Q & A

Henry Higgs

Henry (nickname Harry) grew up near Philadelphia. His college career included year-long stints at Penn State and Cambridge University, before graduating from Lafayette College. Post-college, Harry worked in labs in Chapel Hill and Strasbourg, France, before doing his PhD at the University of Washington with John Glomset. During his PhD, he conducted old-fashioned ‘bucket biochemistry’, purifying and characterizing phospholipases from mammalian tissue extracts. His post-doctoral research with Tom Pollard at the Salk Institute elucidated mechanisms of the regulation of actin polymerization. Starting his own laboratory at Dartmouth Medical School in 2001, Harry has progressively become more and more ‘cellular’ in his focus, incorporating microscopy and cellular assays along with his first love (biochemistry) to reveal novel functions of low-abundance and transient actin populations that conduct important cellular processes. His current obsession is the roles of actin in mitochondrial and metabolic regulation.

What turned you on to biology in the first place? In my teens, I wanted to be a large-animal veterinarian, through working on horse farms and reading James Herriot books. However, I was always drawn to chemistry and cell biology out of intrinsic interest (rather than as a means to an end, such as to cure a disease). I spent my junior year of college at Cambridge University, where the amazing history of discovery and the very natural style of ‘active learning’ with which they teach pretty much locked me into the career I chose. I still toyed with the idea of vet school for a few more years, but never seriously.

Who were your key early influences? I have been lucky to have inspirational mentors at every stage of my career, and still feel that I receive mentorship. As a laboratory technician at UNC, I worked with a post-doctoral fellow, Dennis Lubahn, whose enthusiasm for science was boundless. He gave me several books when I left the lab, including Thomas Kuhn’s The Structure of Scientific Revolutions, which I still have. In Strasbourg, at the Laboratoire de Genetique Moleculaire des Eucaryotes (LGME), I kept learning (in halting French) from another post-doc, Xin Min Zheng. My PhD advisor, John Glomset, was an inspiration, both in terms of scientific rigor and in teaching me that it’s not only young people that can think creatively. He was in his 70s and had more fascinating ideas in a morning than most have in a lifetime. He also taught me that science isn’t that far from art in terms of dreaming/envisioning things, with the cool difference being that you can find out whether your dreams/visions have any basis in reality. When I was a post-doc, Tom Pollard provided me with principles I use every day, in how to address a scientific problem effectively, how to run a lab, and how to manage situations with dignity (I’m still working on that one). When I started my lab, older faculty like Gus Lienhard and Bill Wickner, along with investigators closer in age like Duane Compton and Charlie Barlowe, showed me the way. I now get mentored by my peers (Dean Madden, Larry Myers, and Surachai Supattapone), younger colleagues (Jamie Moseley, Amy Gladfelter, Margot Quinlan, Yasemin Sancak, and Mike Hoppa) and trainees or trainees of others (numerous). One is never too old to be mentored.

What is the best advice you’ve been given? In my first year of grad school, I was trying to decide which of my three rotation labs to join (assuming perhaps erroneously that they all wanted me). The problem was that, while I was most drawn to John’s lab and to John himself, students largely avoided his lab (he’d had only one PhD student graduate in over 30 years as an investigator). The other two labs were much ‘cooler’, with lots of students. When I asked another faculty member their opinion, they said “You do science because it’s funner than fun. Go to the place where you have the most fun.” I never looked back and never regretted it.

If you had not made it as a scientist, what would you have become? I have no idea and am very glad I never had to find out. Growing up, I imagined myself pitching for the Philadelphia Phillies baseball team, but I couldn’t hit the same spot twice with a ball even at 60 miles per hour, let alone 100. And, of course, there was the vet thing, which would have been lovely. Frankly, some days when everything’s going sideways in the lab, I wish I was back on the horse farm, mucking stalls. Overall, however, I feel extremely lucky that I picked exactly the right career for me.

What is the best decision you made? At some point in one’s career as a professor, the path divides. To one side, there is the opportunity to take on greater administrative responsibilities, like being department chair or entering into academic administration. To the other side, there is the prospect of focusing primarily on research. Right down the middle, there is the possibility of doing a bit of both. Despite valuing Buddhist philosophy, I decided not to take the Middle Path but to hug the path of research as closely as possible, with forays into administration only out of necessity or the desire to serve. In most ways, the research path is more risky. You must keep up funding in an uncertain world, constantly keeping the ideas fresh. It was the only choice for me, though. I deeply admire those who devote time and energy to administration. I lack several qualities required to do that effectively.
For many young scientists, the academic research path seems to have few attractions (long hours, uncertainty of finding a position, low success rate for grants). Can you provide some perspective on the current situation? When I started grad school in 1990, I could see the situation pretty clearly. At best, there was a 10% chance of having my own academic research lab (I’m rounding up, a lot). Still, I never had a back-up plan. The odds haven’t gotten any better, but the alternative opportunities have. Biotech has changed a lot in scope and variety since my early days. Other opportunities such as consulting offer a dynamic and varied career.

Why go into academic research? My first (and perhaps only) answer is ‘freedom’. When I started my lab, I was given a reasonable dollop of money and told to get on with it. Nobody told me how to spend that money, who to hire, or what scientific questions to ask. I have no real boss. My department chair can hand me more administrative duties (I’ve been lucky to have really awesome chairs, though), but cannot tell me what to do research-wise. It’s like running a small business, with the benefit that a whole bunch of infrastructure is provided and there is some (perhaps meager) form of a safety net. Although I was very worried about how I might do in such a situation, I was able to sort things out. I came close to ‘going out of business’ two times. Even then, though, I was still having fun. Sometimes I pinch myself now to see if I’m dreaming. Nobody tells me when to come in, when to leave, or how to spend my time when I’m there. I am constantly provided with my drug of choice: data, upon which I can hallucinate. I get paid to solve puzzles. Once you reach a certain stage, the pay is pretty good — I’ve put my daughter through law school, drive a Tesla, bought some land on which I do New England-type things, and generally don’t feel too pinched. Wow.

How does one know whether a career in academic research is for them? I do think there’s a core ‘phenotype’ shared by many academic scientists. Grad students and post-docs might ask themselves the following questions. Do you like science for its own sake, in addition to the possibility of developing a ‘product’? Do you get very excited when looking at data, and think of what it means for future experiments? If you ride your bike to the lab, do you ride a little faster in the morning to get started? Does an unexpected result say ‘opportunity’ to you, rather than ‘drat’? Do you daydream about possible experiments, or even actually go ahead and draw them out, and consider that ‘fun’? Answers of ‘yes’ to most of these questions are suggestive. One doesn’t have to work a zillion hours per week to do this job, but one does have to enjoy the trip, not just the destination. It’s not a career for everybody but, for those who fit the bill, there’s not much like it. I don’t meet many people outside of science who like going to work, but I certainly do.

What is your favorite experiment? I’m not 100% sure I am getting the spirit of the question, but I will tell you the experiments I like doing. I really like the ‘craft’ in science. It’s like doing pottery or painting or things like that: it’s work with your hands that requires creativity and discipline. My favorite crafts are biochemical experiments, such as purifying a protein (preferably a native protein from some sort of animal tissue by conventional chromatography) or conducting a biochemical assay. A good co-pelleting assay to test binding of proteins to actin filaments or microtubules is very satisfying. I like every part of the process: planning, execution, analysis, and dreaming about what to do next. It’s therapy, I’m less interested in imaging experiments. Too fiddly and too little ‘doing’ most of the time. Perhaps I just don’t know those well enough.

What do you find frustrating in the scientific enterprise? I’ll provide two frustrations, somewhat related. There is a bit of human nature in both. I have learned to accept aspects of these but think some changes could be made on the second one. One thing that continually frustrates me is the tendency towards cliquishness/clannishness in any given scientific field. Basically, most fields develop an ‘in-group’ that can end up seemingly dominating the field but is not necessarily made up of the field’s best scientists. Because members of this group run the meetings in the field, they tend to invite each other to speak. Because members of this group are often asked to review manuscripts, especially for the high-impact journals, the views of this group might be disproportionately represented. Being somebody who tends to follow the Groucho Marx saying “I wouldn’t want to belong to a club that would have me as a member”, I rarely end up in this group despite sort of wishing I could be. Interestingly enough, I realized after a while that not being in the in-group didn’t seem to hurt me too much funding-wise. I feel lucky that the NIH’s review system is very fair in that respect (although tough).

My second frustration is the emphasis on publishing ‘big’ papers in high-impact journals. This has always been a thing, but it seems to be increasing in importance. Some colleagues have told me that they wouldn’t waste effort to assemble a manuscript for anything but the highest impact journals. This attitude has several negative consequences. First, it reduces the publication of good, solid work that forms a stable basis for further discoveries, which I think is bad for science. ‘Incremental’ is often a bad word in science, but I do not see why. It’s moving things forward. I’ve always loved the concept of ‘punctuated equilibrium’, and science works well that way (going back to the Thomas Kuhn book I mentioned earlier). Fields grow steadily (incrementally) for a period of time, but inconsistencies develop. At a certain point, there is a quantum leap when one researcher (or several simultaneously) resolves those inconsistencies. Second, I think the pressure to only shoot for big discoveries opens the door wide for overinterpretation of results, as well as fraud. If you’re told you need to find something really big to get a job, you will ‘find’ something big. Finally, and perhaps most importantly, it is extremely discouraging to trainees, and makes the process appear needlessly pressured and stressful.
Trainees can feel that their work is useless if it doesn’t appear in a high-impact journal, even if it is tremendous work. Again, I feel extremely lucky that high-impact journal publication is not an overriding consideration in the NIH review system (at least in my fields).

**Do you feel a push towards more applied science? How does that affect your own work?** Honestly, I feel lucky to be in a research environment in which I can be valued for doing very basic, curiosity-based research, but where I am also welcome to try my hand at disease-based applications. I am in a basic-science-oriented department, but, as part of a medical school with lots of translational research, I rub shoulders with people going directly at cures. I will freely admit that, earlier in my career, I viewed the latter people with suspicion, as not really being pure scientists. Over the years, however, familiarity has not bred contempt but appreciation. Knowing more, I see that, by and large, translational researchers are incredible scientists, highly creative, and very interested in basic questions. I also had an interesting experience a few years ago that gave me perspective. At 4pm on a Tuesday afternoon, I gave a talk to a cancer group, telling them about some of our basic research with possible relevance to cancer. There were three clinicians in the front row who, within 10 minutes, were fast asleep. I felt indignant: “How dare they?! Can’t they see the value in this?” On the next Tuesday, I attended my first ‘tumor board’ where all of the various care-givers for that particular type of cancer (oncologists, surgeons, radiologists, genetic counselors, and others) get together weekly to go over every current patient and their progress. That meeting started at 6am and was very intense. Those three clinicians were at that meeting too and were centrally involved. It was very much an honor to be present at such a meeting, where I saw the depth of care that these people have for their patients. I realized that, from their perspective of trying to find ways to treat people who have cancer RIGHT NOW, my ramblings of somewhat remote possibilities for treatment might be difficult to get too invested in, especially since they had started work about 10 hours before I had given my talk the previous Tuesday. I learned a lesson: that we all come to things with our own perspective, and that all perspectives have validity. Having said that, I do worry that fundamental, curiosity-based research is getting pushed out. There seems to be a tendency to think, after every big fundamental discovery or landmark, “Ok, that’s the LAST thing basic research can give us. Now, we just need to put it all together and cure things.” When I started my career in the late 1980s, there was a plethora of discoveries linking individual genes to diseases. Headlines tended to imply or overtly state that a cure was just around the corner. In many cases, we are still waiting for those cures. To me, discoveries such as the unfolded protein response (UPR) only get made in ‘simple’ model systems, and then get expanded out to mammals and disease implications when there are some clear targets. In the example of the UPR, imagine trying to find that first in mammals, which have three distinct branches of the response, rather than in budding yeast, which has only a single pathway, conserved with one of the mammalian pathways.

My personal model system is the cultured mammalian cell (fibroblasts or cancer cell lines). The criticism is “those cells aren’t depicting anything remotely physiological, being grown on plastic for generations”. My response is that I can do three or four experiments a week in this system, as opposed to one per week/month/year, depending on what one’s ‘physiological’ system is (which generally has some compromises of its own). It’s probably better that I focus on moving quickly on such a system, rather than dissipating effort and money by also working up a ‘physiological’ system. Somebody else who has those skills can do that.

**DECLARATION OF INTERESTS**

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**Quick guide**

**Geladas**

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**What is a gelada?** Gelada monkeys, known as the ‘bleeding heart baboons’ because of their distinctive red chest patches, are one of the most striking and charismatic primate species (Figure 1). Although they share a number of features alloying them with baboons — most notably their ground-based lifestyle — they are not, in fact, true baboons of genus *Papio*; rather, they form their own genus, *Theropithecus*. The common name ‘gelada baboon’ is therefore a misnomer. Geladas are endemic to the highlands of Ethiopia, where they assemble in large herds on the high-altitude savannas and forage for roughly 50% of daylight hours. At night, they sleep on steep cliffsides. Geladas rarely climb trees — and when they try, they do so poorly — making them the most terrestrial primate apart from humans. As one of the most ecologically specialized primates, geladas consume a primarily graminoid–based diet (i.e. grasses and sedges).

**What is the evolutionary history of Theropithecus?** Geladas are the last remnants of a once-diverse and highly successful primate radiation. The rise and fall of the genus *Theropithecus* is one of the most fascinating stories in primate evolution. As savanna habitats expanded in Africa during the Pliocene and Pleistocene, numerous species of *Theropithecus* became widespread across the continent, even venturing into Europe and Asia. Notably, there is no fossil record for geladas, but there is an abundant fossil record for the extinct species. Some species, such as *T. oswaldi*, were two to three times the size of geladas. These other species went extinct roughly 50,000 years ago, which is likely to have been a result of climate change and predation by our hominin ancestors. The gelada is the smallest member of the genus, but in most respects, it is morphologically similar to its extinct relatives, making...