Biomedical Research as a Team Sport

For as long as I can remember, I have been captivated by the idea of belonging to a dynamic team that explores a frontier relevant to humanity. Some of my earliest childhood memories were of being transfixed by NASA's Apollo missions to the moon. Like many of my friends, I dreamed of becoming an astronaut. In the fourth grade, Michael Crichton's *Andromeda Strain* shifted my imagination from far away space to the mysteries of our own bodies. In this best-selling medical science fiction thriller, an eclectic team of talented, curious scientists work together to save the world from a lethal, highly infectious pathogen from outer space. Although Crichton's storyline was pure fiction, the excitement of a dynamic team coming together to solve a problem relevant to human health is very real. Participating in such teams over the past three decades has been a true joy as I have gradually transitioned from being a trainee to a leader. This path has been deeply gratifying in terms of personal growth, wonderful friendships, and a sense of having advanced medical science in a meaningful way. At a time when there is significant uncertainty among trainees about embarking on a biomedical investigative career, I am pleased to add my own story to illustrate why research can be an intensely gratifying career.

Getting started

In 1998, I fit the standard profile of a young person hoping to start a biomedical research career in many regards. Having completed medical school, graduate school, and a dermatology residency, I was an undifferentiated trainee hoping to develop a career that would be interesting, meaningful, and sustainable. I often tell young people that the most critical career decisions begin after completing initial training and during one's postdoctoral period. The decision to go back to the lab after clinical training and to invest several additional years to develop research momentum was not an easy one. I watched with some envy as my colleagues headed off in more practical, secure, better-paid directions. At that critical juncture, as I started my research fellowship, I received wise counsel from wonderful mentors and peers, many of whom are shown in Figure 1. With their advice to be bold in the next step of my career, I chose to join an extremely exciting, but truly unfamiliar research environment led by Stuart Schreiber in the Harvard Department of Chemistry and Chemical Biology. Although there were no other physician-fellows in Stuart's lab at the time, I was drawn there because of exciting basic work that had great relevance to dermatology and immunology. Stuart had built an incredible team of nearly 50 chemists and biologists who had recently unraveled the molecular mechanisms of what we now know as the calcineurin inhibitors (cyclosporine and tacrolimus), the first histone deacetylase inhibitor (trapoxin), the target of rapamycin (mTOR; sirolimus), and many more. I worked on a challenging but central problem of how UV-DNA damage is sensed by the ataxia telangiectasia and Rad3-related (ATR) protein kinase that had also been recently discovered in Stuart's lab. This project took time to get off the ground, in part because ATR was very difficult to manipulate, and in part because I needed to develop relevant research skills. During nearly three initial years without publishable data, my commitment to an academic research career was tested. I had to accept that quick, guaranteed return on investment is not a characteristic of research. I felt reassured about my investment in research training by speaking with people who took their careers in a variety of directions, such as to pharmaceutical companies where they were also happy, productive, and meaningfully engaged in research. We eventually developed ways to manipulate ATR, and my studies on the basic mechanisms of UV-DNA damage responses (Nghiem et al., 2001b) remain NIH-funded to this day. This work also led to a translational observation that caffeine (an ATR inhibitor) selectively eliminates UV-damaged, premalignant skin cells. Extensive recent epidemiologic data demonstrate that caffeinated beverage intake is associated with a reduction of hundreds of thousands of skin cancers each year in the United States (an approximately 5% decrease in all types of skin cancer for every daily cup of coffee, with no effect for decaf). Genetic evidence indicates that the relevant mechanism is indeed via ATR inhibition (Kawasumi et al., 2011). *Lessons learned:* In research, one sometimes must "risk failure to succeed," but also take psychological care of oneself during prolonged periods with minimal progress.

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Figure 1. The 1998 Harvard Dermatology Department. These are the mentors and colleagues I trained with, captured in the annual photograph of the Department during my final year of residency training. During this third year of training, I began spending most of my time in postdoctoral research in Stuart Schreiber's lab, supported by the Department's NIH training grant, while maintaining a continuity clinic and attendance at weekly didactic events. Many key research/career mentors were in the front row and include Harley Haynes (3rd from left), John Parrish (5th from left), Thomas Kupper (8th from left), Thomas Fitzpatrick (9th from left), and Arthur Sober (10th from left). The author is in the 5th row, 3rd from left. The photograph included with permission of Harvard Department of Dermatology.

Serendipity and kissing frogs

Although basic DNA damage studies were intellectually interesting, I yearned for a way to connect my scientific effort more directly with patient care. As is often the case with what later turns out to be an amazing career opportunity, my focus on Merkel cell carcinoma (MCC) did not start off in an auspicious manner. Indeed, I was quite certain that my efforts in this new area would ultimately be a waste of time. Harley Haynes, an inspiring mentor/professor who had first exposed me to the wonders of dermatology, asked me to write a book chapter on MCC. I had seen one case of this rare cancer as a resident with him, thus was effectively an expert in MCC. Because Harley was a wonderful mentor and one can never be certain what assignment might be worthwhile, I said yes to his request. On reading the literature on this cancer, it became clear that MCC was interesting due to its tendency to "jump" centimeters beyond pathologically clear margins, its links to immune dysfunction, and its behavior that was far more aggressive than melanoma. To my surprise, publication of this chapter (Nghiem et al., 2001a) quickly led to a steady flow of patient referrals and the realization that clinical management of MCC needed attention. I began keeping a list of patients we had seen, although I still did not believe this could be a fruitful research direction. Soon though, we had enough patients to apply for an early genetic study with seed funding from Tom Kupper's skin cancer SPORE grant. The 2008 discovery of the Merkel cell polyomavirus by Patrick Moore and Yuan Chang's team in Pittsburgh added fascinating new etiologic and translational dimensions to this disease. By 2017, this assignment that initially appeared to be "low-yield" had grown beyond any reasonable expectation in terms of the number of patients with MCC studied (over a thousand), funded grants (over a dozen), and translational research publications (over 60). Recent progress by our MCC team includes a better understanding of the immune responses against the polyomavirus (Afanasiev et al., 2013) and against UV-neoantigens (Goh et al., 2016), a clinically validated blood test to identify early disease recurrence (important for patients because immune therapy works better on less advanced disease; Paulson et al., 2016), and numerous clinical trials of immune stimulating agents that have significant activity in patients with advanced MCC (Nghiem et al., 2016; see www.merkelcell.org). *Lesson learned:* Keep an open mind because a truly important development may come from any direction, take any form, and initially appear to be an unproductive distraction.

Cultivating a virtuous cycle

Many people who have had long, productive careers in research have told me that their interactions with trainees are what most importantly sustained them personally and professionally over the years. I had my first taste of this fulfillment when I started to mentor a few talented students and fellows when I was a senior postdoctoral fellow. As I began to take on research mentees, I was immediately surprised at how much I enjoyed working with others as a team to tackle a problem. Such a team brings more sources for ideas to overcome roadblocks, the fun of coaching others as they grow in understanding, extra hands to share the workload, friends to commiserate with at times of disappointment, and partners with whom to celebrate at times of progress. In addition, guiding others as they develop their careers offers a special type of gratification. "Paying it forward" is a wonderful way of honoring one's mentors and returning the favor to the next

Figure 2. The 2016 "Team Merkel" on the night of the annual Seattle Merkel Dinner Meeting, attended by over 230 people including patients, their families, and the extended team. This photograph captures the diversity of a team that has come together to form a virtuous cycle that improves our understanding of a disease while developing the careers of the trainees involved. The group includes students, academic faculty, pharmaceutical company collaborators, research scientists, nurses, postdoctoral fellows, and administrative staff. The author is third from the left in the front row. Photo courtesy of Masaoki Kawasumi, MD, PhD, front row, far left.

generation. Somewhat surprisingly, one does not need to (and in academia, could not possibly) directly fund all members of a diverse and large team. By investing the time and thought to ensure that reaching a shared goal will benefit all involved, it is often possible to form powerful and enduring partnerships across institutions, departments, geographies, and all along the academic-industry spectrum. Figure 2 captures the diversity of the team that has coalesced to focus on MCC. Creating such a productive and genuinely supportive team sustains itself by recruiting talented trainees and collaborators that further drives the impact that the team can have. *Lesson learned:* biomedical research is no longer a "solitary" endeavor—forming an effective team is productive both professionally and personally.

The family juggle

My wife is a physician-scientist who has also needed to find ways to develop her career (Lee, 2013) while balancing family. We now have two wonderful boys, but at the time that each came along (17 and 11 years ago) we simply had to have faith that the new responsibilities would not derail our careers. In 1999, when our first son was born, I had put two intensive years into my fellowship, but progress was slow. I knew that having a child would decrease the time I could devote to research. Coincidentally, just as he arrived, experiments finally began to work. The timing of our second child required a bigger leap of faith, as it was clear we would need to "move home" to Seattle where our families still reside to have more support. We were both very happily ensconced professionally in Boston and received advice that this would be an unwise move. Nevertheless, we decided this was the correct move for us at the time. Happily, with extended family, good fortune, and the collaborative environment in Seattle, work-life balance issues have gone incredibly well. *Lesson learned*: Sometimes you have to do what is right for your personal life and trust that with careful planning and hard work, your professional life will work out too.

Helpful advice for a research career

Since graduate school, I have collected ideas that have helped keep me on a productive research career path. I will end this story with some thoughts that might help guide others through unpredictable times. Many are paraphrased and attributions relate both to the person who passed them along to me, and to the original sources.

Mission statement: To be deeply involved in thought on research problems that can make a difference, to have limited clinical responsibilities that I enjoy and that make a difference, and to maintain idealism-enthusiasm-wonder-fun in work and in life.

-my guiding principles written during postdoctoral fellowship, 2001

In science, happiness comes from carrying out daily duties joyfully and in looking at progress on the scale of many years.

-my mantra while doing tissue culture

Regarding science and medicine, it is good to be bilingual if not ambidextrous.

-Thomas Fitzpatrick (reassurance given to me as I worried that time spent as a postdoctoral fellow might not lead to a sustainable research career)

People who have never stumbled or redirected themselves on their climb up the ladder of success sometimes just don't get it. Occasional inner struggle is important in relating to others and in living life fully.

-John Parrish (on the benefits of personal struggle associated with taking risks and not always succeeding promptly)

Plan, focus, and think hard about directions in life, but be at peace with the vagaries of destiny.

-Thieu Nghiem (my Father)

Happy is the person who searches the cause of things.
-Virgil

To succeed in academia, enjoy yourself, do what you do well, and take the advice of others.
-Alice Pentland

Don't let hearsay about what others are doing stop you from doing what you believe is the right experiment. Stay the course.
-Stuart Schreiber

The habit of viewing things cheerfully and of thinking of life hopefully may be made to grow up in us like any other habit.
-Thomas Fitzpatrick

The journey is the reward.
-Steve Jobs

If you love what you are doing, you are on vacation 365 days per year.
-Allan Conney

I'm a strong believer that ignorance is important in science. If you know too much, you start seeing why things won't work. That's why it's important to change your field to collect more ignorance.
-Sydney Brenner

If you want to go quickly, go alone. If you want to go far, go together.
-African proverb (as quoted by Doug Lowy)

CONFLICT OF INTEREST

The author states no conflict of interest.

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