Career pathways, part 6

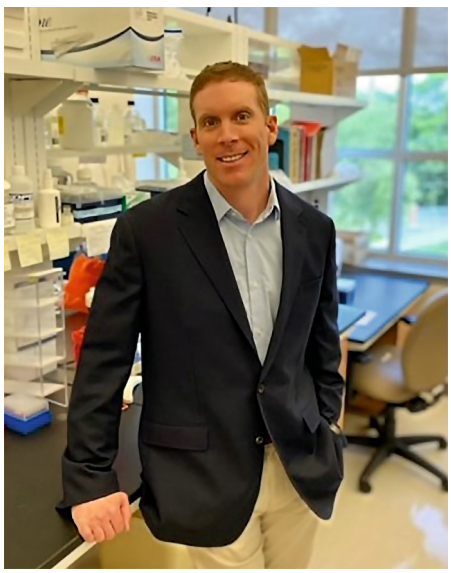
In this instalment of Career pathways, James White and Wenjing Du reflect on the importance of recruiting the right people, staying excited and making work and home life coexist.

James P. White and Wenjing Du

James White: fit and environment

My interests in human biology and exercise physiology started at an early age. I was heavily involved in sports throughout my childhood and remember being very interested in how the body worked: how it responded to exercise, weight lifting and even how we recover from injury. I was admittedly not a distinguished academic early on. As a student–athlete throughout high school and college, I placed more focus on football (American) than exams. It wasn't until my final undergraduate years at Southern Connecticut State University that I took anatomy, physiology and nutrition courses, which sparked my intellectual interest and enticed me to continue down the academic road. I remember the surprise on my advisor's face when, in the last month or so of my undergraduate, I said, "I think I want to go to graduate school". From there, I received a Master's from Florida State University and a PhD from the University of South Carolina under the mentorship of Jim Carson.

In regards to finding the right PhD program, it only took an introductory phone call to feel 'at home' in the Carson lab. For one, I learned that Dr Carson also played and coached football, at Ohio State University, before starting his academic career. In the same conversation, he told me he mentors his students with the same intensity and drive as when he coached. Although this approach was foreign to some, I knew what that meant and was excited to get to work in his lab. I guess this scenario would be a good example of matching yourself with a PhD advisor you see eye to eye with. A good PhD program will take 5+ years, so having a good relationship with your advisor and sharing research interests will make your time a little easier. As I made my way through my first few projects in the Carson lab, the challenges of academic research, including the discoveries and setbacks, fuelled the same competitive spirit of athletic competition, drawing me in further to research. I continued to study various aspects of muscle biology and was able to publish several papers along the way. Although my initial start into graduate school was on a whim, I was hooked on research and eager to continue my training.



Credit: James White

After graduation, I took a postdoc position in the laboratory of Bruce Spiegelman at Harvard Medical School. Although Dr Spiegelman's lab is famous for discoveries in adipose tissue biology, at the time his group had just published several papers on muscle metabolism that captured my interest. After a few e-mails and an official interview, I quickly saw how passionate Bruce was about his work. Although Bruce has already accomplished more than most scientists dream of, our initial discussions were very collegial: just two scientists talking muscle and metabolism. I was impressed with his sincere interest in my opinion, especially around exercise physiology and muscle biology. By the end of my interview, we had already crafted out experiments I would start on in his lab. It was an exciting challenge for me to take a deep dive into the molecular mechanisms of muscle and adipose tissue biology. Initially, I found the molecular depth of the lab challenging, having limited experience with many techniques and terminology. With time and help from members of the lab, many of whom are still close friends and colleagues, I got up to speed and was able to incorporate the molecular techniques into my projects. One such project was a collaborative effort to identify secreted factors regulating brown fat thermogenesis. We identified a protein (Meteorin-like (Metrnl)) secreted from muscle during exercise, which ultimately opened several lines of investigation within the lab and eventually led to our publication in *Nature Metabolism*.

At the tail end of my time in the Spiegelman lab, we started to observe the association of damage-inducing exercise, like downhill running, and increased expression of Metrnl within muscle. We designed a few pilot experiments to test the role of Metrnl in muscle regeneration just as I accepted a position at Duke University. The results looked promising and we decided I would follow up on these findings in a collaborative effort while I was at Duke. The Metrnl project was a major focus from the start of my lab. Serendipitously, another junior PI at Duke, Gurpreet Baht, was working on the same protein in bone, unbeknownst to my group. I presented my work at a local departmental seminar and we started talking about our respective projects. Two years later, we published Baht et al. (https://doi.org/10.1038/s42255-020-0184-y) in *Nature Metabolism*. This publication has been critical for putting our labs on the map and showcasing our techniques. My lab continues to investigate this intriguing protein, and we hope to have several follow-up stories coming out soon.

Starting your own lab is like moving from your parents' house to your own apartment. You are super-excited to get started, but quickly realize you are now on your own. It was fun putting my lab name on all my new equipment. This felt very official. Recruiting people was more difficult than I expected. Understandably, most postdocs would rather commit to a more established lab than take a risk on a new PI. It took nearly 2 years to find my first postdocs, which meant I was my own postdoc during the day and wrote my K award (career development grant) application during incubations and evening

hours. Even though this was hard to juggle, I didn't want to rush the hiring process because I knew how important it was to acquire good help in the early years. I would advise others to be patient and selective because your first postdoc(s) is very much an extension of yourself. You must build trust to hand over projects and allow them to manage projects your own hands have started. I am happy to say I was lucky to get two very talented and collaborative postdocs in my first two years and then added one more during my third year. I can say that this was a huge factor in the early success of the lab.

As for the advice I give to my postdocs in obtaining faculty positions, I stress 'fit and environment'. As a postdoc, I would have taken a faculty position based purely on the offer letter and prestige of the university. Now, I know the importance of fit and environment. I ask them to think of themselves sitting in their own office 5 years from now. What does your lab look like? Who do you collaborate with? Do you have trusted mentors? I was fortunate to find that fit at Duke, but I have seen others who have not and have struggled in their first few years. As for running a lab, your team will feed off your passion and the excitement you bring to your work. If your grant doesn't get funded or your paper is rejected, show them how you bounce back and move forward. Don't dwell on the negatives, as it will affect the mood of the lab. Academic science requires some resilience. You have to stay excited about your work and take time to enjoy the small victories and accomplishments. Some words of encouragement or simply acknowledging a job well done go a long way. Occasional lab lunches and outings are always fun to escape the everyday grind.

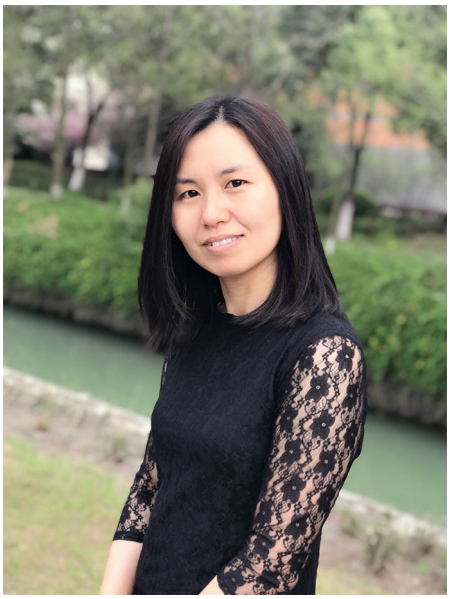
Being a PI is similar to running your own business. On the surface you see the grants awarded, publications and related publicity. But what you don't see is the tremendous amount of work that was put in and the rejections that came along with the success. Speaking from my own experience, for every grant awarded there are several that didn't make the cut. It's the same deal with publishing. So, the reality is you will find more failure than success, especially early on, but it is somehow addictive and drives your curiosity to keep pushing.

Work–life obligations are a tough balancing act that is never in perfect equilibrium. I would not say I completely separate work and home lives, since I am always thinking of new ideas and don't mind quick 'off-hour' discussions if I can help someone in the lab. However, I equally enjoy spending time with friends and family, so my home life seems to coexist and naturally balances itself with work. In addition, my kids are now getting into sports, so I often swap my lab coat for my coach's whistle, which allows quality time with them and allows me to be around sports again, which I enjoy. I don't think there is a magic solution to managing your work–life balance; it's all about how it fits into what you want to achieve.

Wenjing Du: find the right people

Biology was one of my favourite classes when I was in high school, so I chose biological sciences as my major during my undergraduate study. However, before my PhD training I never thought my career would take me towards being a PI. I undertook my PhD studies at the University of Science and Technology of China (USTC), where I worked on cell apoptosis and cancer biology under the supervision of Mian Wu. The training experience during my PhD studies drove my personal decision to further my studies as a postdoctoral researcher. I liked the uncertainty of scientific research and the journey of going from an initial interesting phenomenon to revealing the processes behind it. In 2008, I joined Xiaolu Yang's lab at the University of Pennsylvania as a postdoc, where I continued my study of p53 in tumours. Xiaolu provided guidance and gave me the freedom and support to explore what I was interested in, which allowed me to develop my own research direction. During my postdoctoral training, I focused on how metabolic changes in NADPH production underlie p53-medicated tumour suppression and found that p53 unexpectedly regulates NADPH metabolism through the pentose phosphate pathway and malic enzyme pathway, either transcriptionally or post-translationally. One of the studies was published in *Nature* in 2013. It was the most exciting thing I had experienced since I began research. At that moment, I realized my passion for research and wanted to continue working towards an academic career as an independent investigator.

In 2016, I was back in China and started my own lab at the Institute of Basic Medical Sciences (IBMS), Chinese Academy of Medical Sciences (CAMS) and School of Basic Medicine Peking Union Medical College (PUMC). Starting my own lab as a PI was difficult, and running a new lab in China is different from running one in the US, especially in terms of waiting for funding and equipment from overseas. In the first year I encountered unexpected challenges, such as starting a lab with only one small room that still had to be furnished and equipped, recruiting people



Credit: Wenjing Du

and securing funding. Eventually, with the help from friends and colleagues, I overcame the difficulties and was fortunate enough to recruit talented people who wanted to work with me.

When everything settled down, we began to do experiments in early 2017. The research in the lab centred on a few topics, such as how cancer cells rewire their metabolism, the role of tumour suppressors and oncogenes in their metabolic regulation, and how nutrient alteration is sensed by cancer cells. Based on my previous study and others' findings, NADPH scarcity is believed to be a limiting step in cell proliferation. I have always been curious about the physiological role of NADPH in cells beyond its role in antioxidant defence and many biosynthetic reactions. To this end, we started to study how cells sense cellular NADPH change. Manipulating cellular NADPH levels was the important step for this project. We knocked down or overexpressed the NADPH-producing enzymes (malic enzymes, glucose-6-phosphate dehydrogenase or mitochondrial methylenetetrahydrofolate dehydrogenase/cyclohydrolase) to reduce or increase cellular NADPH levels. However, as editing metabolic enzymes could be affecting intermediary metabolism beyond NADPH, we needed to find a way to directly manipulate NADPH concentration in cells. We could not add NADPH to cell culture medium because NADPH is unable to cross the cell membrane. We wondered whether NADPH could be transfected into cells like DNA. We tested this possibility from a variety of angles and

finally found one reagent that could indeed transfect NADPH into cells. We tried it on several cell lines and examined the cellular NADPH concentrations after transfection, and it worked! In 2021, the first major paper that came out of my lab, on how NADPH was sensed and the function of NADPH in modulating cellular epigenetic status (Li et al., https://doi.org/10.1038/s42255-020-00330-2), was published in *Nature Metabolism*. The paper describes a metabolism-independent function of NADPH in modulating epigenetic status and transcription. Mechanistically, NADPH directly interacts with histone deacetylase 3 (HDAC3) and interrupts the association between HDAC3 and its co-activator nuclear receptor corepressor 2 (Ncor2; SMRT) or Ncor1. By interrupting the complex between HDAC3 and Ncor, NADPH suppresses HDAC3 activity and reprograms histone acetylation and gene expression. Although how NADPH acts on HDAC3 needs further clarification, NADPH may have broad impacts on cell physiology through modulation of epigenetic status and transcription.

The challenge for us during this project was that the COVID-19 pandemic forced us to close the lab for around two months during manuscript revision. Then, with a gradual reopening, only one or two people were allowed to work in the lab simultaneously. During that time, we worried about the slow progress. We were fortunate to meet thoughtful editors who supported us and gave us sufficient time, so we could fully address the reviewers' comments. And we were also lucky to have the support of my collaborators, who helped us perform docking and molecular dynamics simulation experiments between NADPH and HDAC3 during the revision of the paper. Moreover, we felt lucky and encouraged to have help from the editorial team and professional reviewers. The comments from reviewers were constructive, and the editor summarized the points that were particularly important, which was especially helpful in showing a young lab how to revise a paper. I am also fortunate to have passionate trainees who work hard and devote their careers to research.

The paper in *Nature Metabolism* gave my lab a good start and was also meaningful for my professional life as a junior PI. It brought many positive things for my team and for myself and opened a new direction and collaboration for my research team. After the paper was published, it drew some attention to my work and my lab, including awards and invitations to speak at conferences, and I hope that this will manifest itself more in the future, in terms of recruiting people and securing funding.

Being a PI is not easy. Having my own lab is exciting but challenging, as I must fulfil my responsibilities for my trainees, my collaborators and my department. As a new PI, I encountered many challenges that I had not anticipated, although these are probably common to most new PIs. Finding the right postdocs and students was more difficult than I expected; for example, when I recruited the first scientist for my lab, the candidate cancelled the appointment one day before the interview. Fortunately, I managed to recruit talented and passionate staff scientists and students who wanted to join my lab and work with me. My lab slowly grew from a small lab with only one staff scientist and one student in 2017 to a bigger lab with two staff scientists and six students today. I think recruiting people is the most important thing for a new PI and I would suggest being patient until you find the right people for your lab.

As a woman, I have always been asked how I balance my personal life and my professional obligations. I have to say that it is hard to clearly separate personal and professional lives. As a PI, it seems that you have tons of work to do all the time, such as writing funding proposals, writing manuscripts, teaching, supervising trainees, and attending seminars and meetings. Balancing the workload was especially challenging during the COVID-19 pandemic in 2020, when schools were closed. My two kids had to stay home and take their classes online. During the daytime, I had to care for them and take on the role of an elementary school teacher, and only after they went to bed at night could I start my own work. It was a hard time and I am proud of everything that I have overcome. I am fortunate to have a very supportive family, which includes my especially supportive husband, Peng Jiang, who is also my scientific collaborator. Therefore, I never try to separate my personal and professional life; I always take my job with me wherever I go. I think keeping these parts of your life separate doesn't matter if your family is supportive. However, I still think some work–life balance is necessary. The optimal work–life balance will vary over time because we all have different priorities and obligations and there is no perfect model that fits everyone. The balance is right as long as you receive a sense of achievement and enjoyment from your work or your life, and personally, I hope that I will progress far in my career and at the same time enjoy life with my family. ❐

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