Priestley Medal Address 2025: A random (mostly) uphill walk

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(A version of this essay was presented at the American Chemical Society Spring 2025 meeting by 2025 Priestley Medal winner Frances H. Arnold, Linus Pauling Professor of Chemical Engineering, Bioengineering, and Biochemistry at the California Institute of Technology.)

I have been accused of being a chemist, although usually not by chemists. My first foray into chemistry as a mechanical and aerospace engineering student at Princeton was neither inspiring nor memorable, and my success in that field was on par with my interest. That changed, however, 7 years later, when I took organic chemistry for the first time as a graduate student in chemical engineering at UC Berkeley. Perhaps I was simply more mature, but I think it was because I was more open minded, having spent the intervening years stretching and exercising my brain by living and working in different countries.

In the decades since, the puzzles, and the art, of chemistry have been endlessly fascinating, as has the stunning artistry of the biological world, truly the best chemist of all. The living world is also the finest engineer: nature's design process of evolution has created all the glorious life we depend upon, and it works at all scales, from molecules to ecosystems.

I decided to ride along with evolution in my chemical journey. Perhaps not surprisingly, my life journey has also resembled the evolutionary searches that proved so effective in the lab. On a walk that has appeared fairly random and mostly uphill, I'm still trying to find the right balance between exploration—that is, looking for new opportunities—and exploitation—making the most of the opportunities that are presented.

For this address, I will start at the top of my career and work my way down. While there are many highlights, the true pinnacle of success was going down the road to Warner Bros. Studios in Burbank to play myself on *The Big Bang Theory* (*TBBT*).

For the maybe two or three people on the planet who haven't heard of it, *TBBT* is a television show about science nerds. It's about endearing physics graduate students who over 12 seasons go on to become annoying professors lobbying for Nobel Prizes. It's probably a good thing that the show is over. I wasted a perfectly good morning filming "The Laureate Accumulation," where my contribution was to throw Sheldon's bribe of oatmeal raisin cookies into the trash.

This is why I have a SAG-AFTRA [Screen Actors Guild–American Federation of Television and Radio Artists] contract to play myself. In fact, I was the first and only woman scientist to cameo on the show. Please go ahead and watch that episode—every time you do, I get a few cents in residuals. I learned an important lesson from this experience: although a small fraction of the world follows chemistry, a very large fraction follows good stories about science, and especially about scientists. Stories help science touch people. Yes, 2019 was all about exploitation, and those residuals keep trickling in.

2018 was not bad either. I went to a marvelous party in Stockholm. Although it's dark and cold in December, the city sparkled for this celebration of science. This was such a good event—if you ever get invited, you have to go. I invited 60 of my friends and family to join me, including many former students and postdocs. Other people just showed up because word got out that I was buying dinner. The wonderfully choreographed Nobel celebrations lasted an entire week, and I was exhausted by the end. It’s not often that we see an entire country, and also much of the world, celebrating achievements in science, literature, economics, and peace.

Another big event was my 60th birthday in 2016, when many former students and postdocs came together at Caltech. Those of you in earlier stages of your careers will at some point realize that it's not about you. It's about the students and postdocs and your impact on the next generation and the generations after that. I feel that I'm mother of hundreds now and grandmother of countless. I take immense pleasure from keeping in touch, which I do in part with a yearly Arnold Lab newsletter with input from former group members. The newsletter has documented lab gossip for more than a quarter century and reached 20 tightly packed pages in its latest version.

My life and science explorations have taken me down various paths, many of which are now relegated to the “extinct” pile. As we always do with such stories, I will selectively choose which ones to reexplore and which to leave buried. I have gone through a number of transitions in career and life, but perhaps the most meaningful one happened in the middle, when I suddenly realized that my family was missing me.

It was 2003, and I had three boys, ages 5,6, and 13. The teen was not doing well in school: he spent more time in the hall than the classroom. The hall is a poor solution to boredom. (When I was disruptive in elementary school, they shipped me off to typing class.) In a previous era, one would have sent the boy (not a girl, of course) around the world with a tutor or packed him off to boarding school.

The boarding school was to come later, but going around the world sounded like a magical idea. As a young adult, I had traveled and worked in Italy and Spain during a year off from college, and I explored South America and worked in Brazil before graduate school. I

wanted to both relive and share that sense of freedom and adventure with my boys. “It's time to take some time away,” I announced to my husband, Andrew, who was also a professor with a large group and big projects to run. He wasn’t thrilled at first, but eventually he warmed to the idea and became a fantastic partner in adventure. This was to be a year of pure exploration.

Thus 18 years into my professional career, four boys and I put backpacks on and went around the world. Andrew and I had both accumulated enough sabbatical time to take an entire year away. Our first stop was Australia, where we acclimated by spending 2 weeks in the Red Centre. The five of us stayed in “million-star hotels” with Aboriginal people hundreds of kilometers from the nearest city, sleeping in “swags” under the Southern Cross with the smell of fire in our noses, and everywhere else. We also lived with a million things that could sting and kill you, but the swags were well designed to keep them out. Our Aboriginal hosts simply flicked the worst of them into the fire without a thought.

We learned to eat honey ants (delicious) and witchetty grubs we pulled from mulga branches; they taste like scrambled eggs when roasted in the ashes of the desert fire. We learned how to paint our bodies and dance by firelight. We listened to origin stories and learned respect for people whose cultures reach back more than 40,000 years—people who made room on their desert mattresses for their dogs, kids, and my little boys, who went feral within 2 days.

After this miraculous desert adventure, which was life changing and something most Australians would never even think of doing, the younger boys started kindergarten and first grade in Melbourne. We parked the older one, James, in a fancy Melbourne boarding school, which he enjoyed almost as much as he loved the Australian meat pies. James occasionally joined our weekend trips to farms, caves, gold mines, and parks, where we met some very strange marsupials.

After 3 months and a brief stop in California, we moved on to Egypt, South Africa, Namibia, and Madagascar. We did not have much money, but then you did not need much there. Ranchers in Namibia were thrilled to host us, as were the families at simple homestays one could find all over. In these early days of the internet, we found many of our outings by word of mouth and arranged adventures in remote places by email.

We were incredibly lucky to visit Himba people at the border between Namibia and Angola (a very bumpy 3 h flight from Windhoek in a six-seat plane) and Bushmen in the Kalahari (400 km on a gravel road in a rented Toyota Corolla with several groups of natives who were grateful for a lift to the next town and held the little boys on their laps). The younger boys played with the local children, sharing no language other than a common understanding of fun—building forts, painting their bodies, lighting fires, and making weapons.

Before heading to Africa, we had parked James, then 14, in a tiny boarding school in Shropshire England for ninth grade. For his break, James made his way, on his own, to Heathrow Airport, where he caught a flight to Cairo to join us for our travels in Egypt and Madagascar. Even at a very young age, James was fearless and capable of handling complex situations. We did not doubt that he could make his way to Egypt, although we were relieved to see him at the Cairo airport.

In Egypt, in addition to the usual astonishing pyramid visits, we hired an ancient felucca to take us down the Nile for several days and crossed the Sinai desert on camels (warning: 5 days on a camel leads to a sore seat). Although not designed for passenger comfort, camels are the ultimate biofuel-powered vehicles, consuming everything from egg cartons to orange peels.

We slept under the stars in the cold desert with our camels and Bedouin guides. Their flat bread made from scratch and cooked over the fire tasted heavenly at the end of a long day, even with the sand that permeated everything. According to the Bedouins, sand is better than a toothbrush for keeping your teeth clean. Not sure I bought this advice, as few of them had any teeth remaining.

On this journey, my children continued to learn how to enjoy very different cultures, including different cuisines and languages. The youngest two attended a public school in Cape Town, South Africa, where only 10% of the students were White. Everywhere I went with little children, I was treated with respect, and the boys were treated as precious. Imagine that. Traveling with little children is uplifting: children break down barriers because everyone shares a love for children. Children also have the eyes that we adults lost years ago—they see everything and from a very refreshing perspective (and not just close to the ground). All three of my boys came back from that year with a great love and appreciation for different cultures and races.

My sons all became adventurers. James stayed a year and a half in the English boarding school before returning to California. His life journey took him to 6 years in Army aviation, including 2 years in Germany and deployment to Afghanistan. The youngest, Joe, went back to South Africa after high school to volunteer in a big-cat sanctuary. And my middle son, William, volunteered each summer starting at age 16 in Kenya (building houses), then India (teaching at an orphanage), and finally South Africa (working with rehabilitated monkeys).

William died at age 20, but he packed a lot of life into those few years. I miss him every day. He was a kind and generous person who loved people more than anything, except perhaps monkeys. You never know how long you'll have with people. Yes, you can work all the time, but you will miss out on some things truly worthwhile if you do.

During that year around the world, we saw firsthand how special our beautiful planet—our shared home—is, and sadly, how many of its treasures will soon be gone. Many of the people we enjoyed meeting, Aboriginal people of Australia, Himba people, Bushmen, Bedouins, and much of the stunning wildlife we reveled in in Australia and throughout Africa have almost disappeared, in a single generation, as a result of our voracious consumption of natural resources to fuel our wasteful lifestyles. I also learned that happiness does not rest on the acquisition of things but rather in sharing, especially sharing experiences.

That year also taught me a very different lesson, about research management: if you make your research group responsible for the group, they will step up. Because I was in places like Madagascar or the Sinai desert, where there was no telephone service or email, my group didn't hear from me very often. Yet they did wonderful work, and more postdocs and students from that period became professors than at any other time. Apparently they had really enjoyed doing my job!

Motivated and generous people love responsibility. Group dynamics are important, though: before leaving, I hired people who helped others and set a culture of teamwork and responsibility. With the admirable help of my wonderful longtime lab manager, Sabine Brinkmann-Chen, I continue to staff the group the same way. This has created many young leaders and makes for a productive group. Their stepping up to do much of my job gave me the freedom to do things beyond science in subsequent years. I have exploited this learning for many years now.

In the spirit of working my way down the career ladder, I'll share another transition that took place soon after tenure, when I realized I would never be the best in the world at several of the things I was pursuing (the early years were devoted to exploration). So I switched all my research effort to what I enjoyed most: directed evolution.

I knew already in the early 1990s that I had a treasure in my hands, a method for enzyme engineering that circumvented our near-complete ignorance of how sequence encodes function. (Of course, the rest of the world took much longer to see my vision.) I also knew that I could do something that no one else could do: reliably engineer enzymes to perform a variety of nonnatural but very useful tasks.

When I started out engineering proteins, hoping to make versions that would be useful to humans, the paradigm was rational design. Protein engineering was mainly the domain of structural biologists, who delighted in terrorizing them to try to learn their secrets. The few groups that tried to engineer *useful* proteins felt that you should be able to sit down and, with your big brain and vast knowledge of biochemistry, figure out what mutations would

give rise to new properties. The problem was that rational design did not work—my brain was clearly not big enough, and my understanding of biochemistry and proteins was not up to the task. Thus, rather than pursuing biochemical illumination, I respected protein complexity and turned to the blind watchmaker for help. Evolution was so obviously the answer, and I happily threw my chips into a basket full of gold that at the time few others could see.

Of course, crazy people also see gold where others see trash or—worse—see nothing at all. And, believe me, what I did was considered lunatic fringe. Many claimed that because the mutations were made randomly (God forbid, not hypothesis driven) and especially because it was and still is difficult to interpret the results of evolution (reverse engineering of evolution is a whole field called biochemistry), it wasn't science. That did not bother me so much, because I was an engineer and wanted most of all to create useful enzymes. Full understanding could come later. (Note, however, that new science can come from the interpretation of the results, even if the science is just to explore what is possible at the edge of known biology. Starting with answers is also very good for building confidence, and it pleases research sponsors.) A number of people, however, told me that directed evolution wouldn't even work, that you couldn't make proteins do nonnatural things because nature never did it. What an odd argument, I thought, because that's precisely why we can. (Of course, one should avoid trying to break the laws of thermodynamics.)

Those years were challenging, as I was still early in my career, but I chose evolution and never looked back. Just a few years later, I would be elected to the National Academy of Engineering (NAE) for having pioneered a generally useful engineering process that was almost immediately taken up in industry. It even led to one of the first “unicorn” biotech companies, Maxygen, cofounded by my friend and sometime collaborator, immunologist Pim Stemmer, in 1997. Maxygen is no longer around, but the enzyme arm of Maxygen, Codexis, is still a major player in industrial enzyme engineering. Pim and I shared the NAE’s Draper Prize in 2011; he died (in 2013) before the Nobel committee awarded the Nobel Prize in Chemistry to directed enzyme evolution.

I should probably say something about *why* I do what I do. Today we are creating the world that our children and grandchildren will inherit. I believe we have a responsibility to pass on a world that is in better shape than we found it. I am sad that my generation has not done a good job of this; I hope that your generations will do better. I engineer enzymes because I envision a future where much of our chemistry is done cleanly, with little waste, using renewable resources, just like nature does it. Wouldn’t it be wonderful to replace dirty chemical processes with microbes? Today more than ever I believe that much of our chemistry will be DNA encoded, and that also includes the wonderful chemistry invented by humans. Nature is so talented at assembling molecules, materials, and machines, and that capability can be exploited and expanded.

Directed evolution is a powerful means to explore the unknown and discover new chemistry. By freeing enzymes from the constraints of supporting current life, we can step into the universe of functions that lie beyond where life has gone. Plenty of chemistry, including some of our most useful transformations, have no counterparts in natural enzymes, as far as we know. And many more transformations not found in nature *or* in human chemistry await discovery. Beyond the tiny fraction of possible chemistries represented in current biology lie the solutions to the climate crisis, the cure to cancer, and maybe even the cures to death and taxes. Evolution, the process that created everything in the biological world, is well suited for exploring this *nonbiological* world, as humans have done with artificial selection to create highly productive crops, farm animals, or hairless cats and French bulldogs.

Our first demonstration, in 2012, of such enzyme novelty was a “carbene transferase” that could cyclopropanate styrenes, a reaction unknown in biology. We discovered that various heme proteins could generate a reactive carbene intermediate and transfer it to a second substrate, not unlike how cytochromes P450 use oxygen. Importantly, this “promiscuous” cyclopropanation activity, unrelated to the proteins’ native functions, could be enhanced and tuned by directed evolution to generate highly active and selective biocatalysts. Alkene cyclopropanation, well known in transition-metal catalysis, had never been reported in an enzyme. But it was easy for the enzyme to adapt to this new job and indeed take on many more, related jobs that exploit carbene intermediates.

Not long after, we generated a carbene transferase to make carbon-silicon bonds never previously reported in biology. There are probably 50 products in the room where you are sitting that contain human-made siloxanes and silicone polymers. But no one has ever found organosilicon compounds in biology, and no enzymes were known to forge Si–C bonds. In 2016, we reported a laboratory-evolved heme protein that inserts a carbene into an Si–H bond, with perfect enantioselectivity, in bacterial cells. The new-to-nature enzyme catalyzed the asymmetric reaction many times better than chemists had done with iridium, rhodium, and other precious-metal catalysts; the enzyme used earth-abundant iron.

The news of our enzyme went all over the world. No one read the paper because it was a boring chemistry paper with 130 pages of supplemental information. A news article, however, said that we were taking a step toward silicon-based life, something we did not discuss in the publication, and illustrated the story with a scene from the Horta episode from *Star Trek*. Now, many people, perhaps almost as many as have watched *The Big Bang Theory*, have wondered whether silicon-based life is possible. Thus, that news story went around the world. And it mutated as it went, so that by the time it hit the UK *Daily Mail* we were putting silicon chips in people's brains. Only a few of the outlets that covered the story had scientists on their staff, so the speculation was unconstrained by fact and often

hilarious. The attention was nonetheless helpful because what we wanted to do was open people's minds about the possibilities for DNA-encoded chemistry. That we certainly did, with a little help from *Star Trek*.

Siloxanes are not biodegradable and are accumulating everywhere on the planet. We produce billions of pounds of these compounds every year. Some products are banned in Europe. I feel that if you make it, you should also be able to break it. Thus, in 2024, we reported the first enzymes that *break* carbon-silicon bonds, perhaps taking the first, small step toward making these human-made materials biodegradable.

I've given you just the tiniest taste of the chemical possibilities that this marvelous algorithm of mutation and artificial selection can access (with a little human ingenuity, of course). The creativity of the enzyme engineering community has exploded in the past 10 years, and there are now hundreds of new-to-nature reactions that can be performed by repurposed and evolved enzymes. Excitingly, a number of these reactions were not previously reported in (human) chemistry!

I would be remiss if I did not mention the role of artificial intelligence and machine learning (ML) in creating new enzymes, especially given last year's Nobel Prize in Chemistry. It is still very early days for the generation of useful enzymes using AI, but promising demonstrations are starting to appear, especially for functions for which natural solutions already exist. I predict that we will soon have good methods for obtaining novel reactivities as well, based on what we understand of mechanism or can intuit from structure, just as we currently do to repurpose nature's designs. Suboptimal designs can be improved by directed evolution, of course, and the painful evolutionary optimization process is now enhanced using ML models working with mutational data. I look forward to the day when that, too, will be done entirely in silico, but I predict we will need experimental data for a while. Thus, because nearly every step in most directed evolution workflows can be automated, we are entering the era when complex enzyme engineering will be performed by AI generation, experimentation, and a few active learning cycles, at the touch of a button. My graduate students and postdocs will be glad to say goodbye to those long days of repetitive experiments. With these new tools, we will be able to generate a new universe of DNA-encoded chemistry.

Science and I have come a long way from where I started, and many of the steps were rather blindly taken. Some steps were forced but opened whole new paths. Back in 1986, I did not choose Caltech—life chose it for me. My husband had a job there, and I was the trailing spouse. But sometimes what life selects can turn out to be great, although it took me a while to feel that way. I was only the ninth woman to be hired in the history of Caltech and the first woman in chemical engineering. Expectations were very high: 10% of the chemistry faculty had Nobel Prizes, and other Nobel laureates in physics and physiology or

medicine were often seen around Caltech's tiny campus or having lunch at our faculty club, the Athenaeum. I believe in high expectations—people often live up to them, as they often live down to low expectations. No one expected me to get a Nobel Prize, however, as I was in chemical engineering, and engineers didn't win Nobel Prizes. I do love surprises, don't you?

I've had a somewhat different career after the Nobel Prize from the earlier one I shared mainly with enzymes. In 2020, I agreed to cochair President Biden's Council of Advisors on Science and Technology, or PCAST. At the end of 2020 I was in the hospital saying goodbye to my dying brother; my mother had died of COVID in a nursing home 2 months before. When incoming science adviser Eric Lander asked me to cochair PCAST, I did not hesitate for long. We had just come through a painful 4 years of anti-science, and I think we were all grateful that science would be on the agenda again.

I want to end with these quotes from my rollout speech in January 2021, a few days before the inauguration of President Biden. These words are even more valid today. (Thank you, speechwriter Dan Cluchey.)

"As an engineer by training, there is a certain temptation to see the work ahead of us as a series of difficult problems to be solved. But the truth is, that is not what drew me to this role. Like the rest of this extraordinary team, I am here today because of love—a love of science, yes, but also a deeper love of our planet, and of our people, without whom science has no purpose or meaning.

"I embarked on my own labor of love in the 1970s, beginning my career in solar energy at a time when our nation was in the grip of an energy crisis. In the years since, my belief has only grown that our highest responsibility, in each generation, is to preserve our fragile planet, prepare our economy and our workforce for the future, and pass on a better world. Science-based decision-making has always been our most powerful tool for meeting that responsibility, perhaps never more so than today. As a pandemic rages, taking so much, and threatening all that we love, we look to science and technology for answers: technology to stay connected to one another, science to find vaccines and light the path out of the darkness.

"As climate change looms, we look to science and technology once more, to save the precious jewel of our planet so that we might pass it to future generations intact and in good health, as it was passed to us. In a time of economic crisis, we look to science to develop the industries of the future—the ones that will breathe new life into our livelihoods and provide the good jobs that lift up families and communities and bring dignity and security to all our people.

“And in a moment of torrential divisions, science offers us a common shelter of facts and truth within which we can begin to come together and, in time, begin to heal.

“Science, once again, is not the cold solving of problems. It is a warm and beautiful exploration of the unknown, an expression of human curiosity that propels us forward and allows us to fulfill our most important responsibilities. The moment we fail to nurture it, we resign ourselves to living in the past and lose the chance to guide the future.

“When we put science back to work for the benefit of all people, revitalizing our economy, fueling our climate response, broadening our perspective as we rebuild around greater opportunity, we are making a society worth passing on to our children and our grandchildren.”

Thank you.