

Office of Education  
Division of Intramural Research

# Fellows Newsletter

November 2013

The Fellows Newsletter is published monthly by the Office of Education, Division of Intramural Research, National Heart, Lung, and Blood Institute and distributed to NHLBI DIR members to promote the interest of DIR Fellows.

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## From the Director of the Office of Education

We hope all of you are recovered from the shutdown. I know that my lab is still not yet recovered from the lapse in animal breeding, but otherwise we have survived.

This month, our correspondent Kevin Ramkissoon continues our feature of interviews with NHLBI DIR PIs and Postdocs about themselves, their research and their activities, with an interview with PI Keji Zhou and postdoc Jue Chen. Let us know if you would like to be interviewed and/or if you think your PI would make a good subject for a feature.

One major issue that is getting a lot of attention these days is the fact that many experimental results can't be repeated. This situation affects both individuals and the scientific enterprise in general, and my column this month addresses this problem and offers some suggestions for solutions.

Finally, if you missed our Halloween Dessert party, we bring you some images of the winning confections. Hopefully, this will whet your appetite for our next party to celebrate the December holidays.

## NHLBI DIR Holiday Potluck



Wednesday, December 11th  
3:00- 4:00 PM  
Building 10CRC, Room 5-2550

Please bring something to share.  
A prize will be given to the top voted dish.

## Meet the New Fellows



**Allison Zajac, Ph.D.**, is a new IRTA Fellow in the Cell Biology and Physiology Center under Dr. Nasser Rusan. Dr.

Zajac received her Ph.D. in Cell and Molecular Biology from the University of Pennsylvania. Her initial project at the NIH will involve imaging the dynamics of centrosomal proteins in drosophila aimed at understanding how the centrosome is organized at different stages of the cell cycle.



**Martin Lang, Ph.D.**, is a new Visiting Fellow in the Center for Molecular Medicine under Dr. Hong Xu. Dr. Lang

earned his Ph.D. in Human Genetics at the Università di Torino. His initial project at NIH is finding a way to perform a targeted mutagenesis of the mitochondrial genome.



**Vanessa Leone Alvarez, Ph.D.**, is a new Visiting Fellow in the Theoretical Molecular Biophysics section under Dr. Jose

Faraldo-Gomex. Dr. Alvarez received her Ph.D. in Structural and Functional Genomics. Her initial project at the NIH is focused in the rotary membrane ATP synthases, the enzymes responsible of ATP production in cells.

**Yap TL, Gruschus JM, Velayati A, Sidransky E, Lee JC (2013) Saposin C Protects Glucocerebrosidase against alpha-Synuclein Inhibition. Biochemistry 52:7161-7163.**

The presynaptic protein  $\alpha$ -synuclein ( $\alpha$ -syn), particularly in its amyloid form, is widely recognized for its involvement in Parkinson disease (PD). Recent genetic studies reveal that mutations in the gene GBA are the most widespread genetic risk factor for PD identified to date. GBA encodes for glucocerebrosidase (GCase), the enzyme deficient in the lysosomal storage disorder, Gaucher disease (GD). GD causes fat accumulation in the liver and spleen and the organs subsequently become enlarged. In PD, it is believed that this presence of large amounts of fats might lead to  $\alpha$ -synuclein build-up, and also, to the progressive cell death in the brain that is common to Parkinson's. People who carry mutations in one copy may have up to five times the normal risk of developing PD. However, the role of this gene in the development of PD remains unknown. Because of the wide phenotypic heterogeneity associated with PD, much work has gone into identifying disease modifiers that can alter the Gaucher phenotype. One promising candidate is saposin C, an important cofactor in the degradation of glucosylceramide (GluCer) by GBA. In humans, saposin C deficiency results in a Gaucher-like phenotype, despite normal in vitro GBA activity. Saposin C deficiency has also been shown to modify phenotype in one mouse model of Gaucher disease.

In the study by Yap et al. the authors set out to understand the molecular pathways that modulate GCase activity and  $\alpha$ -syn-GCase interactions in vitro. They used a range of biophysical techniques, including nuclear magnetic resonance spectroscopy, site-specific fluorescence, and Förster energy transfer to show that

Sap C interacts with GBA and displaces  $\alpha$ -syn. They present convincing work uncovering a direct role of saposin C as an activator required for normal GBA function and as a potential modifying factor in patients with GD. This interaction suggests that Sap C might play an important role in GD-related PD. Previous research published from the lab uncovered that  $\alpha$ -syn (under acidic conditions) physically interacts with lysosomes, a site of  $\alpha$ -syn degradation. Consistent with these results, Yan et al. showed that the GCase activity was significantly inhibited ( $IC_{50} \sim 0.4 \mu M$ ) in the presence of  $\alpha$ -syn. However, this inhibition is completely abolished in the presence of small amounts of Sap C. Rescue experiments established that at high  $\alpha$ -syn concentrations ( $\sim 10 \mu M$ ), this inhibition of GCase activity can be alleviated with increasing concentration of Sap C. Since it has been proposed that Sap C might directly bind to GBA, the researchers used NMR spectroscopy to confirm a possible interaction. First, they monitored the molecular tumbling associated with  $\alpha$ -syn in the presence and absence of the GCase and found that the isotopically labeled  $\alpha$ -syn showed significantly reduced tumbling (or dynamics) at the C-terminus, which was identified as the site of interaction of  $\alpha$ -syn with the GCase. Next, they directly monitored the dynamics of Sap C and found that this protein undergoes a much slower tumbling upon interaction with the GCase, suggesting a direct interaction between the two proteins.

In separate biochemical studies, Yap et al. used site-specific fluorescence spectroscopy to study the  $\alpha$ -syn-GCase interaction in both so- [Cont'd on next page](#)

**2013 NIH Research Festival  
November 6-8  
Building 10**

**More information can be found at:**  
<http://researchfestival.nih.gov/2013/schedule.shtml>  
<http://researchfestival.nih.gov/2013/posters.cgi>

## Recent Publications by NHLBI Fellows

**Billington N**, Wang A, **Mao J**, Adelstein RS, Sellers JR (2013) Characterization of three full-length human nonmuscle myosin II paralogs. *J Biol Chem*.

**Cherkasova E**, **Weisman Q**, Childs RW (2013) Endogenous Retroviruses as Targets for Antitumor Immunity in Renal Cell Cancer and Other Tumors. *Front Oncol* 3:243.:243.

Chuang ML, **Leslie RW**, Massaro JM, Manders ES, Fox CS, Hoffmann U, O'Donnell CJ (2013) Distribution of abdominal aortic calcium by computed tomography: impact of analysis method on quantitative calcium score. *Acad Radiol* 20:1422-1428.

**Jiang Z**, de MM, Lee JC (2013) Membrane Remodeling by alpha-Synuclein and Effects on Amyloid Formation. *J Am Chem Soc*.

**Kidder BL**, Hu G, Yu ZX, Liu C, Zhao K (2013) Extended self-renewal and accelerated reprogramming in the absence of Kdm5b. *Mol Cell Biol*.

**Lerit DA**, Rusan NM (2013) PLP inhibits the activity of interphase centrosomes to ensure their proper segregation in stem cells. *J Cell Biol* 202:1013-1022.

**Li H**, Rodriguez-Canales J, Liu W, Zhu J, Hanson JC, Pack S, Zhuang Z, Emmert-Buck MR, Rodgers GP

(2013) Deletion of the olfactomedin 4 gene is associated with progression of human prostate cancer. *Am J Pathol* 183:1329-1338.

**Nguyen TT**, Wong RP, **Menazza S**, Sun J, **Chen Y**, **Wang G**, Gucek M, Steenbergen C, Sack MN, Murphy E (2013) Cyclophilin D Modulates the Mitochondrial Acetylome. *Circ Res*.

Olszewski MB, **Chandris P**, **Park BC**, Eisenberg E, Greene LE (2013) Disruption of clathrin-mediated trafficking causes centrosome overduplication and senescence. *Traffic*10.

Pophali PA, Klotz JK, Ito S, Jain NA, Koklanaris E, **Le RQ**, Hourigan CS, Savani BN, Chawla K, Shanbhag S, Barrett AJ, Battiwalla M (2013) Male Survivors of Allogeneic Hematopoietic Stem Cell Transplantation Have a Long Term Persisting Risk of Cardiovascular Events. *Exp Hematol*10.

**Yap TL**, Gruschus JM, Velayati A, Sidransky E, Lee JC (2013) Saposin C Protects Glucocerebrosidase against alpha-Synuclein Inhibition. *Biochemistry* 52:7161-7163.

**Zhuang J**, Wang PY, Huang X, Chen X, Kang JG, Hwang PM (2013) Mitochondrial disulfide relay mediates translocation of p53 and partitions its subcellular activity. *Proc Natl Acad Sci U S A* 110:17356-17361.

## Meet the New Fellows



**Todd Schoborg, Ph.D.**, is a new IRTA Fellow in the Cell Biology and Physiology Center under Dr. Nasser Rusan.

Dr. Schoborg received his Ph.D. in Biochemistry from the University of Tennessee. His initial project at the NIH will be developing techniques to quantitatively analyze chromatin structure of promoters of key cell cycle regulators in *Drosophila*; role of calmodulin (CaM) and abnormal spindle (asp) in mitotic spindle function.



**Michael Brenner, Ph.D.**, is a new IRTA fellow in the Biochemistry and Biophysics Center under Dr. Jay

Knutson. Dr. Brenner earned his Ph.D. in Chemistry at the University of Illinois. His initial project at NIH is on STED probe development.

### Beat, continued

lution and in the presence of vesicles. Consistent with the NMR data, the authors found in either case, that addition of Sap C to  $\alpha$ -syn-GCase complex results in decrease in fluorescence intensities and a spectral "red-shift" from  $\alpha$ -syn, suggesting a that Sap C does disrupt the interactions between  $\alpha$ -syn-GCase. To further characterize the dissociation of  $\alpha$ -syn from GCase induced by Sap C, the authors performed Förster energy using intrinsic tryptophan residues in GCase as donors and danyl- $\alpha$ -syn as the acceptor. Similar to results from the NMR and fluorescence spectroscopy experiments, the additions of Sap C reduced the efficiency of energy transfer as a result of  $\alpha$ -syn displacement.

In summary, Sap C protects GCase from  $\alpha$ -syn inhibition and competes with  $\alpha$ -syn binding. The results from Yap et al. taken together with the reported inverse correlation between GCase and  $\alpha$ -syn levels derived from tissue culture, animal models, and patients, Sap C could act as a modifier in the homeostasis of  $\alpha$ -syn. Further investigation is clearly needed to determine if and to what extent Sap C and/or the interplay among Sap C,  $\alpha$ -syn, and GCase is involved in PD. Resolution of these different viewpoints will require quantification of the physiological concentrations of  $\alpha$ -syn, Sap C, and GCase in lysosomes from brain samples of patients with GBA1 mutations as well as PD, GD, and healthy individuals.



**Wenli Du, Ph.D.**, is a new Research Fellow in the Cell Biology and Physiology Center under Dr. Nihal Altan-Bonnet.

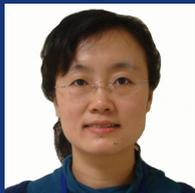
Dr. Du received her Ph.D. in Animal Nutrition from Zhejiang University. Her initial project at the NIH will be related to human disease.

### Meet the New Fellows



**Yanzhu Lin, Ph.D.**, is a new Visiting Fellow in the Systems Biology Center under Dr. Susan Harbison. Dr. Lin received her

Ph.D. in Statistics from Purdue University. Her initial project at the NIH includes data analysis for RNS-Seq data and genome-wide association study of flies sleep data.



**Zhen Yu** is a new Pre-Doctoral IRTA in the Center for Molecular Medicine under Dr. Manfred Boehm. Zhen is a PhD student at the Peking Union of Medical College, Beijing. Her initial project at NIH is on Adenosine deaminase contributing to the degradation of extracellular adenosine.



**Aaron Fullerton, Ph.D.**, is a new IRTA Fellow in the Immunology Center under Dr. Lance Pohl. Dr. Fullerton received

his Ph.D. in Pharmacology and Toxicology from Michigan State University. His initial project at the NIH is assessing the role of the innate and adaptive immune response in the pathology of drug-induced liver injury.

Postdoc Kevin Ramkissoon interviews Dr. Keji Zhao, Senior Investigator of the Laboratory of Epigenome Biology

**Kevin Ramkissoon (KR): When did you decide that you wanted to become a scientist?**

Keji Zhao (KZ): I wanted to become a scientist when I was in college.

**KR: As a young scientist you studied, trained and worked in China, Switzerland and the United States (others?). What did you enjoy about the research environment or culture of the places you have been?**

KZ: I started my research work in organic chemistry in China when I got into graduate school. Although the research then was “primitive” as compared to the leading edge research work in other countries, I enjoyed the environment that encouraged me to use my imagination and the a society that still held a high respect on for science and scientists.

While I did my Ph.D. studies in Switzerland, I really enjoyed both the research and cultural environments. In terms of research, I did my thesis work in the laboratory of Dr. Ulrich Laemmli who is well known for having invented the SDS-PAGE technique and being a pioneer in of chromatin researcher. Thus I benefited a lot by pursuing important questions in the field of chromatin studies.

When I did my postdoctoral re-

search in the laboratory of Dr. Gerald Crabtree, I fully enjoyed the freedom of imagination and thinking, and the spirit of collaboration, from which I have been benefiting till this day.

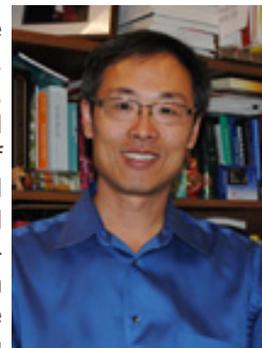
Regarding the cultural environment, I enjoyed the close relationship with family members and friends in China and all kinds of delicious foods. In Switzerland, I enjoyed the beautiful landscapes, quiet and well guided hiking paths in the nearby mountains, convenient skiing resorts and peaceful life. In the US, I enjoyed the diverse diversified cultures and all kinds of foods.

**KR: How would you compare or contrast the training and expectations of fellows in these countries?**

KZ: Cultural differences have major impacts on the training of junior scientists from different countries. For example, some tend to follow their supervisor’s instructions and strive to complete supervisor-assigned projects/tasks, while others tend to think more independently.

**KR: You have been with the NHLBI for over 10 years. How has the your research landscape changed in that time?**

KZ: Yes, my research [Cont'd on page 6](#)



#### Dr. Keji Zhao, Bio in Brief

Keji Zhao, Ph.D., received his undergraduate and M.S. degrees in China before completing his Ph.D. at the University of Geneva, Switzerland. At Stanford University he was a Damon Runyon-Walter Winchel Cancer Research postdoctoral fellow. Dr. Zhao joined the NHLBI in 1999 and was appointed as Senior Investigator in 2007. He is currently the Director of the Systems Biology Center. Dr. Zhao is a recipient of multiple NIH Merit Awards including the 2011 NIH Director’s Award in recognition of innovative contributions that have provided novel insights into epigenetic control of gene expression. A key aspect of his ongoing research has been the development and application of computational strategies and sequencing-based methods, such as ChIP-Seq, which combines chromatin immunoprecipitation (ChIP) with Next Generation Sequencing, towards studying epigenetic mechanisms of development and differentiation across the mammalian genome.

## Q&A with Postdoc Jue Chen



Postdoc Kevin Ramkisson interviews Dr. Jue Chen, Postdoctoral Fellow in the Biochemistry and Biophysics Center

**Kevin Ramkisson (KR): What factors were most important in your decision to come to the NIH?**

Jue Chen (JC): The first important factor was the research resources available at the NIH. Not only are there advanced equipment and well-staffed core facilities, there are also world-renowned investigators on campus within reach for collaboration. The second important factor was the support for postdoc fellow career development. The NHLBI's Office of Education (OE) and the NIH's Office of Intramural Training and Education (OITE) offers various workshops, seminars, classes, and career consulting services to help postdocs move forward in their career. I first learned about these opportunities during the NIH National Graduate Student Research Conference and by talking to people I know at the NIH.

**KR: What do you enjoy most about the research environment here?**

JC: Like I said in the first question, I particularly enjoyed being here for the great research resources available on campus. There are so many labs on the NIH campus and you're more likely to find the equipment and the person who knows how to operate the equipment here than elsewhere. I love the Fellows list and have borrowed reagents and asked for help in troubleshooting from other fellows at NIH. I think it's a great way of sharing resources and expertise. I have also received help from investigators by just dropping an email and asking questions.

**KR: In addition to research, have you participated in additional professional/career building activities during your time at NIH? Were these experiences beneficial and would you recommend them to other fellows?**

JC: I have participated in organizing the annual NIH career Career Symposium for the past two years. It was a good opportunity to learn about different career paths and get to know other fellows. I have also joined Felcom and recently became one of the two FAES liaisons this year. This has allowed me to meet FAES staff and relay fellows' needs to FAES. I've also recently joined the NHLBI Fellows Advisory Committee and have become more engaged in NHLBI fellows' activities and events. In addition to that, I have attended several OE and OITE sponsored workshops and seminars, such as the teaching for science class and writing class, various career exploration workshops, and work dynamics workshops. These workshops have helped me understand myself better and know what I want to do in the future as a career. I'm less confused about career choices than before. I've also taken some FAES courses to strengthen my knowledge in relevant fields.

**KR: What advice would you give to a first year fellow just entering the NHLBI training program?**

JC: I am still one of the many struggling postdoc fellows trying to figure out what the next step in my next career will be. I am not sure if I am in the position of giving out advice but I will share what has been helpful for me personally with new fellows. In addition to my research in the lab, for my first year, getting involved in some activities outside the lab has given me different perspectives and a chance to network and meet more colleagues and friends. Communicating with my mentor about my career goals has been important towards getting their support and has helped me to make plans for my future.

## Meet the New Fellows



**Claudio Anselmi, Ph.D.**, is a new Research Fellow in the Biochemistry and Biophysics Center under Dr. Jose Faraldo-

Gomez. Dr. Anselmi earned his Ph.D. in Chemical Sciences at the University "La Sapienza". His initial project at the NIH is about AcrB, a H<sup>+</sup>-coupled antiporter conferring E. coli with multidrug resistance aiming to study the mechanism of proton coupling of the transporter.



**Jennifer Boylston, Ph.D.**, is a new IRTA Fellow in the Systems Biology Center under Dr. Tish Murphy. Dr. Boylston received her

Ph.D. in Molecular and Cellular Biology. Her initial project at the NIH is to analyze the effect acetylation has on a protein component of the mitochondrial pyruvate carrier, MPC2.



**Fabrizio Marinelli, Ph.D.**, is a new Visiting Fellow in the Theoretical Molecular Biophysics section under Dr. Jose

Faraldo-Gomez. Dr. Marinelli received his Ph.D. in Statistical and Biological Physics from the International School of Advanced Studies. His initial project at the NIH is the study of molecular mechanisms for ion binding and inward-to-outward conformational change in the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger; a prominent transporter involved in Ca<sup>2+</sup> signaling.

# THE NHLBI DIR HALLOWEEN DESSERT POTLUCK

## Meet the New Fellows



**Sofiya Shevchenko** is a new Postbaccalaureate IRTA in the Hematology Branch under Dr. Neal Young. Sofiya is a recent graduate of University of Toronto where she received her Bachelor of Science in Molecular Genetics and Microbiology.



**Christina Chen** is a new Postbaccalaureate IRTA in the Hematology branch under Dr. Neal Young. Christina is a recent graduate of the University of Chicago where she received her Bachelor of Science in Biological Studies.



**Whitney Thompson** is a new Pre-doctoral Fellow in the Systems Biology Center under Dr. Robert Balaban. Whitney is currently in the Oxford Cambridge Graduate Partnerships Program.

*Correction: The October newsletter featured the photo of Michael Brenner in Martin Lang's bio. The correct pictures and bios are featured in this issue.*

Thanks to everyone who participated in making the NHLBI DIR Halloween Potluck a success. It was a tough choice for voters but Dr. Javier Traba Dominguez took the prize for favorite dessert: chocolate banana cake (featured in photo on right).



## Q&A with PI, continued

landscape indeed has changed during the last 14 years, from studying single genes to a more systems approach.

**KR: Do you feel that your approach to training and mentoring fellows has evolved during the same period?**

KZ: I was more hands-on, (including working on at the bench myself) during the first few years of my time at NHLBI. My fellows initially worked on projects that I suggested to them, but nowadays, they are encouraged to develop their own projects. Although I give advice to them, they need to come up with solutions to specific problems with their projects because they are usually better than I am on their specific projects. With the systems approaches used for most of our projects, I strongly encourage collaboration between experimental and computational fellows in the lab. This kind of collaboration has proved to be productive.

**KR: What piece(s) of advice would you give to NHLBI fellows pursuing a career in biomedical research?**

KZ: My advice includes: (1) develop a well thought plan ahead of time, no matter if it is a plan for a specific experiment or a long-term plan for your postdoctoral training; (2) spend the necessary time and try your best to execute your plan; (3) be open minded to suggestions, and (4) be rigorous with your data.

**KR: You have had a very successful career as a scientist. What characteristics of your personality would you say have been most influential to your success?**

KZ: I think I benefited from having an open mind, being open minded to others' suggestions and from daring to try new things.

**KR: Had you not chosen your current path, what career do you think you be in today?**

KZ: A college professor

**KR: What hobbies or activities do you enjoy away from the lab?**

KZ: I enjoy spending time with my family and practicing Tai Chi.

## Featured Article

### Should All Scientific Results be Reproducible?

By Herbert M. Geller

If I took a survey of NHLBI researchers, my guess is that 100% would answer in the affirmative - of course our results should be reproducible. However, I have another hunch that very few of our published results have been independently confirmed. It's hard to measure the actual cost to science of this situation, but it's clearly significant in many different contexts.

The first cost is in the perception of science. While the major scandals of scientific misconduct have revolved around deliberate alteration of experimental results, the trust in science is eroded when the public reads articles saying that a high proportion of published studies cannot be replicated. For example, there has been much recent press about the large number of studies that fail to replicate the efficacy of cancer drugs Begley CG, Ellis LM.C. Drug development: Raise standards for preclinical cancer research. Nature. 2012 483:531-3| cancer research.

The second cost is in wasted personnel time sometimes leading to loss of careers. Fellows have arrived in my office nearly in tears describing the major arguments in their labs that follow an inability to replicate published results. The argument generally centers around the lack of technical prowess of the fellow, with the PI refusing to accept the fact that not everything that is published is true.

Even if the ultimate conclusion that the original study was not correct, trying to correct the literature is often an enormous but thankless task, because editors and reviewers are not eager to publish negative results, and even more wary of antagonizing the original authors. An example of such a conflict was recently reported on the Discover web site (<http://blogs.discovermagazine.com/notrocketscience/2012/03/10/failed-replication-bargh-psychology-study-doyen/>), where the original author of a large psychology study attacked the paper that refuted his study. I have

called such events as following the Gresham's Law of Science — 'Bad science drives out good science' – analogous to the economic Gresham's law "Bad money drives out good money".

Another cost of negative results to the system is what we call 'Publication Bias' – the desire to only publish positive results. Because we endeavor to do high-risk science, there will be many experiments that do not yield the expected result. While some of these, if they were well-designed, lead to other fruitful directions, even if they did not the results should also be informative to others who might follow the same blind alley. The longer you are in science, you will find that you have more and more conversations that end up "Oh, yes, our lab tried that a while ago and we got the same result you did, but it wasn't worth publishing".

So what's to be done? Some labs actually take the time to have independent verification within the lab of any major result. This also has its cost, since the person doing the verifying is often not the first author of the paper. The NINDS actually paid some labs to attempt to reproduce the most significant published findings in experimental spinal cord injury. Only 2 of 12 were totally replicated (Steward O, Popovich PG, Dietrich WD, Kleitman N. Replication and reproducibility in spinal cord injury research. Exp Neurol. 2012 233:597-605). Another way is to use a new service called the Reproducibility Initiative, where, for a fee, you can have your experiment conducted independently and get the report of the results in confidence. This Initiative recently received \$1.3 million to reproduce certain cancer studies (<https://www.scienceexchange.com/reproducibility>). Or if you are lucky, as we recently were, another lab gets the same result using a different approach, so you can both publish.

Overall, trust in published results is very high, likely too high. I am always mindful of a statement which has lost its original source "You trust your mother, but you cut the cards", which suggests that we should be aware of both our own failings and those of the literature.

## Meet the New Fellows



**Marianita Santana** is a new Pre-Doctoral Fellow in the Cell Biology and Physiology Center under Dr. Nihal Altan-

Bonnet. Marianita is currently working on her Ph.D. at Rutgers University with expected graduation in Fall 2015.



**Jamie Solis** is a new Pre-Doctoral Fellow in the Cell Biology and Physiology Center under Dr. James Sellers. Jamie

is currently in the Oxford Cambridge Graduate Partnerships Program.



**Ying-Han Chen** is a new Pre-Doctoral Fellow in the Cell Biology and Physiology Center under Dr. Nihal Altan-

Bonnet. Ying-Han is currently pursuing a Ph.D. from Rutgers University.

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