Journal of Pediatric Surgery 50 (2015) 15–22

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Robert E. Gross Lecture

Standing on the shoulders of giants: a scientific journey from Singapore to stem cells

Diana Lee Farmer

Department of Surgery, UC Davis Children's Hospital, University of California Davis, Sacramento, CA, USA

ARTICLE INFO

Article history:
Received 13 September 2014
Accepted 6 October 2014

Key words:
Fetal surgery
Spina bifida
Stem cells
Global surgery

ABSTRACT

Cellular therapy was introduced in the early 1980s as adoptive immunotherapy for cancer and has now expanded to stem cell treatment for a wide variety of indications. During the same period, the concept of the fetus as a patient evolved from fantasy to everyday reality. The intersection of these two fields offers great potential for cures in childhood diseases. The fetal treatment of spina bifida is one such disease. Global surgery has also emerged as a cost effective approach to reducing the worldwide burden of childhood disease.

Diana Farmer MD.

1. Surgical science and regenerative medicine: more than just cells

Sir Isaac Newton once said "If I have seen further, it is by standing on the shoulders of giants [1]." That sentiment—that scientific discoveries do not occur in a vacuum, but are rooted in the fertile intellectual soil tilled by others—resonates with me today as I deliver this year's Gross Lecture. Dr. Gross is one of the indisputable giants of pediatric surgery, who helped create the model of clinical excellence coupled to scientific inquiry. As a resident, Gross performed the first successful ligation of a patent ductus arteriosus. Previously, Gross had diligently conducted what would now be called pre-clinical research on cadavers and animals [2]. The success of that first human operation established him as a pioneer in the emerging field of pediatric surgery. The rest of his career was similarly characterized by innovation and success, guided by hard work and diligent research. Dr. Gross is a role model for those of us who aspire to follow in his footsteps as surgeon-scientists, even if we come to that path by a roundabout way.

My professional journey has been one full of surprises. Had I been a year earlier in giving this talk, I would have called it "serendipity" and described all the ways that chance meetings and unexpected opportunities led me to where I am today. However, the brilliant Jessica Kandel claimed that title last year [3]. This journey has not been a solo voyage. Every step of the way, I have been in the company of established and up-and-coming surgery giants, who have inspired me and helped me see farther than I would have ever thought possible.

Just after medical school the University of Washington, I had the opportunity to study medicine in Asia, as a Luce Scholar (that LUCE not LOOSE—important because my father said you've always been a loose scholar). Most advised me not to accept saying that only "family medicine and pediatric types" did that "overseas stuff" and that I would "never get into a serious field like surgery". Well, I went to Singapore. Over the course of an amazing year, I worked in the Department of Surgery at the National University of Singapore, studied traditional Chinese medicine and became certified in acupuncture. This early international experience, unbeknownst to me, would later become the springboard for my work in global surgery.

Following my return to UW, I came to know David Tapper, the first pediatric surgery giant to give me guidance. He encouraged me to follow my interest in scientific research, which was 30 years ago, somewhat unusual, both for women and for surgeons (in fact "there were only 3 woman on the wall at UW" one of whom was Karen Guice—spouse of Keith Oldham, last year's APSA president). Tapper directed me to UCSF to work with pediatric surgery giants numbers two and three: Alfred De Lorimier and Michael Harrison. These early interactions would lay the fundamental foundation for my career as a surgeon-scientist.

Along the way, I have discovered that scientific research is more complicated, more beautiful, more messy and more rewarding than

E-mail address: Diana.farmer@ucdmc.ucdavis.edu.

http://dx.doi.org/10.1016/j.jpedsurg.2014.10.025
0022-3468/

the elegantly written journal articles would lead one to believe. This truth is nowhere more evident than in the burgeoning field of regenerative medicine. Regenerative medicine seeks to harness the therapeutic potential of stem cells to treat a broad range of diseases. At the APSA meeting in 2011, Dr. Anthony Atala delivered an excellent Grosfeld lecture on Regenerative Medicine Strategies [4]. I will not re-create that speech, which beautifully described stem cell-based strategies to regenerate a wide variety of tissues and organs. I will, however, briefly describe key points in the evolution of cell-based therapy that correspond to my own research career. From my early research on cellular immunotherapy [5–7] for cancer to my current research on *in utero* cell therapy for spina bifida [8], I have learned that regenerative medicine is about much more than the cells we culture or the delivery vehicles we select.

In research, we strive for objectivity. However, there is no way to completely remove the subjective from science. Scientific progress is inspired by human dreams, driven by human will, re-directed by human politics, saved by human faith, and sometimes doomed by human hubris. The untold stories—those funny, frustrating, unbelievable moments that we leave out of the textbooks and manuscripts—form the everyday fabric of surgical science. Today, I want to pull back the curtain on surgical science in all its warty glory and share some of the lessons I have learned along the way—about surgery, about stem cells, and about science overall.

2. Early cell therapy: investigating new treatments for cancer

As a general surgical resident, I made my first attempt to join a surgical science laboratory—Michael Harrison's fetal surgery lab at the University of California, San Francisco. Al De Lorimier had made the first animal model for fetal surgery [9], and then recruited and helped launch the extraordinary career of Mike Harrison, now considered the father of fetal surgery. The Harrison lab seemed ideal: aspiring pediatric surgeons conducted research under the tutelage of an established great, laying the foundations for a new and daring branch of pediatric surgery. However, it was not to be. The lab did not have space for an additional resident (and I was an outsider from UW). Mike Harrison did, however, direct me to a cancer immunology and immunotherapy lab down the hall. I did not realize at the time that this work on cell therapy, an early foray into a field which can be viewed as the predecessor of stem cell therapy, would set the course for my own research career.

The lab ran the extramural arm of Steve Rosenberg's National Cancer Institute trial of autologous lymphokine activated killer (LAK) cells to treat metastatic melanoma and renal cell cancer. We lymphopheresed patients, harvested their white blood cells, cultured them in giant roller bottles with the cytokine inlerleukine 2, and injected the cells back into patients. We hypothesized that these cells, once re-injected into patients, would home to the cancers and augment the body's native ability to destroy them. By studying the cellular profile of treated patients with flow cytometry, our lab found that the activated effector cells were actually natural killer (NK) cells [7]. That discovery has served as the foundation for ongoing research on the role of NK cells in tumor suppression, and developing NK cell-based cancer therapies [10–13] used today.

Over the past 20 years, this type of research has spurred a number of important discoveries in cancer therapy, including engineering patient-specific T-cells and developing novel drugs that impact the function of the immune system [14–16]. Indeed, in 2013 the journal *Science* named cancer immunotherapy the breakthrough of the year, noting that "Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself. Oncologists, a grounded-in-reality bunch, say a corner has been turned and we won't be going back [17]." On a personal note, I found it a tragic irony that Dave Tapper, who had first encouraged me to pursue my interest in scientific research, later developed renal cell cancer and even received IL-2/LAK cell therapy, because conventional therapies were of little help in the face of this devastating cancer. Sadly, even after treatment with this experimental therapy, he eventually succumbed to metastatic disease, just after completing his tenure as APSA president.

I spent 2 years working in the immunotherapy lab. In that time, I gave my first bit of unsolicited career advice to a new attending, N. Scott Adzick, who has since distinguished himself as another giant of pediatric surgery. (Having come into possession of one of the academic promotion handbooks for UCSF faculty, and seeing a faculty fail promotion, I passed it along to Scott, a bold move for an uppity research fellow. A decade later, when I myself joined the faculty at UCSF, he would send it back to me.)

In that time, I also became friends and colleagues with the junior members of the Harrison Lab: Jack Langer, Tim Crumblehome, and Mike Longaker. Each had been assigned a project. At first, it seemed that Jack and Tim landed the plum projects: fetal surgery models for gastroschisis and hematopoietic stem cell therapy. The hematopoietic stem cell project seemed particularly exciting, because it followed up on the promising work conducted by the previous year's fellow and emerging pediatric surgery titan Alan Flake. In comparison, Longakers's project—wound healing—seemed decidedly less interesting. In fact, it seemed a lot less likely to jumpstart a career as a surgeon and a scientist.

Fast forward to today: Mike is now primarily a scientist. He is also the Vice Chair and the Co-Director of the Institute of Stem Cell Biology and Regenerative Medicine at Stanford University. In fact, Mike Longaker is now arguably one of the most prolific surgeon-scientists in the world. His trajectory, to me, is a powerful lesson: there is great potential even in the seemingly unglamorous project. Or, in the words of the great Mick Jagger, "You can't always get what you want/But if you try sometime, you just might find/You get what you need [18]," a recurring theme in the rock and roll world of surgical science.

My early research years also taught me that science is not as pure and fair as I had previously believed, and that the competition can be fierce, much more so than in clinical medicine. Grants do not always get funded on merit, *who* you know can be more important than *what* you know, and some people will go so far as to sabotage other's work in order to advance their own. One experience in particular profoundly impacted me. A veterinarian researcher down the hall appeared to be on the verge of an important medical discovery. The powers that be decided, however, that the research was too important to be left in the hands of a "mere veterinarian". In order to prevent him from carrying the project though, over a weekend, they had the locks changed on his lab and took control of the data and the project.

There may very well have been a more complex back story to the situation, but what I saw as a student investigator were politics and subterfuge. My naivete shattered, I became somewhat disillusioned with science: where were the integrity and objectivity supposedly at its core? My disillusionment taught me life-lesson #2. Leaders, mentors and senior investigators always have eyes on them. It is important to realize that our students, trainees and junior investigators are watching intently. What we model about honesty and integrity in research, not what we say, is what they will learn.

3. The "other" option for research: industry

In my third year of research, I joined DuPont-Merck Pharmaceuticals in Philadelphia (assisted by Morie Ziegler). I divided my time between continuing my research on cellular immunotherapy as a senior scientist in the Glennolden laboratory conducting basic work on tumor infiltrating lymphocytes and serving as the Assistant Medical Director of Cancer Clinical Trials. I gained invaluable experience running large-scale multi-center clinical trials, explored what a career in industry could look like, and even traveled to Italy to help establish our technologies at a Sicilian cancer institute. Having had little international experience outside of my Luce Scholarship year in Singapore, I was energized by the opportunity to work, once more, in another country. There I learned again, that care always occurs in a local cultural context and that money significantly influences the distribution of health care resources in sometimes illogical