Career pathways, part 1

The transition from senior postdoc to early-stage investigator is a pivotal step in the careers of academic scientists. In this series, early-stage investigators reflect on their labs' first publications and the journeys that led them there.

Lydia Finley and Lawrence Kazak

In our first year, *Nature Metabolism* strove to publish some of the most exciting developments in metabolism and physiology from researchers worldwide. These teams of scientists behind the discoveries can be big or small, established in their field or newly venturing beyond the borders of their established scientific program. Last year, *Nature Metabolism* was lucky enough to provide a platform for several early-stage investigators to publish their first major papers with their newly formed labs.

Although we in science may idealize a formulaic path toward becoming an independent investigator, the scientific community is like any community: a diverse group of individuals from all walks of life brought together by their passion for science. Our individual life experiences equip us with the unique tools and perspectives to approach and solve the most complex scientific and societal problems.

In this three-part series, we asked six early-stage investigators whose work has been featured in our pages about their experiences in publishing their first 'big' paper, hoping to better understand how journals such as *Nature Metabolism* can help facilitate the establishment of newly formed labs. What we found were six lives, all connected by their passion for science, devotion to mentorship, gratitude for the past and uncertainty about the future. Here, we begin our series with reflections by Lydia Finley and Lawrence Kazak.

Lydia Finley: a future of little wins in the face of COVID-19

Almost exactly 3 years to the day after the Finley lab opened, the COVID-19 pandemic forced us to close. The process of preserving reagents, winding down projects and powering down equipment threw into relief just how far we had come since opening. Over the past few years, we gained trainees, grants and papers—achievements that seemed unthinkable back when the lab was just an empty, echoing room that gradually accumulated unopened boxes, pristine glassware and idle machines. Slowly, the boxes got unpacked, the glassware was labelled, and the machines were switched on. My mantra was that each minor victory

Credit: Memorial Sloan Kettering Cancer Center

was to be celebrated. Successfully thawed cells? Celebration! First GC–MS run? Celebration. First student? Big celebration. I treasured each assay re-mastered in the new lab as much as or more than I had savoured the pride of learning it for the first time. I documented each first—immunoblot, colony formation assay or qPCR—with pictures, like a proud parent on the first day of school.

Our first manuscript was, like everything else in science, the product of stringing together little wins. We began with an observation that we had made countless times: whenever we removed glutamine from the culture of a heterogeneous population of mouse pluripotent stem cells, the cells that appeared to be the most committed were the first to be eliminated. This observation led us to wonder whether the phenotypic heterogeneity of pluripotent stem cells might occur alongside metabolic heterogeneity. The first experiments in the lab tested this hypothesis from a variety of angles. We all worked side by side to maximize our throughput, and we enlisted complementary collaborators to extend our experimental range. Once we convinced ourselves that, indeed, the most highly self-renewing pluripotent cells inherently exhibit unique metabolic features and that this distinctive metabolism could be exploited to enrich pluripotent cells from a heterogeneous population, it was time to write.

Writing was an opportunity for us to celebrate the hundreds of experiments we had done—with both positive and negative results—that collectively led to our first story. We were proud, and we were nervous. With great trepidation, we read our first reviews, and we were encouraged to find that they were thoughtful and constructive. Clear editorial direction on which experiments to prioritize was especially helpful for a young lab with limited personnel. We knew what we had to do, and more importantly we knew how to do it. All our little wins had gotten us to this point. With a few more wins strung together, we were able to have a big win: our first published manuscript (S. A. Vardhana et al. *Nat. Metab.* **1**, 676–687; 2019).

Throughout the shutdown, and as we inch toward a gradual reopening, we've again relied on the mindset of the lab's initial opening: stringing together little wins. Although we have accepted that progress will be slow, perhaps imperceptible, for many weeks or even months, this does not mean that progress is not occurring. The challenge for us, and my major goal as a mentor, is to continue to find the little wins. As always, the definition of a win is continuing to evolve. In the first few weeks of shutdown, our goal was simply to re-establish some sense of routine. Lab meetings and journal clubs restarting? Celebration! As the shutdown continued and we became accustomed to the new normal, our goals changed. The obvious victories—a passed qualifying exam, a finalized manuscript—were the easiest to celebrate. However, there were other wins that we had to look closer to find, whether it was organizing reams of data, finding the perfect way to visualize old data or mastering new pieces of code. Just as we routinely break our scientific questions into small, achievable experimental units (grow cells, isolate RNA, quantify gene expression), we now focus on breaking large goals into definable, achievable tasks. In this way, we are reminded that each small step we take moves us ever forward.

We don't know what the next year or two will look like, but we remind ourselves that we've been in this same position before. This

group has already built the lab from a room of unopened boxes and new equipment. We have first-hand experience with how incremental progress accelerates over time. Did we get to thaw cells? Win! Did we get to run GC–MS again? Win! And hopefully, before too long, we will all be allowed in the same room together. This will be a big win, and we will make it a party. By counting and savouring the little wins, we will be able to build up strings of victories that lead to future successful projects, papers and PhDs.

Lawrence Kazak: a scientific journey of focus and refinement

My interest in molecular metabolism and mitochondrial biology stems from when I first learned that genes are responsible for the training benefits of exercise. My scientific career path was not straightforward. As a young boy, I spent a lot of time cataloguing plants during walks with my grandmother. I loved chemistry in the first years of high school; however, the science education I received at that time was subpar. In contrast, the fine-arts program at secondary school was incredibly strong, with dedicated teachers who took pride in their work. After high school, I pursued fine arts and simultaneously began training in Brazilian martial arts for the next 8 years. It was during that time that I realized I still had a passion for science but had never had the encouragement that I needed when I was younger to give me the confidence to pursue it. Despite this, with a 'toe in the door' in martial arts, I began my scientific career by studying exercise physiology, during which I developed a love for mitochondrial biology. I quickly understood that I needed to attain proficiency in biochemistry and molecular biology. So I undertook PhD studies at the Mitochondrial Biology Unit at the University of Cambridge, where I worked on DNA replication and protein trafficking in mitochondria, under the supervision of Ian J. Holt, who was the first to identify a connection between deletions in mitochondrial DNA and human myopathy, in the late 1980s.

My personality is such that I dive deeply with both feet so that I can be fully engaged with my interests, and because of this, I felt it was time to stop my martial-arts career and devote 100% of my time to the scientific pursuit. In retrospect, I don't have regrets about that decision, as my participation in martial arts was a critical step that brought me back to a path based in science.

My parents emigrated from the USSR in the late 1970s and worked multiple jobs to make ends meet. Like any parents, they loved and supported me as I grew up, but because they were always working, they

Credit: Owen Egan

were unable to provide me with the formal guidance or mentorship toward intellectual pursuits that some kids receive on their path toward a scientific career. I had to piece a lot of this together on my own, and, looking back, I see that I would have benefited from more scientific guidance and encouragement during times when I struggled with some concepts. My journey has affected my approach toward mentoring my trainees for the better. Encouragement during this critical time in a trainee's life is paramount for their future careers, and I try to be aware of when trainees are struggling and to provide motivation and encouragement when they need it.

For my postdoctoral work, I joined the lab of Bruce Spiegelman at Harvard Medical School, where I continued to work on mitochondrial biology, but with a focus on adipose tissue and bioenergetics. The work in my own lab is a direct extension of the research I started there. The Spiegelman lab was a great environment, and I learned a lot about myself as a person and the type of scientist I wanted to be. Most importantly, I learned the importance of focusing on one problem at a time and trying to solve it to the highest molecular resolution of my ability. Detailed focus on a biological problem does not make for myopic research. On the contrary, a diversity of scientific outgrowth appears naturally as you dive deep, provided, of course, that you are not dogmatic in your thinking. A single manuscript cannot contain an entire body of work. However, a multitude of papers, each building upon the findings of the previous ones, is a style of science that I have found to be incredibly satisfying and an approach that my trainees also appear to take satisfaction in.

Of course, this style of science does not suit everyone's taste; the style of science that investigators pursue will be heavily influenced by their funding environment and available resources, and the capabilities of their trainees. After a move to a new city or institute, it takes time to familiarize oneself with the local research network and the collaborative opportunities available. Once settled in, with more resources and funding secured and a familiarity with the local research community, one can cast a wider scientific net and take on riskier projects. Therefore, considering all these distinct variables, I have personally found it beneficial, and maybe even necessary, to focus the scope of my research program early on, starting slow and gradually spreading out to different areas of biology.

I started my lab in 2018 with one research assistant and one trainee. Currently, my lab hovers between four and six people, and most trainees work on some aspect of the same pathway. In 2019, the first major paper that came out of our lab, on creatine transport in thermogenic adipocytes and obesity, was published in *Nature Metabolism* (L. Kazak et al. *Nat Metab* **1**, 360–370; 2019). This paper was incredibly important because it gave the lab a good start within the first year. No doubt, it played important roles in speaker invitations to conferences, grant success and stimulating a high calibre of trainees applying to my lab.

New research areas in the lab can be traced back to our starting point: creatine biology in thermogenic adipose tissue. This type of focus has been successful for us so far, because although all trainees have independent research projects, there is room for synergy if they choose. This approach has also benefited troubleshooting in the lab and has catalysed scientific partnerships within the lab. My advice for late-stage postdocs or early faculty is to choose a biological problem that is important to you and to focus on solving one problem at a time. I would strongly advise against spreading yourself thinly, especially at the start of your career. In my experience, to obtain grants, the community needs to see that you can take a problem and solve it, and to do this well, you need to focus. ❐

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