

# Biotechnology Leadership Predoctoral Training Program in Micro/Nanomedicine

[trainingbiotechleaders.caltech.edu](http://trainingbiotechleaders.caltech.edu)

## Frances H. Arnold, Director

Linus Pauling Professor of Chemical Engineering, Bioengineering and Biochemistry

## Kim Mayer, Program Coordinator

Executive Director, Donna and Benjamin M. Rosen Bioengineering Center

Welcome to the inaugural newsletter from Caltech's Biotechnology Leadership Predoctoral Training Program (BLP). Most of the pieces in this newsletter were contributed by the trainees. It was also exciting to see our young program featured in a Caltech news piece (<http://www.caltech.edu/node/81334>), with quotes from several trainees (February 2018).

In the newsletter, we have highlighted many of the activities that make our program special. For example, to help expand the career-related learning experiences of our trainees beyond what is covered in typical instructive workshops, seminars and courses, the BLP includes site visits to biotechnology companies and organizations. In 2017, eleven BLP trainees, accompanied by the Rosen Bioengineering Center's Executive Director Dr. Kim Mayer, traveled to La Jolla, California for the day. We were hosted by Illumina in the morning and the J. Craig Venter Institute in the afternoon. The goal of the day was to give the trainees a chance to engage directly with scientists who work in non-academic research positions. Activities during the visits included presentations by company representatives, panel sessions, poster sessions, working lunch discussions, and tours. The trainees reported uniform success, as did our hosts. Planning for our 2018 visits is underway!

Several of the newsletter pieces also mention the BLP's monthly learning lunches. These were instituted in response to an early request by the trainees to meet informally more often than the formal progress update meetings, with the goal of getting to know each other and drive cohesiveness of the program. The format of each lunch is a short presentation by invited guest(s) followed by open discussion. Recent topics and guests have included:

- Identifying and Applying for Postdoctoral Fellowships – Guests Andrew Buller (Frances Arnold's lab) and Sujit Datta (Rustem Ismagilov's lab), who were both postdoctoral scholars at the time, joined the BLP cohort to provide advice for identifying postdoctoral fellowship opportunities. Both also shared their best practices for preparing competitive proposals for advanced fellowships, including the NIH K99/R00 and

Burroughs Wellcome Career Awards at the Scientific Interface. Trainees received handouts summarizing key details about both of these programs, as well as the NIH F32 program.

- Managing Your Professional Brand – Guest speaker Kim Mayer (Executive Director of the Rosen Bioengineering Center at Caltech) gave a PowerPoint presentation and led a discussion on several of the tools used to disseminate skills and capabilities, including the differences between CVs and resumes, how to effectively utilize LinkedIn, and how to prepare NIH/NSF biosketches.
- Intellectual Property from a Graduate Student Perspective – Guest Hannah Dvorak Carbone (Director for Innovation, Patents & Licensing at Caltech) led an educational discussion about what constitutes intellectual property and how it is protected, then fielded questions from the trainees about how IP impacts and influences their own research.
- Career Paths Outside the Lab – Three Caltech guests with PhDs who have followed career paths outside of the laboratory joined the cohort to discuss careers that have spanned federal-level policy work and corporate partnerships (Mary Beth Campbell, Director of Corporate Partnerships), technology transfer and management consulting (Hannah Dvorak Carbone, Director for Innovation, Patents & Licensing), and patent law and law clerk service (Chantal D'Apuzzo, Associate General Counsel). Discussion included transferrable skills, people skills, and problem solving. Our guests also shared insights on "going with your gut," dealing with "the 2-body problem," the need to "get out of the lab to learn," how to "demonstrate you are a well-rounded scientist," and the importance of doing informational interviews with scientists whose roles are intriguing.

*We hope you enjoy our 2018 Newsletter!*



Donna and Benjamin M.

**Rosen Bioengineering Center**



# Biotechnology Leadership Program Trainees

Anupama Lakshmanan Advisor: Mikhail Shapiro	Bioengineering	Joined 2017
Benjamin Laccetti Advisor: Julia Kornfield	Chemical Engineering	Joined 2016
Bradley Silverman Advisor: David Tirrell	Chemical Engineering	Joined 2015
Daniel Martin Advisor: Changhuei Yang	Electrical Engineering	Joined 2017
Daryl Yee Advisor: Julia Greer	Materials Science	Joined 2017
Heidi Klumpe Advisor: Michael Elowitz	Chemical Engineering	Joined 2017
Ruijie "Kelly" Zhang Advisor: Frances Arnold	Chemistry	Joined 2015
Kevin Yang Advisor: Frances Arnold	Chemical Engineering	Joined 2015
Joshua Brake Advisor: Changhuei Yang	Electrical Engineering	Joined 2015
Pradeep Ramesh Advisor: Mikhail Shapiro	Bioengineering	Joined 2015
Reem Abdel-Haq Advisor: Sarkis Mazmanian	Biology	Joined 2017
Robert Hurt Advisor: Mikhail Shapiro	Neurobiology	Joined 2016
Xinyan Liu Advisor: David Tirrell	Chemical Engineering	Joined 2016
Zhewei Chen Advisor: Niles Pierce	Bioengineering	Joined 2016
Zixuan "Zach" Shao Advisor: Julia Kornfield	Bioengineering	Joined 2015

## Networking at the 2017 BASF Graduate Student Conference

*Contributed by: Ruijie "Kelly" Zhang, 2015 BLP Cohort (Advisor: Arnold)*



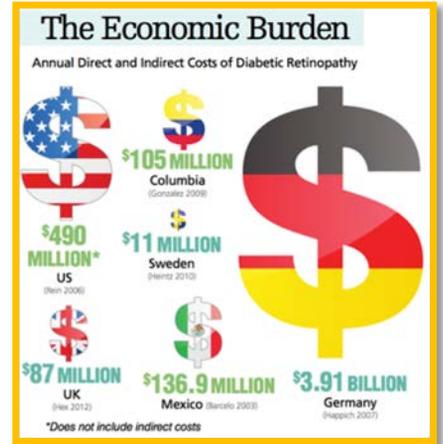
I love the research I am able to pursue as a graduate student at Caltech. I work on engineering enzymes, the catalytic workhorses of biology, to perform reactions that are not found in nature. I have often wondered, though, how research findings are translated into a technology that can be used by companies to produce products for society. One great aspect about the BLP program is that it aims to address this question by giving trainees exposure to industry. During our monthly "learning lunches", we often have guests that have pursued different career paths within the science umbrella. For me, one memorable guest was a research scientist at Amgen, a biotechnology company that focuses on developing medicines. During lunch with the Amgen scientist, we had a casual conversation about what research is like in an industry setting and how the research directly impacts products. Curious to learn more, I enthusiastically accepted an opportunity to attend a conference hosted by global chemical company BASF. For this conference, a small group of PhD students from fields including chemistry, chemical engineering, materials science, and

biotechnology were invited to the Tarrytown, New York facility. The company had many activities planned for us, which included presentations by BASF scientists, discussions, lab tours, and social events. Students were also given the opportunity to present their graduate school research during a poster session – to my delight, several BASF scientists came to my poster to discuss my research and offer their views! The conference was an immersive experience, giving students the opportunity to closely interact with BASF representatives. For me, this experience was deeply valuable for learning how research is structured at a company. I am inspired by the industry approach to first identify challenges in society and then develop and produce the appropriate products. The BLP program has played an instrumental role in my professional development, providing me with information and a group of colleagues to explore careers in industry.

## My Voyage of Discovery in the BLP: a Course on Management of Technology

*Contributed by: Anupama Lakshmanan, 2017 BLP Cohort (Advisor: Shapiro)*

In the Fall of 2017, shortly after joining the BLP, I enrolled in the 'Management of Technology' course taught by Kenneth Pickar. As early as the first lecture, I realized that this course would be very different from any other that I had taken at Caltech – one that would require me to step out of my comfort zone as a scientist and engineer to critically evaluate the relevance, future trajectory and impact of scientific inventions and emerging technologies from a consumer and business standpoint. The next ten weeks were a period of intense learning and networking for me, with guest lectures by illustrious scientists, industry CEOs, entrepreneurs, venture capitalists and project managers to elucidate key roadblocks and real-world challenges involved in converting a scientific idea/invention into a useful and viable end-product.



In conjunction with in-class discussions and case studies, the final term project comprised the bulk of the deliverables, where we had to work in teams to present a technology assessment and projection report. As a bioengineer, I teamed up with two medical engineering graduate students to evaluate next-generation ocular phototherapeutic devices for the prevention of diabetic retinopathy, an eye disease that threatens the vision of more than one-third of diabetic patients worldwide. Working on this project required us to be well-acquainted with the technical details of the invention. At the same time, we worked to separate the wheat from the chaff by identifying potential failure modes of the technology, interviewing key stakeholders, defining competitor landscape and making astute predictions. To top it all, we got a chance to present our findings and projections to David Baltimore, a Nobel laureate and former President of Caltech, who gave us expert feedback. In addition to the valuable connections, this course has helped me gain a deeper understanding of how rapidly evolving technologies are harnessed to build successful companies and useful products, knowledge of which is crucial in the modern era that we live in today.

Figure credit: Colin Cook, Anupama Lakshmanan, Aubrey Shapero. *Technology Assessment Report, E103: Management of Technology (2017)*; adapted from Alliance, "The Silver Book : Diabetic Retinopathy," Alliance Aging Research, 2016.

## BLP Trainee Participates in Caltech Y Science Policy Trip to DC

*Contributed by: Daniel Martin, 2017 BLP Cohort (Advisor: Yang)*

Historically speaking, PhD programs are primarily aimed at producing academic researchers. However, an academic career is a path many of us are unlikely to follow. The great thing about the BLP program at Caltech is that it recognizes this problem and offers students like myself exposure to non-academic employment. One of the ways it does this is through our "learning lunches" that we hold on a monthly basis. Topics for these meetings can range from general "soft" skills to guest speakers who highlight their own career paths. This past year, we hosted a diverse group of guest speakers from entrepreneurs to patent lawyers. One of our guest speakers, Mary Beth Campbell, Caltech's Director of Corporate Partnerships, talked about her experiences in science and technology policy. This was a domain I had never considered before and was excited to learn more about. Through this experience, I was introduced to the science policy trip in Washington DC that is hosted by the Caltech Y. During this trip, I visited the NIH, the NSF, the Department of State, and the Office of Science and Technology Policy. I even met other Caltech alumni

involved in science policy along the way! Overall, it was exciting to learn about the many ways science influences government decision and *vice versa*. I learned a great deal about this potential career path and I never would have been led in this direction were it not for the BLP program. I'm appreciative that joining BLP at an early stage in my career, has given me the time to explore what paths best align with my skills and interests.



## Industrial Internship – Ambray Genetics

*Contributed by: Kevin Yang, 2015 BLP Cohort (Advisor: Arnold)*

During the summer of 2017, I was a computational intern in the bioinformatics department at Ambray Genetics in Aliso Viejo, California. Ambray Genetics is a genetic testing and diagnostics company that develops, manufactures, distributes, and interprets genetic tests. At Ambray, I worked with a structural biologist and statistical geneticist to develop predictive models for human genetic variation. As part of this work, I applied many ideas and computational skills I learned at Caltech while also learning new techniques as needed for my project. Working with patient data also introduces privacy issues, and I saw how Ambray strives to balance patient privacy with a belief in open data.

Compared to academic research, research at Ambray was much more focused. Generally, scientists there were focused on helping interpret specific cases or on building the scientific and technical framework to make more accurate or novel tests. Many of the scientists there were motivated by seeing their results used directly to help patients, which is much rarer in the academic setting.

I am grateful to Ambray Genetics and to the Biotechnology Leadership Program for the opportunity to work at Ambray. As decisions about my post-PhD

career approach, the experience doing research in a commercial environment will help me to make a better-informed decision about the type of work I want to do and where I want to do it.

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- Pinpoint Genetic Factors That Caused Your Disease
- Predict How Severe Your Disease Might Be
- Choose the Best Medicine and Correct Dose
- Discover Genetic Factors That Increase Your Disease Risk
- Find Genetic Factors That Could Be Passed to Your Children
- Screen Newborns for Certain Treatable Conditions

<https://www.genome.gov/19516567/faq-about-genetic-testing/>



## Site Visits Highlight Collaboration Also Happens Outside of Academia

*Contributed by: Ben Laccetti, 2016 BLP Cohort (Advisor: Kornfield)*

While research in the life sciences can be frustrating and tiring, Caltech is a place where graduate students relish the process of doing research. Why? Because we play (do research) on a team full of superstars. There are smart graduate students at every university, but at Caltech, when things get challenging, wherever you are there is a high concentration of brilliant and often more cheerful minds to offer support and expert knowledge into the problems we are tackling. Having teammates like this is invaluable. In our site visits to Illumina and the J. Craig Venter Institute, the BLP cohort found that we could thrive working for similar "teams" after graduate school. At Illumina, a company with \$2.4 billion in revenue last year, we witnessed production of technology that is catalyzing the movement for personalized medicine that permeates almost every facet of the healthcare industry today. We saw how biologists and engineers combined automation, state of the art optics, and DNA sequencing to create technology that is invaluable to this movement. The collaborative nature between physicists and life scientists at this

company was very similar to life at Caltech. At the J. Craig Venter Institute, it was hard not to be jealous of the research atmosphere, even coming from Caltech. In a facility that makes its own electricity using solar power and that recycles all of its water, talented researchers work on benches right next to one another studying groundbreaking new subjects, like multi-gene interactions and protein mediated hydrogen synthesis. It was impressive to see renowned synthetic biologists, whose work I admire, literally working side-by-side. Our visits to both of these places showed us that the collaborative nature of Caltech, which we all benefit from so much, can hopefully continue to benefit us, regardless of our future career paths in research.



## Seeing Industrial Biotech in Action at Illumina

*Contributed by: Xinyan Liu, 2016 BLP Cohort (Advisor: Tirrell)*

"Working in a biotechnology company can be as enjoyable as working at Google." While a bit tongue-in-cheek, this was indeed the general impression of the BLP trainees who visited Illumina, a biotechnology company located in San Diego. The young company encourages technicians, engineers, and scientists to work together to advance the development of sequencing technology. This approach makes the culture feel vibrant and exciting. Our day began with a tour of the campus, led by Brian Steffy (Sr. Manager, CS Applications Lab). It was clear from our tour that efficiency is a priority at Illumina; we saw several examples of automated manufacturing processes using robots and programmed equipment. Several scientists we met noted that the interdisciplinary communication at Illumina makes it more efficient and easier to achieve certain goals than they had seen in academia. And while their current work might be commercial, their scientists do keep reading academic papers to generate ideas which could be translated into technological advances. Over lunch, we heard from a panel of three Caltech alumni who now work with Illumina. Dr. Amanda Cashin (Head of Illumina Accelerator), Dr. Alex So (Sr. Scientist, Oncology Dev), and Dr. Pamela Sontz (Scientist, Consumables Dev) all shared anecdotes, provided advice, and answered

questions from the trainees about their career paths. Later in the afternoon, Dr. Cashin treated us to a presentation about the Illumina Accelerator, which provided insight into the initialization and organization of new biotechnology start-ups. We learned that industry scientists feel a responsibility to educate the public and help shape scientific policy since these will directly affect research of the future. During the drive back to Pasadena at the end of the day, we shared our opinions and experiences; it was clear that several of us are now interested in working at companies like Illumina.

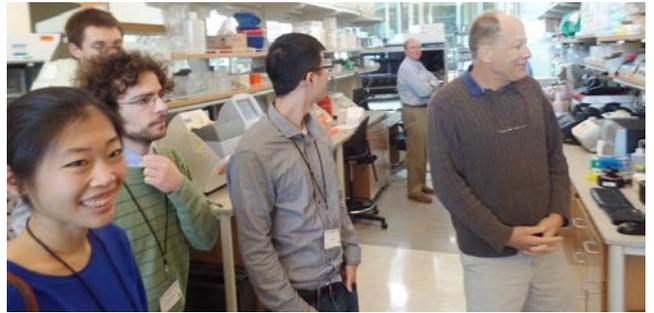


## Exploring Not-for-Profit Research at J. Craig Venter Institute

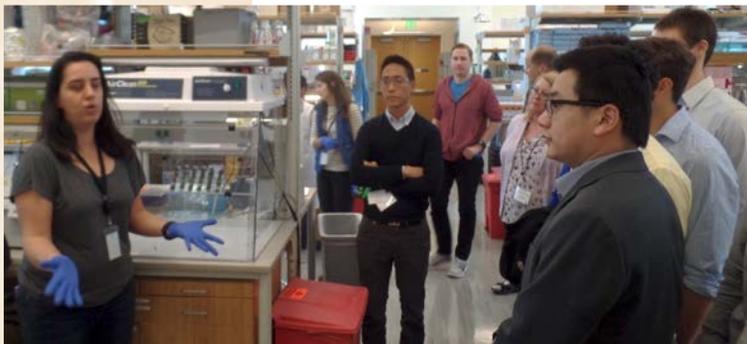
*Contributed by: Bradley Silverman, 2015 BLP Cohort (Advisor: Tirrell)*

When we arrived at the J. Craig Venter Institute, we were immediately met by Professor John Glass, Caltech alumnus and leader of the Synthetic Biology and Bioenergy Group. He gave us a tour of the incredibly environmentally friendly laboratories that actually generate all of their own electricity. This is impressive, considering that laboratories generally are highly energy intensive workspaces. During the tour we talked with several scientists who are working on varied projects, particularly in the environmental genomics space, where JCVI is a world leader in characterizing the earth's genetic diversity. After the tour, we were treated to several presentations by JCVI scientists, including one by JCVI Distinguished Investigator Clyde Hutchison describing JCVI's 20-year project to build the minimal synthetic cell. That project that culminated in a groundbreaking paper last year in *Science*! Next, we heard from Sarah Smith, a visiting Research Fellow at JCVI and postdoc at Scripps Institution of Oceanography. Sarah shared her research on diatom gene regulatory

networks. Finally, we heard about the "Green Monster" technique for genome engineering from its developer, Assistant Professor Yo Suzuki. After presentations by the scientists, it was the trainees' turn to share their science at a poster session. Many JCVI scientists engaged with the trainees as they discussed their research and future career plans, including Distinguished Professor and Nobel Laureate Hamilton O. Smith who serves as JCVI's Scientific Director Synthetic Biology and Bioenergy.



*"I was talking with my colleagues about the visit and the consensus is we cannot remember enjoying the visit of a group of students more than yours. I hope you can come visit us again with a new crop sometime soon." – John I. Glass, Ph.D. (Professor & Group Leader, Synthetic Biology & Bioenergy Group, J. Craig Venter Institute)*



*"I'm really happy we were able to get this to the finish line since it's been something the students clubs wanted to do for a long time, but always out of reach due to the insurmountable amount of logistics needed to pull it off. I'm really glad we did it and personally got a lot of great connections through this trip." –Zach Shao, 2015 BLP Cohort*

*"Fun to have the opportunity to do some of these activities through the BLP that would be harder to coordinate otherwise. Making good connections and meeting interesting people is a big deal!" –Josh Brake, 2015 BLP Cohort*

## Trainee Publications, Posters, and Presentations

- *Please note: we included comments from several of our trainees.*

### Anupama Lakshmanan (2017 Cohort, Shapiro)

- RW Bourdeau, A Lee-Gosselin, A Lakshmanan, A Farhadi, SR Kumar, SP Nety and MG Shapiro. Acoustic reporter genes for non-invasive imaging of microbes in mammalian hosts. *Nature*, 553: 86-90 (2018). Cover article.
- A Lakshmanan\*, SP Nety\*, D Maresca and MG Shapiro. "Engineering acoustic biomolecules as dynamic molecular sensors for ultrasound," 10<sup>th</sup> World Molecular Imaging Congress, Philadelphia, PA (2017). \*Equal contribution; oral presentation.
- A Lakshmanan\*, SP Nety\*, D Maresca and MG Shapiro. "Engineering acoustic biomolecules as dynamic molecular sensors for ultrasound," IEEE International Ultrasonics Symposium, Washington, DC (2017). \*Equal contribution; poster presentation.
- A Lakshmanan, A Farhadi, SP Nety, A Lee-Gosselin, RW Bourdeau, D Maresca and MG Shapiro. "Biomolecular engineering of the mechanical, acoustic, surface and targeting properties of genetically-encoded gas nanostructures for multimodal imaging," 7<sup>th</sup> International Conference on Biomolecular Engineering, San Diego, CA (2017). Poster presentation.

### Benjamin Laccetti (2016 Cohort, Kornfield)

- B Laccetti. "Synthesis of monodisperse drug microparticles and high-velocity bombardment as a strategy to traverse epithelial layers and treat pathologies of the cornea." American Physics Society: Biophysics of Cellular Organization and Dynamics Across Multiple Spatial Scales, Los Angeles, CA (2018). Oral presentation.
  - *This presentation was important to me because it made me realize I was a part of a larger scientific community. While I work on a project that is completely different than the people around me, there is a whole community of scientists outside of Caltech interested in the mechanical stresses experienced by epithelial layers. It was nice that even though I am the only one that works on these things at Caltech, I still don't feel out of place presenting my observations and conclusions to more established groups in the field.*

### Bradley Silverman (2015 Cohort, Tirrell)

- M Obana, BR Silverman, DA Tirrell. Protein-mediated colloidal assembly. *J Am Chem Soc.* 139 (40), 14251-14256 (2017).
- Silverman B, Kozlowski M, Tirrell D. "Genetically programmable assembly of microbial communities for enhanced biosynthetic efficiency," AIChE Annual Meeting, Minneapolis, MN (2017). Oral presentation.
  - *This was my first public presentation of my research. I got a really good response, with a few people telling me that they wanted to try my methods out when they got back to their labs.*

### Daryl Yee (2017 Cohort, Greer)

- DW Yee, MD Schulz, RH Grubbs, JR Greer. Functionalized 3D architected materials via thiol-Michael addition and two-photon lithography. *Adv Mater* 29, 1605293 (2017).
- DW Yee. "Genomic DNA functionalized architected materials fabricated via two-photon lithography for drug capture." American Chemical Society National Conference, Washington, DC (2017). Poster presentation.

### Heidi Klumpe (2017 Cohort, Elowitz)

- YE Antebi, JM Linton, H Klumpe, B Bintu, M Gong, C Su, R McCardell and MB Elowitz. Combinatorial signal perception in the BMP pathway. *Cell* 170 (6), 1184-1196 (2017).
  - *Our study showed that cells can perform complex computations on combinations of signaling proteins from the important BMP pathway. Interestingly, these computations arise not from intracellular machinery, but receptor-ligand interactions at the membrane. I'm working on measuring the full set of computations in different cell lines to determine if it is possible to reprogram responses and potentially use the BMP pathway as a rational tool for controlling cell fate.*

### **Joshua Brake** (2015 Cohort, Yang)

- H Ruan\*, J Brake\*, JE Robinson, Y Liu, M Jang, C Xiao, C Zhou, V Gradinaru and C Yang. Deep tissue optical focusing for optogenetic applications with time-reversed ultrasonically encoded light. *Science Advances* 3(12), eaao5520 (2017). \*Co-first authors
- J Brake. "Improving light delivery for optogenetics using wavefront shaping." *Advances in Optics for Biotechnology, Medicine and Surgery XV*, Snowmass Village, CO (2017). Oral and poster presentations.
  - *I won 2<sup>nd</sup> place in the poster competition (out of ~30, mostly grad students and post docs), giving me the chance to give a talk over dinner to the whole conference (~150 PIs/students/postdocs). Normally only PIs speak at the conference.*
- M Jang\*, Y Horie\*, A Shibukawa\*, J Brake, Y Liu, SM Kamali, A Arbabi, H Ruan, A Faraon and C Yang. Wavefront shaping with disorder-engineered metasurfaces. *Nature Photonics* 12(2), 84-90 (2018).
  - *Breakthrough highlighted by Caltech News (<http://www.caltech.edu/news/engineered-metasurfaces-replace-adhesive-tape-specialized-microscope-81458>)*

### **Kelly Zhang** (2015 Cohort, Arnold)

- CK Prier\*, RK Zhang\*, AR Buller, S Brinkmann-Chen and FH Arnold. Enantioselective, intermolecular benzylic C-H amination catalysed by an engineered iron-haem enzyme. *Nature Chemistry* 9, 629-634 (2017). \*Equal contribution
  - *This work was highlighted in a 'news & views' article (R Fasan, *Nature Chemistry* 9: 609-611), PNAS (JP Johnson, "Journal Club: Engineered enzyme could streamline synthesis of nitrogen containing compounds," posted June 15, 2017), *Nature Chemical Biology* (C Deane, *Nature Chem Bio* 13: 817), and *Synfacts* (B List, JL Kennemur, *Synfacts* 13: 981).*
- RK Zhang. "Enantioselective, intermolecular benzylic C-H amination catalysed by an engineered iron-haem enzyme." BASF Research Forum, Tarrytown, NY (2017). Poster presentation.

### **Kevin Yang** (2015 Cohort, Arnold)

- CN Bedbrook \*, KK Yang \*, AJ Rice, V Gradinaru and FH Arnold. Machine learning to design integral membrane channelrhodopsins for efficient eukaryotic expression and plasma membrane localization. *PLOS Computational Biology* 13(10): e1005786 (2017). \*Equal contribution.
- KK Yang. "Machine learning to design integral membrane channelrhodopsins for efficient eukaryotic expression and plasma membrane localization." Gordon Research Seminar on Proteins, Holderness, NH (2017). Oral presentation.
  - *This presentation and paper were the culmination of the project I worked on for the first two years of my PhD. At the Gordon Research Seminar and Conference, I learned much more about the state of the field and what other groups are working on or interested in. This work demonstrates that machine learning methods can work on small sets of proteins with properties that are difficult to measure. This enables engineering of protein properties that would be difficult to design by other means.*

### **Pradeep Ramesh** (2015 Cohort, Shapiro)

- HC Davis\*, P Ramesh\*, A Bhatnagar, A Lee-Gosselin, JF Barry, DR Glenn, RL Walsworth and MG Shapiro. Mapping the microscale origins of magnetic resonance image contrast with subcellular diamond magnetometry. *Nature Communications* 9: 131 (2018). \*Equal contribution.
  - *I'm co-first author on my first paper. This work is the significant in that we use a custom built optical magnetometer to map microscopic magnetic fields in biological samples and show how variations in local magnetic fields lead to macroscopic MRI contrast that is observed.*

### **Zach Shao** (2015 Cohort, Kornfield)

- TD Luccio, K Ramachandran, Z Shao, et al. "Impact of tungsten disulfide nanotubes on the crystallization of poly (L-lactide) for thinner and stronger bioresorbable vascular scaffolds." *Bulletin of the American Physical Society*, March 2018.