellow 2007 - 2008) was honored for her research in evolutionary biology.
- **Sung-Hou Kim** (Miller Professor 1983-1984, 1996) was recognized for his "*landmark discovery of the structures of t-RNA, H-Ras and B-Raf, and for the mapping of the protein structure and genome sequence universes.*"

Richmond Sarpong (Miller Professor 2017-2018) has been recognized with the **2019 Mukaiyama Award** for his outstanding contributions to synthetic organic chemistry. Professor Sarpong will deliver an award lecture at the SSOCJ meeting in Tokyo next year.

Norman Yao (Miller Fellow 2014-2017) is a recipient of the **2018 Packard Fellowship in Science and Engineering**. He is one of the 18 innovative, early-career scientists and engineers will receive \$875,000 over five years to pursue his research in complex quantum mechanical systems.

Mikhail Shapiro (Miller Fellow 2011-2013) received the **2018 Roger Tsien Award for Excellence in Chemical Biology** for making significant contributions to the field of molecular imaging in the area of chemical biology. This includes the creation and/or use of novel chemistries to probe biological systems using noninvasive imaging approaches.

Alison Feder (Miller Fellow 2018-2021) has been named winner of the very first **Milner Prize** by the Milner Centre for Evolution.

Omar Yaghi (Visiting Miller Professor 2009), one of the most brilliant scientists working in the field of crystalline-porous solids research is awarded the **2018 Eni Energy Transition Award** for exceptional innovation in the hydrocarbon sector towards the decarbonization of the energy system.

Bin Yu (Miller Professor 2016-2017) is on a team of 8 colleagues from UC Berkeley, UCSF and Stanford that received a highly selective **Chan-Zuckerberg Intercampus Research Award** for their proposal called "Multi-scale deep learning and single-cell models of cardiovascular health".

Jennifer Doudna (Miller Senior Fellow 2017) moved part of her research efforts to the Gladstone Institutes in San Francisco, where she launched new collaborations that will help advance this breakthrough technique to solve some of humankind's most intractable diseases.

Douglas Hemingway (Miller Fellow 2015-2018) is a co-author of the **research on lunar swirls** that provide clues about the possible origins of the Moon's crustal magnetic anomalies.

Two Miller members **named the 2018 Cottrell Scholars** based on their innovative research proposals and education programs:

- **Claude-Andre Faucher-Giguere** (Miller Fellow 2010-2013) - astronomy, *The Physics, Observational Signatures, and Consequences of Galactic Winds Driven by Active Galactic Nuclei*
- **Meredith Hughes** (Miller Fellow 2010-2013) - astronomy, *The Last Gasp of Planet Formation: Gas and Dust in Debris Disks.*

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



Gifts to the Miller Institute

The Miller Institute gratefully acknowledges the following contributors to the Miller Institute programs in 2018. These generous donations help support the Miller Research Fellowship program, the general programs of the Institute, and the Gabor A. and Judith K. Somorjai Visiting Miller Professorship Award (SVMP). (* = 5 years of giving)



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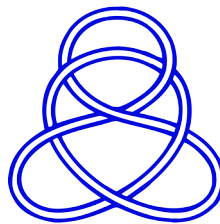
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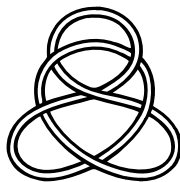
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Fall Dinner 2018



Advisory Board Members Steve Block & Tim Stearns, guest speaker Carlos Bustamante and Silvia Bustamante



Miller Fellows Alison Feder, Thibault de Poyferre, Georgios Moschidis and Sarah Slotznick

Birth Announcements

Meredith Hughes (Miller Fellow 2010-2013) & her husband Geir Helleloid welcomed Leif Bjorn Hughes, born in November 2018.

Bekki Dawson (Miller Fellow 2013-2015) & Marc Rigas announced the arrival of their daughter, Anna Rose, born in September 2018.

Alex Hayes (Miller Fellow 2011-2014) & his wife Lindsey announced the birth of their daughter, Jordan Alexis Hayes, born in August 2018.

Lian Xue (Miller Fellow 2016-2019) & her husband Han welcomed their daughter, Linyao Yue, which means "a fortunate beautiful stone", born in August 2018.

Elchanan Mossel (Miller Fellow 2002-2005) & his wife Saleet announce the arrival of son, Nathan, born in April 2018.



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.