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IN THIS ISSUE

Research Spotlight

Tet1: A regulator of DNA methylation and imprinting during development

1-2

Special Interest

Experiences and advice from successful women in science

Helen Davies: An infectious passion for teaching, 50 years and counting

PCI - Penn Center for Innovation

2-5

Welcoming New CAMB-ers

Melike Lakadamyali, Ph.D.

5

LETTER FROM THE EDITORS

Dear CAMB students, faculty, and alumni,

We'd like to extend a warm welcome to our newest CAMB 2018 matriculates. Orientation begins Tuesday, August 28th, with the CAMB happy hour on Thursday, September 6th, at 4:30 pm in the Biomedical Research Building (BRB) lobby. We hope that you enjoy meeting your new classmates and faculty members, and we are excited to have you as members of the CAMB community.

In this issue, we focus on women in science. We spoke with two amazing faculty members, Dr. Mary Mullins and Dr. Monserrat Anguera, about the changing climate of women in the sciences and their own experiences. We also highlight an exciting CAMB student research project from recent Genetics and Epigenetics (G&E) alumna Jennifer SanMiguel. We had the privilege to speak with Dr. Helen Davies about her incredible story as a professor of over 50 years at Penn. Finally, we introduce new CAMB faculty member Dr. Melike Lakadamyali, and discuss the Penn Center for Innovation's Fellowship program in our Special Interest section. Incoming students should also check out the blog for a discussion on lab rotations and picking a thesis lab.

For additional articles, past publications, and to learn more about the CAMB Newsletter team, visit our blog at **cambnewsletter.wix.com/blog**. Current students, including our 2018 matriculates, interested in contributing to the CAMB Newsletter can contact us at **camb.studentnews@gmail.com**. We hope you enjoy the August 2018 Issue!

Sincerely,

Lexy Stanley and Somdutta Mukherjee

Editors-in-chief

RESEARCH SPOTLIGHT

Tet1: A regulator of DNA methylation and imprinting during development

Camille Syrett

Stemming from a relatively recent explosion of research, the epigenetic regulation of gene expression is now appreciated as an important biological phenomenon. The prefix "epi-" means above or around in Greek, as epigenetics is defined by the study of DNA modifications that do not change the underlying sequence of the DNA. Importantly, these additions change cellular gene expression to diversify the functionality of cells with the same underlying genetic code.

Chemical modifications to DNA such as methyl groups (mCpG) are dynamically regulated to govern cell fate during development. The family of DNA methyltransferase enzymes, or DNMTs, covalently add mCpGs to DNA to allow cells to change their transcriptional output. These epigenetic marks can also be erased through either the downregulation of DNMTs and subsequent DNA replication, or through the activation of the Ten-Eleven Translocation (TET) family of enzymes to begin multi-step oxidation of mCpGs. During mammalian germ cell formation in early embryonic development, DNA methylation is dynamically regulated during the process of epigenetic reprogramming. First, the DNA methylation patterns of the egg and sperm are erased, leading to the formation of a totipotent zygote. Next, tissue specific DNA methylation occurs to guide differentiation. Later, these marks too are erased when the primordial germ cells (PGCs) migrate from the epiblast and differentiate into cells with a germ fate.

While the establishment of DNA methylation is well-characterized, much less is known about the requirement for DNA demethylation during development. When CAMB G&E alum Jennifer SanMiguel joined the Bartolomei lab, research on the function of TET enzymes on DNA

Jennifer SanMiguel, G&E

demethylation during development was already underway. Jen was particularly interested in using previously developed *Tet1* null mice to examine DNA methylation changes at important developmental loci called imprinting control regions, or ICRs. These regions of the genome are unique because their methylation pattern controls genes that are expressed in a monoallelic fashion, from either the maternal or the paternal parental copy. One example of this unique regulation is the *H19/Igf2* locus, where paternal ICR hypermethylation governs paternal- specific expression of *Igf2* and maternal- specific expression of *H19*.

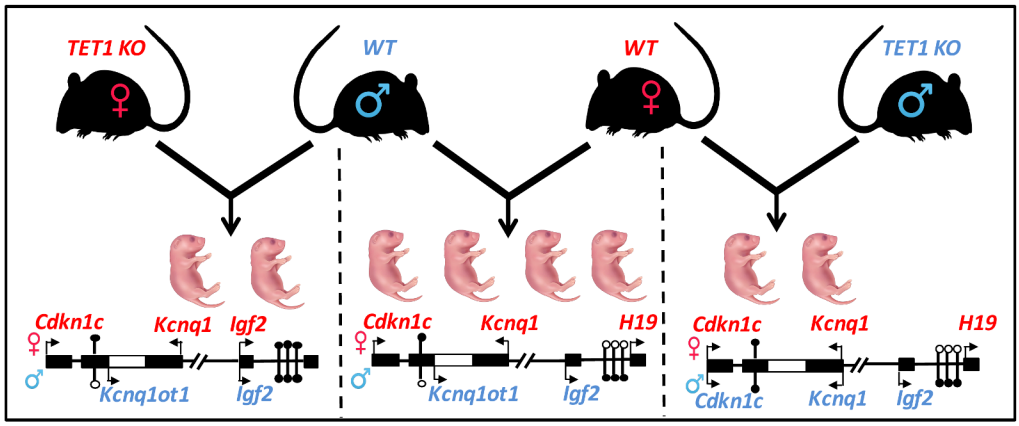

Illustration by Siddharth Kishore

Mating TET1 knockout (KO) males or females their wild type (WT) counter-parts results in fewer live embryos compared to WT controls. This is caused by abnormal DNA methylation at important developmental loci called imprinting control regions (ICR's). Specifically, when TET1 KO females mate with WT males, the resulting embryos fail to lose DNA methylation marks on the maternally derived allele at the H19/Igf2 locus, which leads to the expression of Igf2 from both the maternal and paternal alleles. Conversely when TET1 KO males mate with WT females, the resulting embryos fail to lose DNA methylation marks at the paternally derived allele at the KvDMR locus, which leads to the expression of Cdkn1c and Kcnq1 from both the maternal and paternal alleles.

To understand how TETs function in germ cells, Jen set out to examine how loss of *Tet1* affects DNA methylation of ICRs in both male and female germ cells using *Tet1* null (KO) offspring, as *Tet1* is the most highly expressed TET family member in the germline. Jen hypothesized that TET1 is essential for setting up proper allele-specific patterns of DNA methylation at ICRs. To test this, Jen first examined imprinted methylation with pyrosequencing in female oocytes from pups generated by mating heterozygous *Tet1* (het) mutant animals. Interestingly, two loci that are paternally hypermethylated (*H19/Igf2* and *IG- DMR*) had unusually stochastic DNA methylation in the female germline, with up to ~75% DNA methylation in the normally hypomethylated maternal allele. To determine if the abnormal methylation at ICRs in oocytes affects development or gestation, Jen quantified the number of live versus resorbed embryos at E10.5 in matings with either Het or KO *Tet1* females to wild type (WT) males. A major hurdle Jen faced during data collection was getting the female *Tet1* mice to breed. She described that "I spent months breeding heterozygous pairs of mice to get null females, and when I finally got null females, they were almost impossible to successfully mate. I waited almost an entire year between my second litter and my third litter of maternal knockout mice. It was really important for us to have a decent sample size as well as making sure there were no litter specific effects, so waiting for these mice to breed was painful. Luckily, persistence paid off!" Over time, Jen observed that the number of live embryos decreased while the corresponding number of resorbed embryos increased in embryos generated with *Tet1* KO female mice, consistent with the idea that the proper demethylation of ICRs is essential for embryonic development.

To determine if abnormal ICR methylation affects imprinted gene expression, Jen used *Tet1* KO females bred to WT males harboring multiple single nucleotide polymorphisms at the ICR of imprinted *H19/Igf2* for allele-specific analyses. In WT mice at this locus, paternal ICR hypermethylation dictates exclusive Igf2 expression from the paternal allele, while *H19* is expressed from the maternal allele. Remarkably, three embryos derived from independent litters of *Tet1* KO females had abnormal biallelic expression of *Igf2*. In agreement, embryos with biallelic expression of *Igf2* also had methylation of both the maternal and paternal alleles of the ICR at this locus. Because *Igf2* was expressed from both maternal and paternal alleles, Jen observed a sharp decrease in the expression of *H19* from both alleles, further suggesting that TET1- mediated germline ICR methylation is required for allele-specific gene expression at the *H19/Igf2* locus.

Finally, to investigate the effects of *Tet1* deletion on the male germline, Jen examined imprinted methylation in sperm from *Tet1* Het matings. Similar to observations in *Tet1* KO oocytes, Tet1 null sperm had increased methylation of ICRs that are usually maternally hypermethylated and paternally hypomethylated, such as *Peg3* and *KvDMR*. A similar decrease in the number of live births and increase in resorbed embryos was also observed. To determine how the unusual methylation pattern in sperm affects imprinted gene expression of offspring, Jen again analyzed allele-specific expression, this time at the *KvDMR* ICR. At this locus, *Cdkn1c* is expressed from the maternal allele in WT animals, but in animals generated with *Tet1* KO males, biallelic expression of this gene was observed in multiple adult tissues.

Taken together, Jen and colleagues have demonstrated that *Tet1* is essential for establishing proper DNA methylation patterns at critical ICRs in both male and female germ cells. Moreover, without the appropriate imprinted DNA methylation, biallelic expression is observed stochastically in a distinct set of ICRs. Importantly, the loss of imprinted gene expression at ICRs is observed in human imprinting disorders, and this study establishes *Tet1* as an important regulator of imprinting in both sexes. As Jen begins her postdoctoral fellowship at the Jackson Laboratory in Bar Harbor, ME, she looks back on her time in CAMB. "I think my favorite part of my Ph.D. was the community. I was luckily to have a caring and supportive mentor and thesis committee, amazing, caring lab mates, great technical support from the epigenetics community and people on the 9th floor of Smilow and a great connection with my peers and the faculty in G&E. I really loved being surrounded by so many smart, positive, insightful people and it really made my research and my life outside of grad school that much better."

SanMiguel JM, Abramowitz LK, Bartolomei MS. (2018). Imprinted gene dysregulation in a *Tet1* null mouse model is stochastic and variable in the germline and offspring. *Development.* 2018, 145, dev160622.

SPECIAL INTEREST

Experiences and advice from successful women in science

Somdutta Mukherjee

Women in science face many obstacles throughout their careers. While the proportion of women earning Ph.D.s in the sciences has increased from 37% in 1996 to 52% in 2014, there is still a gap in the number of women hired as junior faculty and an even larger gap among tenured faculty[1]. This disparity may be due in part to sexism and implicit bias. Indeed, a 2012 PNAS paper showed that when reviewing applications for lab manager positions, both female and male faculty display bias against female students[2]. Although things have been getting better for women in science, there is still much to be improved. Dr. Mary Mullins, Professor of Cell and Developmental Biology in the Department of Cell and Developmental Biology in the Perelman School of Medicine, and Dr. Montserrat Anguera, Assistant

Professor in the Department of Biomedical Sciences in the University of Pennsylvania School of Veterinary Medicine, shared their experiences of successfully navigating through academia as women, as well as their hopes for the future.

Being a woman in science is not easy, and the male-dominated world of academia can be an isolating place for women, as Dr. Mullins and Dr. Anguera can attest to. Women continue to face sexism and implicit bias as they advance through their careers. Dr. Mullins remembers a specific incident from one of her undergraduate classes that illustrates how men negatively perceive women in science. She was the only woman in a study group for her thermodynamics class, and one of her male classmates told her that there were fewer women in science because their brains were built differently. "His theory about me was that I must have had some testosterone as a baby or child and that made my brain better," she recalls. This comment angered her, and she worked on her own for the rest of the semester. Although she was determined to do well and succeed, she realized that this was how women become isolated in science.

Dr. Mary Mullins, Professor of Cell and Developmental Biology

Implicit bias is prevalent, and Dr. Anguera believes that the first step to overcome this bias is to recognize it. As Dr. Anguera said, "The only way I think someone can change their behavior is by realizing it, acknowledging it, and actively trying to change it. I think that the more we share our experiences, then the less blinders [there are] to the reality of what's happening." Having a support network has been critical for both Drs. Mullins and Anguera, both of whom noted that there were more females than males in their graduate classes, which helped create a supportive environment to share their experiences of bias. As Dr. Mullins continued on to become an assistant professor, she was able to turn to other women who held faculty positions at Penn to help her with the transition. Dr. Anguera believes that the attitudes of both men and women towards women and science are changing, and she feels encouraged by the supportive male faculty members who are proactive and are willing to help make change happen. Dr. Mullins agrees with this sentiment. "I think slowly but surely things are getting better for everyone. I think there's more awareness about issues [that affect women]. An awareness that we need to think about," she says. For example, Dr. Mullins notes that there is more of an effort to make sure there are more women seminar speakers, since they serve as important role models for students and post-docs Dr. Mullins is also happy that the medical school is finally opening an on-site daycare center, which is something that she and other women senior faculty have been working for. Making the academic workplace more welcoming for mothers is an important step towards supporting women in science.

Dr. Mullins' and Dr. Anguera's experiences and outlooks for the future show that although women in science face extra hurdles, they can have successful careers as academic scientists. Dr. Mullins' advice to women is to be confident. "Don't be afraid. If you feel a little bit uncomfortable, it's okay. I think women have a lot to contribute, but sometimes their voices are not always heard, and we just have to get more comfortable with [speaking up]," she says. Dr. Anguera's advice is to work hard, be persistent, and not to get discouraged. "Nothing is easy, nothing is going to be given to you. When you get beaten down, which biology does, it makes it all that more rewarding when you do experience the highs of discovering stuff," she says. These words from role models like Dr. Mullins and Dr. Anguera help encourage women who are just beginning their careers doing what they love best - science.

Dr. Montserrat Anguera, Assistant Professor in the Department of Biomedical Sciences

[1]**National Science Foundation, National Center for Science and Engineering Statistics. 2017.** ***Women, Minorities, and Persons with Disabilities in Science and Engineering: 2017.*** **Special Report NSF 17-310. Arlington, VA. Available at www.nsf.gov/statistics/wmpd/.**

[2]**Moss-Racusin CM, Jovidio JF, Brescoll BL, Graham MJ, Handelsman J. Science faculty's subtle gender biases favor male students.** ***Proc Natl Acad Sci,*** **2012.**

Helen Davies: An infectious passion for teaching, 50 years and counting

Huanjia Zhang

Every Friday morning, Helen C. Davies, a 93-year-old Professor of Microbiology at University of Pennsylvania Perelman School of Medicine, sets off punctually at 7:45 a.m. to the infectious disease management meeting at the Hospital of the University of Pennsylvania. Helen, who insists people call her by her first name, can't remember how long she has been attending these meetings. "For a mighty long time," according to her.

As a lifelong educator, Helen has taught over 10,000 medical students for more than half a century. She has won the annual "Excellence in Teaching" award 16 times. Her portrait, which can be found in Johnson Pavilion, was done by Nelson Shanks—whose other commissions include Pope John Paul II, President Ronald Reagan, President Bill Clinton, and Princess Diana. Despite her innumerable contributions to the University, Helen has never stopped perfecting her teaching. Her infectious disease class, where she sings to students, has helped generations of medical students learn about pathogens in witty ways.

The daughter of a rabbi, Helen was born in Manhattan, New York, in 1925. After growing up in the Great Depression, Helen went to Brooklyn College, where she received her bachelor's degree in chemistry during World War II. She graduated college when she was 19, as the only female in her class. "I never had trouble finding dates back in college, since I was the only girl," she quipped. Helen received her master's degree in biochemistry from the University of Rochester in 1950, followed by her doctorate in physical biochemistry from the University of Pennsylvania in 1960, and has stayed at Penn ever since.

Her husband, Robert E. Davies, a biochemist, a Benjamin Franklin Professor, and University Professor at Penn's veterinary school, died in 1993 while mountain climbing in Scotland. Soon after her husband's death, Helen moved into the Quad, living with hundreds of freshmen. "I just love the students so much, I want to be part of them," Helen says.

Helen holding a picture of her from the 1960s.

Helen is the eldest and the first woman faculty master—the highest administrator on site—for Ware College House. She leads both the Women in Science and Infectious Disease programs. Her apartment, on the second floor of Ware College House, has two bedrooms and a big living room that Helen adores since "it can host as many students as possible when they come visit me."

Like most students in the building, Helen also has a roommate—Emilie

Anderson, who graduated from Penn in 2005. Before her graduation, Emilie came to Helen for advice—she was offered an incredible job opportunity, but it didn't pay well. Should she keep looking for other jobs, or take this precious opportunity? "Helen told me, 'Sweetheart, if this job is what you love to do, you should take it! Don't worry about the money. I have a spare bedroom in my apartment, and you can crash with me if that can relieve you of your financial burden,'" Emilie said. "And I never moved out—it's been 15 years."

Like Emilie, many others, especially women and other minorities in the Penn community and beyond, have also been infected by Helen's love. Robert Ross, one of the few black pre-med students on campus in the 1960s, persisted in medicine because of Helen's constant attention and encouragement. More than two decades later, Dr. Ross has served as the Philadelphia Health Commissioner and is now the CEO and President of the California Endowment, a major health foundation in California.

"To talk about Helen without mentioning her contribution to the women and minority communities is just diminishing," said Susan Weiss, who is also a Professor of Microbiology. "I mean think about it—she marched with Martin Luther King at Selma, during the Civil Rights Movement in the 60s." Before Dr. Weiss's arrival in the 1980s, Helen had been the only female faculty member in the Microbiology Department since its establishment in the 1970s.

Helen C. Davies, a 93-year-old Professor of Microbiology, working in her office at University of Pennsylvania Perelman School of Medicine.

Helen not only infects people with her passion for her career but also with her love of life. Just two years ago, at age 91, in her wheelchair, Helen went on a trip with Emilie traversing eight countries, from Southeast Asia to the Middle East, in 20 days. "Apparently, not only people who know Helen love her, the entire world loves her," Emilie laughed. "When we were in Burma, I was taking pictures… and I turned around, saw a group of Buddhist monks carrying Helen and her wheelchair all the way up to the top of the monument. And what's amazing was that they were communicating in languages that neither of them could understand."

Only until recent years did Helen start to ease her workload—meaning not leaving for work at 6:00 a.m. and returning home at 11:00 p.m. She now spends most of her day reading in her apartment—sometimes a book a day or sometimes an entire weekly Science Magazine subscription—with the company of "Alexa", who turns on the lights and plays music for her. When asked when she would retire, Helen smiled, "Never."

PCI - Penn Center for Innovation

Kanika Jain

With the constantly advancing technology landscape, it is now a necessity for researchers to evolve as well informed and trained technology architects. The Penn Center for Innovation (PCI) is Penn's one-stop-shop for commercialization. PCI brings traditional technology transfer, corporate contracts, new venture creation, and corporate alliance building together in a single matrix. To bolster their mission, the PCI Fellowship program was started by PCI in 2008. The program aims at equipping graduate students and post-doctoral fellows with technical knowledge and practical experiences in technology transfer. On the tenth anniversary of this program, the CAMB Student Newsletter commemorates the past years of successfully training the highly motivated research community at Penn by presenting a special interview with the director of the PCI fellowship program, Dr. Tomas Isakowitz.

What were the main objectives behind starting the PCI fellowship program back in 2008?

"The program was started to fulfill two major goals. It would provide a low risk, low time commitment opportunity for students and post docs to gain experience in technology transfer by working directly at the PCI office. Along with this, it would fulfill an important need for PCI by supporting its operations. The program is aimed at training students how to evaluate a technology for patentability, write patentability assessments, and create marketing assessments that would be used to find compatible industrial partners for developing the technology. More than one hundred applicants have been trained successfully by the program in the past ten years.''

What is the best route for technology development: to design an intervention, and then perform its market assessment, or to assess the existing needs in the market first and then design an intervention accordingly?

"Usually you have an idea or a product and you sense that it should work. People put a lot of emphasis on developing the product and ensuring that it'll work. But often this is counter-productive. The initial hypothesis is that there exists a problem or need that the intervention would address, but often, in reality that need isn't there, or it is different from what the inventors thought it was. Thus, assessing the market needs and validating your research outcomes from before can make a huge difference."

Can outsourcing for technology development and transfer from lab to marketplace be a getaway for the inventors who have minimal expertise with this process?

"The inventors often outsource the task of talking to the end users. However, the outsourcing end doesn't have the expertise to implement the changes suggested by the end users. It's crucial to have the involvement of the inventors, especially in the initial stages of technology development. Outsourcing doesn't help always."

Do you think there is a gap in the current scientific training system where the practical skill set to assess and translate research outcomes is often ignored? How can we address this gap?

"Many scientists are interested in impacting the therapeutics market, and the impact through their research is fantastic, but often the know-hows of how to make it commercially successful are missing. Scientists are trained in experiment design and statistics, but there isn't any emphasis on understanding what distinguishes one type of research outcome from another in terms of its impact on developing the product or services. It will thus be good to offer opportunities to students who are interested in technology transfer to develop their skills. This will also benefit the scientists that stay in research."

Do you see any new trends or shifts in terms of the projects assigned to the fellows?

"Now there is more work towards the marketing side. We have expanded the program from invention assessment and market assessment to marketing the technology and entrepreneurship. A new program called I-CORPS offers another track to the fellows that want to gain experience towards setting up startups."

Can you tell us a little more about this new program, I-CORPS?

"I-CORPS gives aspiring entrepreneurs an opportunity to setup their startup using National Science Foundation funds. They acquire skills and receive guidance to validate their business idea, clearly articulate what the value of their idea is in the marketplace, and talk to potential customers to understand the existing gaps that their intervention can bridge. Fellows from the PCI fellowship program are also allowed to work with these startups to gain a deeper understanding of what makes a potential idea successful."

What has been your biggest challenge in training the fellows in the past ten years?

"I would say the biggest challenge has been to satisfy the high demand from students and post-docs to participate in the program. The applicants are very qualified, and our program can only take in so many; about 8 to 10 a year are brought in as PCI Fellows."

How has the overall experience been for you?

"The experience has been very rewarding. It's a very congenial work environment and what really makes me happy is to see that our initiative has actually made a difference in people's lives. Most of the people that came through PCI fellowship program ended up joining careers related to product commercialization, tech transfer offices at universities, law firms doing IP law, research positions at industries, medical writing or consultancies.''

Do you have any last words of advice for current students?

"Make use of the opportunity offered by PCI as they can make a big difference when applying for jobs. Follow the patents published every week. Be open to experimenting new things in life. Your experiences are what differentiates you from others."

Dr. Tomas Isakowitz is an Adjunct Assistant Professor of Computer Science in the Translational Neuroscience Program at Penn. He is the Program Director for the PCI Fellowship and I-CORPS programs run by the Penn Center for Innovation at the University of Pennsylvania. He has also been a Visiting Lecturer in The Wharton School, Operations and Information Management Department. Prior to Penn, he was an Assistant Professor at the Information Systems Department at the New York University Stern School of Business.

Welcoming New-CAMB-ers:

A Faculty Profile on Melike Lakadamyali, Ph.D.

Hannah Kolev

Dr. Melike Lakadamyali joined the Penn community in early 2017 after moving her lab from the Institute of Photonic Sciences in Barcelona to the Perelman School of Medicine. She is an Assistant Professor in the Department of Physiology, with a joint appointment in the Department of Cell and Developmental Biology. Dr. Lakadamyali is affiliated both with the Biochemistry and Molecular Biophysics and the Cell and Molecular Biology graduate groups.

Melike Lakadamyali, Ph.D., Assistant Professor of Physiology

Dr. Lakadamyali completed her Ph.D. in physics at Harvard University with Dr. Xiaowei Zhuang, whose lab developed super-resolution STORM microscopy. For her thesis work, Dr. Lakadamyali developed live-cell imaging techniques that she applied to the study of viral infection. By tracking individual viral particles in real-time, Dr. Lakadamyali captured the endocytic processing of the influenza virus and identified significant heterogeneity within the viral population. More specifically, she found that one viral population initiates *de novo* formation of clathrin-coated pits at the site of host cell entry, while a second viral population uses a clathrin-independent mechanism to infect cells. For Dr. Lakadamyali, this discovery highlighted the power of imaging systems to identify biological heterogeneity and visualize cellular dynamics with high temporal resolution.

Excited by her initial imaging work, Dr. Lakadamyali stayed at Harvard University to complete her postdoctoral fellowship in Dr. Jeff Lichtman's lab. Here, she applied her microscopy skills to address new biological questions, this time focusing on neural circuits in the mammalian brain. Utilizing the Brainbow mouse model, which genetically color codes individual neurons, Dr. Lakadamyali used STORM to trace neurons and neural connections. The high spatial resolution afforded by STORM captured complex neuronal wiring patterns, demonstrating the importance of imaging advancements in driving our understanding of fundamental biological systems.

Inspired to continue her development of new fluorescent imaging techniques, Dr. Lakadamyali started her own lab at the Institute of Photonic Sciences in Barcelona, Spain. While this technical environment provided a great opportunity for Dr. Lakadamyali to build new technologies, her curiosity for fundamental biological questions led her to seek new multi-disciplinary collaborations at Penn.

Since moving her lab to Penn in 2017, Dr. Lakadamyali's research has focused on understanding the mechanisms and regulation of intracellular trafficking. Using real-time imaging coupled with super-resolution STORM, Dr. Lakadamyali seeks to understand how motor proteins navigate the complex three-dimensional microtubule network. In an exciting new direction, Dr. Lakadamyali is also using STORM to assess nucleosomal compaction and higher-order chromatin folding, with an overall aim to understand how chromatin structure regulates gene activity.

As a successful woman in science, Dr. Lakadamyali is a source of inspiration for those of us starting our science careers in CAMB. Dr. Lakadamyali cites her strong female role models, such as her Ph.D. advisor Dr. Zhuang, as influential sources of support and guidance throughout her career. Dr. Lakadamyali explains that from Dr. Zhuang, she learned how to navigate traditionally male dominated fields and how to have her voice heard. She acknowledges that women can often face unique challenges in academia, especially given the demanding nature of science careers, but encourages students that may have self-doubts to "believe in yourselves and recognize that you are as good as any other peer that you have." And for all students, Dr. Lakadamyali understands that "a lot of difficult phases during a Ph.D. can be discouraging, but persistence and perseverance can help navigate these difficult times."

For more information on Dr. Lakadamyali and her lab, please visit her faculty profile (https://www.med.upenn.edu/physiol/faculty_lakadamyali) or follow her on twitter (@Melike_Lak). Dr. Lakadamyali is currently accepting new rotation students. For inquiries into potential rotation projects, please contact Dr. Lakadamyali directly (melikel@pennmedicine.upenn.edu).