Biography

Yulong Li grew up in Fujian, China. He studied biophysics and physiology as an undergraduate student at Peking University. During his PhD training, he focused on the fundamental mechanisms of neuronal communication under the guidance of George Augustine at Duke University. He then moved all the way to the west coast and conducted his postdoctoral research in Richard Tsien's lab at Stanford University, where he developed a genetically encoded indicator called pHTomato. Yulong started his own lab at Peking University at the end of 2012. His research interests have been focused on developing advanced biophotonic sensors to understand the communication between neurons. His group has developed a series of novel genetically encoded fluorescent sensors, so-called GRAB (GPCR activation-based) sensors, for real-time detection of neurotransmitters and neuromodulators, such as ACh, DA, and NE, *in vivo*. His group also developed the first entirely genetically encoded optogenetic method PARIS (pairing actuators and receivers to optically isolate gap junctions) for functionally mapping gap junctions. Besides tool development, his group is also interested in illuminating the functions of GPCRs. His was one of the groups that independently deorphanized primate-specific Mas-related GPCR member X4 (MRGPRX4) with its native substrate bile acids and identified its physiological function in mediating cholestatic itch. Yulong teaches neurobiology to undergraduate and graduate students and guides the Undergraduate Research Honors Program in Biology (UHRB) program at Peking University.

In your view, what are the most pressing questions in neuroscience?

I would say the most pressing question is still what are the functions of different neurons and neural circuits. Because of the complexity of the brain, we still have relatively limited ideas of what kinds of neurons play what roles in the behaving animals, especially in humans. There are a great variety of different cell types intermingling with each other even in a very tiny brain region. To make things worse, the same types of neurons might have different functions depending on behavioral states. Given this complexity of the brain, we know very little about the physiological functions and regulatory mechanisms of these neurons. Neuroscientists have been trying to use model animals to investigate the basics of neuronal activity under both normal and disease conditions. For example, neurologists interested in neurodegenerative diseases, such as Parkinson's disease (PD), have been using MPTP-induced PD model mice to study mechanisms of, as well as therapies for, PD. But most of the time, it is hard to find a suitable animal model, and it is still challenging to provide therapeutic means for neurological disorders or diseases.

Where do you see the strongest potential for progress and new breakthroughs in neuroscience?

I think to generally study or untangle the nervous system, we need to have precise ways to control or perturb distinct cells, including neurons and glia cells. And we also want to have ways to read out precise information of cell-cell communication or activities within the cells. We have had a lot of advances over the past few years. For example, optogenetics and chemogenetics have allowed us to control selective groups of cells, like different neurons. Now we also have ways to visualize neuronal activities, mainly from calcium imaging. So, I think the next steps will be to have more great tools to visualize the activity of neurons, especially the chemical communication and dynamics of neuromodulators. I also want to mention that the most current tools can only be applied to model organisms, but not humans. A big breakthrough, in my view, will be made in developing techniques to perform manipulation, visualization, and detection of neurochemical dynamics in the human brain with good precision, chemical selectivity, and non-invasiveness. I think that will help to bridge the gap between fundamental research and human biology, providing ways to understand how humans think and control, at the same time laying the foundation for therapeutic purposes.

With the robust GRAB sensor collection, what new directions are you going to explore next? Do you have any scientific questions that most interest you?

In terms of GRAB sensors to detect neuromodulators, we and others have demonstrated that a number of modulators' sensors, such as dopamine and acetylcholine, can be very sensitive. So, one clear path we are going to take is to enlarge the repertoire of the probes—for using these probes to detect peptides and lipids. And we can even evolve novel designed scaffold to detect any kind of neurochemical or extracellular chemical of interest. For example, D-serine is a known important modulator for sleep and other physiological processes. To my knowledge, there is no such D-serine activator or GPCR. But through rational design and directed evolution, we might find a scaffold sensitive to D-serine and develop turn-on sensors based on such scaffold.

Another future direction for my group is to expand the fluorescence approach into other dimensions. For example, MRI or other approaches can look deep into the brain non-invasively and provide a holographic view or bird's-eye view of the whole brain so that we can map these modulators. But critical contrast agents are still not available.

So, by using multi-module modalities, for example, combining fluorescence, MRI, and PET, we could provide a better understanding of the brain in terms of both the spatial and temporal domains. And, finally, developing or expanding tools to study the human brain's regulation would be challenging but is critical. The simple application of genetically encodable materials would not be suitable for human brain analysis. There should be new strategies designed to suit the purpose of human studies.

Besides tool making, we are equally interested in using our new tools to study the regulation of neuromodulators in release and recycle and in unveiling their precise roles and regulatory mechanisms in physiology and disease.

Artificial intelligence is playing a more important role in neuroscience research. What revolution do you expect it to bring to this field? How can neuroscientists take advantage of artificial intelligence?

I think there are a number of places that artificial intelligence or deep learning can help. For example, it can help to promote progress in connectomics by analyzing data from electron microscopy, which provides huge datasets to reconstruct every connection in the brain. In this way, artificial intelligence can help to save human labor. The recent breakthrough in Alpha-fold is also a good example. Alpha-fold helps to predict protein structure, including proteins functioning in nervous systems. It promotes further advancements, helping to understand protein-protein interaction, dynamics of protein-conformational changes, protein-ligand interaction, protein-RNA interaction, protein-DNA interaction, and so on. It would help to deepen our understanding of the fundamentals of biology and neurobiology. And we already have tools represented by the neuro-pixel electrodes that facilitate large-scale recording and provide large datasets. So, based on these large datasets with more precise information, artificial intelligence might provide ways for us to search the grammar, or the algorithm of neuronal interaction and communication, and how they guide behaviors.

What do you think are the biggest possibilities or challenges for the education of future neuroscientists?

I think one of the most major challenges and opportunities is to educate next-generation leaders with interdisciplinary backgrounds. Neuroscience requires a joint venture of using math, physics, chemistry, biology, and psychology. Although we have defined disciplines to separate neuroscience into different small branches, true understanding of the brain or neural systems requires integration. To make the biggest breakthrough, one often must rely on interdisciplinary approaches. For example, using cutting-edge optical methods to monitor neuronal activities requires the best microscope from physicists, the most sensitive probes from chemists, powerful genetic techniques from molecular geneticists, and unique approaches and thoughts from the psychologists. So, the next-generation leaders need to utilize multi-disciplinary approaches to make big new discoveries. It is important that education with some knowledge of fundamental neurobiology, as well as from other related fields, is provided, which is challenging for educators from different majors. But this is also a great opportunity, as many important questions requiring interdisciplinary approaches, such as mechanisms for emotion, addiction, and neurological diseases, are waiting to be solved.

Part of students' training typically involves giving oral presentations at conferences. Do you think students have had less opportunity to develop their oral presentation skills because of the pandemic? How are you helping your lab members on this part of their training?

I do think that students not being able to attend conference in person is hindering their communication skills and lowering the opportunities to present their work and exchange ideas with their fellow students or colleagues throughout the world. It is true that there are good virtual conferences and presentations that people are attending. But, personally, I feel that during virtual meetings, the multisensory inputs are not exciting enough, or people are distracted, and I noticed people do get fatigued attending online conferences and giving presentations without real-time feedback or eye contact, which makes the intellectual exchanges less fun.

For my own group, thanks to the good control of the pandemic in Beijing, we now have relatively regular group meetings. We can also attend some domestic meetings. We take every single opportunity to host international visitors and encourage the students to give posters and oral presentations whenever it is possible.

In what other ways do you think COVID-19 has changed your life?

My family was in Los Angeles when COVID hit the world, and we were all horrified by the unprecedented pandemic. It took us great efforts to gather medical masks before we returned to Beijing. And even now, the pandemic is still not well controlled world-wide. My wife and I received many invitations to give talks at international conferences and intermingle with colleagues, and all these on-site scientific communications became impossible under the pandemic. Not to mention that our labs were essentially locked down for approximately 8 months last year. We would never imagine COVID-

19 would lead to so many unpredictable changes to the whole world.

How do you manage work-life balance?

Both my wife, Yan Song, and I are scientists, and we have an 8-year-old son in elementary school. To manage work-life balance, what we do is to plan ahead and coordinate well so that we both get to manage our labs and spend quality time with our kid. On the occasions when we are both super busy with out-of-town meetings, we seek some help from our parents for babysitting. In terms of COVID-19, it, indeed, made things a lot more challenging. Fortunately, our university is very supportive. We can hold online meetings to communicate with lab members and colleagues and to establish and maintain international collaborations.

How do you think the pandemic has affected experimental research and the publication process, considering many labs have had to shut down?

Other than research related to the pandemic, I don't think the peer review and publication process has changed much. Now the problem is that many scientists are not able to perform experiments in the lab. Instead, they are trapped or distracted by things like family issues, which is becoming a heavier responsibility under the pandemic. And indeed, some labs are even forced to be shut down. But I don't think the journals have lowered their standard bar. Personally, I think that some experiments required by the journals are not all necessary to get the work completed. Sometimes they become an extra burden, especially at such time when lab work is hard for most scientists. So it might be something that the journals need to consider.

How can we build equity for scientists from underrepresented populations? In your view, what specific policies or steps should be implemented? Or what has been done in this regard at your institution?

It is a known fact that there is gender imbalance in science. For the field of life sciences in China, there are still far fewer female scientists than male scientists. Therefore, I think special attention needs to be paid in terms of job promotion and grant application for female scientists, who traditionally bear a much greater proportion of household and childcare responsibilities. Fortunately, there have already been some encouraging steps; for example, some funding agencies are now taking consideration of maternal leave and age-restriction problems for female scientists. However, a large proportion of female scientists are not yet well represented in scientific society. The whole scientific society should be more supportive and inclusive for female scientists and other underrepresented populations and give them more opportunities to organize conferences, apply for and obtain funding, review papers, etc.

Do you have a role model in science? If so, who and why?

Instead of one specific role model, I would say I have many scientific heroes, including Roger Tsien, Alan Hodgkin, and Bernard Katz. But on top of my list is Roger Tsien, who is also my "scientific uncle" as I was lucky to have my postdoctoral training with Roger's elder brother, Richard Tsien. Roger is brilliant in the way he used interdisciplinary approaches to develop chemical-genetic-encoded probes to visualize live-cell biochemistry, including spying on neuronal signaling. Those optical tools can non-invasively label cells and read out their activities with high spatial and temporal resolution. And with genetic encoding, they can mark specialized cells with accuracy, allowing us to untangle the complexity of the nervous system. In fact, by combining delicate physiological approaches with the tool-developing philosophy I learned from the brilliant Tsien brothers, part of my lab's ongoing efforts is focused on developing advanced tools for spying on important chemical molecules that mediate neural communication or modulate neural activities.

How do you find inspiration?

When I was young, I loved reading science fiction about how the world could become, how one could explore the universe. For example, I loved the book *The Mysterious Island* when I was in elementary school.

And later on, I liked reading great scientists' autobiographies, learning about their adventures into science, how they design and perform smart experiments and got unexpected but exciting findings. For example, I was deeply inspired by Roger's efforts in developing fluorescent probes for detecting calcium ions, which are beautiful both visually and conceptually.

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