PASPCR Commentary: A Colorful Journey with Fascinating Interactions

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Up until my early twenties I had never dreamed that I would be dedicating my professional life to laboratory research, not to mention the genetics of pigmentation. I did not do very well in science classes as a child…so much so that my high school physics teacher told me that I had better think of another career path because I certainly wasn't going to make it as a scientist! In college I hated chemistry and organic chemistry labs. I still have nightmares about labs where we were given three hours to purify a white compound and all I accomplished was isolating brown pasty substances and breaking lots of glassware.

Well, I didn't have to be a scientist. I grew up in a rural town outside of New York City where my father ran a family business installing ceramic tiles. I spent the majority of my weekends and school vacations, as well as mornings before high school, mixing cement and delivering the harvest gold, avocado green and hot pink tiles that were popular in those days. Thinking back, tile installation is not so dissimilar from laboratory science…you get to work with your hands and you can use the creative side of your mind. In tile work you can create beautiful patterns using colors of radiant blues, reds and greens to transform a previously boring wall into a work of art. In science you try to create innovative ways to discover information that no one else in the world knows.

I was unconvinced that tile work would provide enough of a venue for me to explore my more creative (or distractive) urges, plus my knees got really sore from all those floor jobs. So I attended college at UMASS Amherst majoring in animal sciences with the goal of becoming a veterinarian. I was fortunate enough to spend my summers exploring veterinary offices and dairy farms. On the dairy farms I was fascinated by the black and white patterns I saw in the dairy cows. The spotting exhibited seemingly infinite shapes and variations yet it was clear that they were not completely random. Little did I know that I would return to explore this area of research ten years later! My passion for becoming a veterinarian fizzled in my senior year of college and, I graduated not knowing where life would lead me.

With no relevant jobs available for me back home, I took a job changing rat cages. Needless to say, this did not challenge my creative side and after two weeks of sweating in a white jumpsuit, baby-blue head covering and purple latex gloves, I quit. Optimistically, I grabbed the "Help Wanted Section", hopped on a train to Manhattan and searched for a lab to hire me as a technician even though I had zero training and no experience. Luckily Dr. Abramson at the Mount Sinai hospital took a chance and gave me a job in her renal physiology lab. Dr. Beck, a co-investigator with Dr. Abramson, saw some potential in me and convinced me to consider going to graduate school…in fact she knew someone at Johns Hopkins and sent me down to Baltimore to meet with him.

Little did I know that it was really an entrance interview…I met with ten different investigators that day and soon after I enrolled to start graduate school for the next Fall.

Upon entering graduate school, I still wasn't convinced a career in science was for me, but it had to be better than shoveling cow stalls, changing rat cages or carrying cases of tile up stairs, right? Turned out Dr. Beck was right and I loved graduate school. The lab work wasn't timed, and it didn't matter if your purified solution was brown or chartreuse because since it was all novel research you couldn't be wrong! The lab work was viewed as more important than classes, and using your imagination (even in odd directions) was actually encouraged! I found a great lab to work in with Roger Reeves, who was studying Down syndrome using a combination of human and mouse genetics along with techniques in a then developing field that we now call genomics. I focused on developing techniques for studying human disease by modifying large fragments of human genomic DNA in yeast artificial chromosomes. I enjoyed the smell of growing yeast and appearance of pink and white colonies on the agar plates.

Our discussions regarding the potential causes of the attributes associated with trisomy 21 was my first introduction to a truly complex of biological question and clearly highlighted our inability to understand them using current approaches. I was fascinated by how subtle perturbations of gene interactions could be caused by only one extra copy of that subset of genes in an otherwise normal cellular environment. This view of how subtle alterations can influence the balance of network interactions and how alterations of network interactions influence human health and disease has become a main focal point of my future studies. It was almost time to wear my purple graduation gown and I was once again not sure where to continue my training. Dr. Reeves suggested that I apply to Dr. Tilghman's lab, then negotiated a visit and sent me back up the coast to Princeton. Luckily for me she offered a position in her group, and even though their school colors include a shocking shade of orange, I joined her lab.

After several discussions of projects, I chose to work on understanding the biological basis behind coat coloration alterations observed in *piebald* mutant mice. How could I not choose to spend the next part of my career in this area? I read how coat color mutants have been central to many discoveries made over the previous hundred years. Testing Mendel's theories of independent assortment, identification of linkage groups, analysis of complex and quantitative traits, development of chimeras, transgenic, knockouts and analysis of animal models of human diseases were all advanced through the use of coat color variations. If all these really bright people chose to work on coat color genetics, how could I go wrong in choosing this system to explore complex networks? In addition, having been fascinated by colorful ceramic tiles and variations in Holstein cows, what better field to work in than one with mice called *piebald*, *chocolate* and *buff*?

One project initiated at Princeton involved investigating genetic modifiers that contributed to the pattern variations. Most of our scientific ideas are based on work and ideas of our forefathers and this project was no exception. In the early 1900s, Charles and Dunn proposed that genetic modifiers (called the k-complex) contributed to the

variations in piebald spotting that we see. With the new tools being developed in genetics and genomics I readdressed the theories of Charles and Dunn and was able to map and evaluate the interactions of the k-complex loci and their contributions to spotting.

Just as the interactions of loci influence the fate of spotting in *piebald* mice, so did my interactions with colleagues influence the fate of my career. Dr. Tilghman contacted scientists she knew at the new National Center for Human Genome Research at the NIH (now called the NHGRI). She negotiated a visit for me and sent me back down the coast to Maryland. As I was considering the offer, I met Dr. Vincent Hearing and had a long talk about the NIH at the International Pigment Cell Meeting in London. Not only did Dr. Hearing provide extensive help and advice in negotiating this position, he helped me to integrate in the NIH campus and start a wonderful series of very productive interactions with many well-known pigment cell biologists on campus including Drs. Merlino, Arnheiter, Hammer, Bonifacino, Gahl and members of their labs. Ongoing discussions with the large pigment cell community on the NIH campus has been a tremendous help to our research. I have also been tremendously fortunate to have wonderful people work in my group over the years at the NIH. Their intelligence and dedication have been major reasons for the lab's success. Over the years our lab has used mouse models of human diseases to understand molecular defects and to test them as candidates for human disorders and to test therapeutic interventions. We have also used mouse models to test hierarchical relationships and explore their role in genetic pathways.

Our lab continues to focus on understanding the functions of genetic interactions and how perturbations can influence the network to produce biological outcomes. Our lab uses several approaches to compile and analyze the genetic network of pigmentation including analysis of whole genome expression (microarrays and full length libraries) and genetic sensitized screens. My rationale is that by studying networks and identifying nodes where subtle alterations can produce profound outcomes, one might be able to identify ways of perturbing networks in disease situations (neurocristopathies and melanomas). Theoretically, these would provide optimal targets for therapeutic interventions.

While we are far from attaining that goal, I think it is safe to say that my high school physics teacher was wrong…I <u>was</u> able to make a career in science…however some things don't change…when I am able to get close to a lab bench, I still only isolate brown pasty substances and still break lots of glassware.

Some relevant references of our work:

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