An improbable journey: Creativity helped me make the transition from art to curing malaria

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I was recently awarded the Alice and C. C. Wang Award in Molecular Parasitology for my contributions to antimalarial drug development, including laying the groundbreaking work that has led to two new molecular methods for curing malaria. This award means a great deal to me because I have spent much of my scientific career feeling like an impostor—one with the wrong sort of background and poor credentials. I am grateful for the recognition, and I am beginning to recognize that having an atypical background can be an advantage because it gives you a different perspective on a challenge. More generally, diversity in educational and cultural backgrounds is important because it can stimulate new ways of thinking and discovery.

Unlike my peers in science, it did not occur to me that I might become a scientist (although my immediate family is full of academics and teachers). I did not have a microscope as a child and tended to eschew subjects like chemistry. In science classes, we were asked to learn facts and equations and to show that we had mastered the material by reproducing it as quickly and accurately as possible—typically in a competitive, timed exam, and there was usually only one answer. I gravitated toward art classes because in art there is usually no right or wrong way to do something. Even in a middle school art class you are praised for coming up with new ideas and concepts. In science class, you weren’t... or at least not in the science classes I took. In fact, coming up with creative ways to solve problems seemed like a good way to get a bad grade. Also, in art class, you are encouraged to create something, and I always loved creating new things. I could spend hours and hours focused on a drawing or a painting, and I spent many youthful hours doing this. Additionally, I would read anything I could find as a high school student, and I liked writing because this was also a creative outlet. I did keep up with a bit of math and a selection of science classes (which I viewed as necessary to be a well-rounded person) in my portfolio throughout high school and while an undergraduate at Lewis and Clark College, a liberal arts college that nurtured me for 4 years. In addition to a senior thesis in sculpture, I took classes on economics, philosophy, art history, and physics. I went to Eastern Europe to observe the last gasps of Communism firsthand. I explored different languages—I have now taken classes in French, Russian, Hungarian, and German, many on my own time. Although I did okay—mostly As and Bs—I was never a standout student nor one that attracted much attention. As a young woman, I think there was never much pressure for me to go out and earn money or have a career, and I think my family assumed I would get married and have kids.

Having graduated with a degree in art and natural sciences, I was now faced with choosing some sort of career, and I still wasn’t sure what I really wanted to do. A family friend offered to train me to program computers if I was willing to work for the government, and so I programmed computers for several years while I considered my options. I took art classes at the Corcoran School of the Arts and Design in the evenings and Russian language courses. I remained curious and taught myself to play the piano; I also learned cooking, quilt making, carpentry, ceramics, and old car repair, and I traveled. Working for the Bureau of Labor Statistics, I discovered that what I did not want to do was to sit in a cubicle and have a 9 to 5 job, which would result in me thinking about going home. It became clear that if I wanted to be the person who was doing the project design and the person responsible for the project 24/7, I would need to go to graduate school and obtain an advanced degree.

I first applied to a Master’s of Fine Arts program and was rejected. Then, I decided that maybe there would be more of a need for scientists and decided to go for a master’s degree in a science field. Here, I was accepted. I had very good, across the board, Graduate Record Exam (GRE) scores but not much else going for me, although perhaps I had good letters of recommendation. I spent 2 years at Oregon State and discovered that as a result of my training in liberal arts, I could effortlessly convert results into well-written publications, a talent that helped me move on to Stanford University for a Ph.D.

At Stanford, I experienced my first real bout of impostor syndrome. I was a middle-class, public school kid from Reno, NV, with long midwestern roots; now, all my peers were elites—they had attended Harvard or MIT as undergrads, had gone to prep schools, had won Westinghouse scholarships, or were related to other famous scientists. They were the sort of kids who had won awards in high school or were valedictorians. They had been attending Science Olympiads and were from places like Boston, New York, San Francisco, London, Tel Aviv, Beijing.
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University, and Oxford. They had National Science Foundation scholarships. To add to my insecurity, I felt old. I was 28 when I arrived at Stanford, and most of my fellow students were younger. The only solutions for me were to work hard and avoid attracting attention so as not to get thrown out. I loved graduate school though. It was an amazing time, and I never had any regrets or doubts that I had made a poor decision—I actually could not believe that they were paying me to do what I loved best, which was to learn about new things. Perhaps because I wasn’t constrained by a lifetime of trying to come up with “the one right answer,” my creativity soared during these years. My advisor, Lucy Shapiro, was an outstanding mentor for a student like me, perhaps because she dabbled in the arts as well. She gave me free rein to come up with new ideas and experimental plans, some of which bombed tremendously, but I succeeded with enough of them to earn my degree. Those failures have helped me refine my abilities to focus on important problems and to develop specific and testable hypotheses.

I decided to continue my training as a postdoc in Ron Davis’ lab, also at Stanford. There, I began to gain confidence. It was the dawning of the post-genome era, and there was a need for pioneers who were sort of good at all sorts of things, instead of being an expert at just one. I could program computers, work comfortably with big data files, write well, and make figures; I knew molecular biology, microbial genetics, and biophysics, and I could create where there was no template and work hard. I had a great time working on the newly sequenced Saccharomyces cerevisiae genome and published papers that are still being cited today (1–3).

Then came some hard times. I decided at the end of my postdoc that I wanted to apply all the powerful postgenomic methods that we had developed for the model organism to an organism that caused disease, and I became interested in working on another single-celled eukaryote, the organism that causes human malaria. I had a degree in Developmental Biology and was therefore fascinated by the complex life cycle of the parasite, including how it orchestrated the transition from human to the invertebrate mosquito vector (Fig. 1) and its ability to evade the immune system and persist. Having read many novels, I was also interested in the disease from a historical perspective. It has been suggested, for example, that Oliver Cromwell’s refusal to take Jesuit’s Bark resulted in his dying from malaria (4), thus changing English history. My postdoc advisor, Ron Davis, had also been involved in sequencing the Plasmodium falciparum genome, and I was able to meet researchers and ask questions. I was surprised to learn that little was known about the parasite. In contrast to the well-studied S. cerevisiae, many of the predicted genes in the genome had unknown functions; the key transcription factors regulating development were unknown. We did not know the basis for sexual differentiation in the parasite. This all seemed remarkable given that at the time (1999) there were almost a billion malaria cases each year and a million deaths, mostly in children under 5 years. I was hooked.

To help with my transition to independence, I looked for a place where I would have access to the same technology that I had had at the Stanford Genome Center. I found a position that allowed me to work both at The Scripps Research Institute and a new institute, the Novartis Institute of the Genomics Research Foundation, that had been founded by Pete Schultz. Peter Schultz, like Ron Davis, encouraged me to think big and to embrace technological innovation as a way to make new discoveries. I was able to quickly use my background and available technology to publish one of the first whole-genome functional analyses of the parasite genome. I hypothesized and showed that you could gain information about the function of the encoded genes based on when and where they were expressed during the parasite’s life cycle (5). This may seem obvious now, but at the time it wasn’t clear that development would be regulated by the activity of canonical transcription factors or even that genes that were located adjacent to one another in the genome would be independently regulated (as is the case for most eukaryotes). This study (5) attracted a great deal of attention and allowed me to gain a foothold in the malaria field. Using genomic methodology, we were able to map out the elements of transcriptional control in the parasite (6) and to study how genetic variation emerged (7).

The only problem with starting work on a new organism as an assistant professor is that many people thought I wouldn’t be able to manage this. I had many rejection letters on grants from people questioning my background, lack of a malaria pedigree, or a dearth of credentials in tropical medicine (and also problematic may have been my status as a married woman with two small children). I had thought I could do anything as a postdoc, but I was soon to learn that if you write a grant and put the name of your famous male advisor on it, you are going to have a much easier time than if you submit the grant under the name “Elizabeth Winzeler.” I was triaged more than 10 times, and to this day, I have not received a fundable score in the Pathogenic Eukaryotes study section that funds most parasitology work nor its predecessor, Tropical Medicine and Parasitology. However, there were those that were very helpful, such as Dyann Wirth (Harvard School of Public Health), who has served as an Informal external mentor; Sandy Schmid, my department chair at The Scripps Research Institute; and David Fidock (Columbia University), my longtime collaborator. Eventually my persistence was rewarded. I was helped by a number of amazing lab members (Fig. 2) and received support from the Bill and Melinda Gates Foundation, Novartis, the Wellcome Trust, the Keck Foundation, the Ellison Foundation, as well as kind National Institutes of Health (NIH) officers who found workarounds to help me keep my lab funded. Maybe I was too stubborn and high-minded to write impeccable NIH grant applications to study obvious low risk problems, but it seems that my male peers with similar pedigrees were able to submit risky, creative, flawed applications and still receive top scores because reviewers appeared to give them the benefit of the doubt and recognize them for their accomplishments. I am now of the opinion that unconscious bias (e.g. offering an equally qualified woman slightly less, such as fewer high reward/low risk opportunities, than her male peers) is one of the key problems preventing women from excelling at the top levels of academic STEM fields. In addition to sapping one’s self-confidence, if you do not have a firm and stable foundation of funding, you won’t publish as much; you won’t be promoted as quickly, and after 20 years of this, you simply won’t be as impressive as your male
peers. You also won’t be eligible for top jobs or be able to recruit the best postdocs and students. Of course, as a scientist, one tries not to draw conclusions about a single data point, and I always have to consider the possibility that my background and interest in the unknown, the difficult and the never-tried, are what may have caused me problems instead of my gender. I also know women who have been very successful with anonymous peer review and men who have had problems, so if there is bias, it may not be obvious to spot. I am not sure we can devise ways to ensure that applicants who are not part of the dominant clique are treated equally. I would probably advocate for some sort of blinded system that is also able to capture one’s accomplishments as well as productivity per dollar of grant money. In addition, programs that fund the person instead of the idea were very important to me in the early days. It seems that women who have Howard Hughes Medical Institute funding often can break into scientific rock-stardom in ways that women who rely other sources cannot. My New Investigator Award from the Keck Foundation ultimately saved my career.

The work on malaria soon presented opportunities for doing new creative things. The field was concerned about emergence of parasite resistance to artemisinin derivatives (shown in Fig. 1), and it was clear that there was a great need for new treatments for malaria. However, most work on drug development had been focused on making new synthetic derivatives of known chemotypes (e.g. synthetic endoperoxides) or in vitro protein biochemistry with known targets (dihydropyrimidinase or dihydroorotate dehydrogenase), and it seemed there were opportunities to use advances in informatics and small molecule liquid handling to find new, desperately needed treatments for malaria. In addition, it soon became clear that the phenotypic screening strategy could be used to find better antimalaria therapies that had the ability to prevent malaria or block transmission (Fig. 1), especially as the known chemotypes and chemically validated targets often lacked these features. This was, believe it or not, considered a radical approach at the time—the field was focused on vaccines and within pharma and academia, structure-guided drug discovery. My technician,

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**Figure 1. Malaria parasite life cycle and current and future chemotherapies.** A, life cycle. *Plasmodium* parasites are first transmitted when a female *Anopheles* mosquito bites a vertebrate host, releasing hundreds of motile sporozoites into the bloodstream which then head to the liver. Each haploid sporozoite then invades a single hepatocyte. Depending on the species, the parasite may go dormant, becoming a hypnozoite, or it may differentiate into liver-stage schizont, in which thousands of new clonal parasites have been created through schizogony. The liver stage schizont will eventually burst, releasing thousands of merozoites into the vertebrate host. The merozoites invade erythrocytes, which they will devour, replicate themselves, and then burst. This asexual cycle that occurs in red cells is responsible for the symptoms of malaria and has been the target of most antimalarial drugs, such as quinine derivatives or artemisinin derivatives, both natural products with centuries of recorded use. In response to cues that are not well-understood, the parasites will differentiate into male and female gametocytes, the only parasite form capable of surviving in the mosquito midgut. Once the gametocytes enter the mosquito, they differentiate into gametes, which unite to form a brief diploid phase, the ookinete (data not shown). The ookinete will migrate across the midgut of the mosquito to form an oocyst out of which the sporozoites will arise to restart the cycle. B–D show readouts from 1536-well, microtiter plate assays that predict whether compounds will act against asexual blood stages (B) and relieve symptoms (B), act against the liver stage and prevent malaria from developing (C), or act against gametocytes and block transmission (D). Compounds labeled with gray boxes represent chemotypes discovered and developed through the use of these or similar assays (11, 12, 18–20), and they show multistage antimalarial activity, whereas compounds (artemisinin, atovaquone, and chloroquine) labeled with blue boxes are some of those that are used in current treatment regimens. Atovaquone has multistage activity and can be used to both relieve symptoms and prevent malaria, but endoperoxides and 4-aminoquinolines act primarily against blood stage parasites. Thus, someone treated with these may continue to spread malaria to one’s neighbors. Detailed descriptions of where compounds are in development is available from https://www.mmv.org/research-development/mmvp-supported-projects (Please note that the JBC is not responsible for the long-term archiving and maintenance of this site or any other third party hosted site.).
David Plouffe, and I stealthily and quietly worked out the kinks for a low volume, high throughput phenotypic screen aimed at finding compounds that might cure malaria (8). We then assembled a team, including long-term collaborator Yingyao Zhou, ran a very large screen, and soon after published our results (8). It soon became clear that the phenotypic screening method we perfected had worked better than expected and had yielded gold. Several derivatives of molecules (both new chemotypes for malaria) that were identified in our initial screens moved rapidly through clinical trials and are now being developed by Novartis as compounds KAF156 (ganaplacide) and KAE609 (cipargamin). Both have shown efficacy in trials with human malaria patients (9, 10) and have attributes that make them superior to endoperoxides and aminoquinolines (the chemotypes used in most of today’s antimalarial treatments), such as the potential for a single dose cure and the ability to block transmission. I believe this work has also had a great impact on the field especially as we worked to make our studies and molecules public. Others have followed the path we took and have found other interesting molecules that could be used to treat malaria (11, 12). We also developed novel methods for working back from the compounds to find their cellular targets, and the discovery of these new “chemically-validated” targets (13, 14) has spurred drug discovery by others.

I have now learned a great deal more chemistry than I ever thought I would and have published almost 150 papers on malaria, despite my lack of formal training on the topic. I have a passion for data science and look to achieve goals with consortiums that could not be achieved by one person working alone. My laboratory’s current focus is on identifying compounds that can be formulated as long-acting prophylactic compounds and provide lasting protection as a way to eliminate malaria for good (15). This notion is also considered unconventional, but it is slowly gaining some traction within the community. I must confess that I love a challenge and being told that I cannot do something.

I look back at my career and my success still seems improbable. Would it be even more improbable now? I have two daughters in high school, and although I think they are getting an amazing education at their elite suburban high school, I am worried that they won’t have the choices I had and that the hypercompetitive high school system is now forcing kids to decide at an early age what they want to do. In addition, the educational system now wants to focus on grades as a way to promote diversity. I was not mature enough to chase the grades I would now need to be admitted to my current institution (University of California, San Diego) when I was in high school. Would anyone have taken a chance on me if I hadn’t had excellent GRE scores (which I learned how to take with a library manual—the same strategy that I used to learn how to repair an alternator on my old BMW)? I wonder how the educational system can identify the people that are good problem solvers and not just good test takers? I also wonder if I can encourage young women to go into science knowing that they may have to work harder than their male peers.

I do think my liberal arts education provided advantages. First, I learned to write well and to write quickly—if you cannot convert your ideas to grant applications and publications, you will be lost in the business of running a lab, even if you are very talented at doing bench work. Art was also useful. A principal investigator spends a good deal of his or her time making figures and PowerPoint presentations. It is good to have a sense of composition and balance and to understand the color wheel and principles of graphic design. It is also wise to know some...
thing about computers and programming because the head of a small lab may have to be the IT manager as well. Some classes in business and management might also help. Above all, the student should embrace new experiences and learn about what is happening across biology, and maybe even chemistry and physics, because these different experiences ultimately lead to creativity, which leads to innovation and success.

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