

Embracing change

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From the time I was a child I knew my path: I was going to be a cancer researcher and spend my life in the laboratory trying to understand and conquer this terrible disease. However, a career, like a scientific experiment, does not always go as planned. In this short profile, I describe my years as an active cancer researcher and the unexpected new direction into the administrative side of research that I took a few years ago.

I was born in a small town in Quebec, Canada. Although not from a scientifically inclined family, I became interested in everything scientific at a very early age. At the age of 7 or 8, I would spend days reading scientific books and magazines and reproducing the figures using tracing paper. I remember a series of Time Life Science books that left a very strong impression on me. One of the books was simply called 'The Body' and contained illustrations of the various organs or systems, as well as a comparison to various pieces of machinery. I was fascinated by this concept of the human body as a 'machine' and decided that I would become a scientific researcher. In order to get a head start, at the age of 9 or 10, I decided that I should have my own laboratory and asked for a chemistry set and a microscope as Christmas gifts. In addition, my father worked at a rubber molding company and was able to get me 'cool' laboratory supplies such as Erlenmeyer flasks, graduated cylinders, and various chemicals. My bedroom soon became too small for my numerous scientific experiments, and my dad built a small 'laboratory' for me in the basement. It was a small room (10' × 10' perhaps), but

it was my own laboratory space. I felt like I was going to solve all the scientific mysteries and cure all diseases. After a few months of *in vitro* 'experimentation', I thought that it was time to take my research to the next level and bring my findings to an animal model. That year had been particularly dry and our backyard was infested with grasshoppers, and I figured that they would represent a great model for my studies. I did not want to mistreat the grasshoppers in any way, so I decided to study their 'behavior' and I built them a nice comfortable cage out of a cardboard box. I also realized that they needed light and air, so I cut small rectangular holes on the sides of the box, which were then fitted with toothpicks as 'bars'. My estimation of the bar spacing required to keep a grasshopper from squeezing through must have been somewhat off, because 2 days later, I came back from school to find an empty cage. The grasshoppers were all over the basement. That failed experiment unfortunately led to the untimely closing of my first laboratory, but taught me an important lesson on how a poorly planned experiment can wreak havoc on an otherwise well-thought-out research effort.

During my teenage years, I enjoyed reading scientific magazines, in particular, 'Scientific American' and a similar French magazine, 'La Recherche'. La Recherche was somewhat more technical and often included articles on quantum mechanics and other topics in modern physics that completely fascinated me. At that time, these magazines also frequently published articles

discussing molecular genetics and, in particular, how that new area of research could help us understand and even possibly cure cancer. I was convinced that the next big phase of science would be in the application of physics to the biological sciences, so I decided to go to the only University in Quebec that offered a Bachelor's Degree in Biophysics at the time, the University of Quebec at Trois-Rivieres. There, I received a great science background that included classes in physics, chemistry, biology, and mathematics. I did quite well in my classes, and several professors offered me the opportunity to work in their laboratory during the semesters and during the summer. At the time, many of the biophysics faculty members were interested in photobiology and were attempting, using sophisticated physical and chemical approaches, to understand how biological pigments such as chlorophyll and rhodopsin function. Many of these research projects were truly interesting, but I really wanted to study DNA because this topic was closer to my real interest: cancer research. None of the research programs had a particular focus on cancer at the time, but one of the physics faculty members, Dr Gerald Lefebvre, agreed to let me study the effects of u.v. radiation on DNA during bacterial spore germination. I studied this system for 2 years and then continued working on this project as a graduate student. Ultimately, I obtained a Master's Degree in Biophysics based on this work.

For the next phase of my education, my doctoral degree, I was determined to identify a genuine cancer research laboratory. I was accepted at Boston University and chose Dr Thomas Gilmore's laboratory for my thesis research. Tom Gilmore was studying a gene named *v-rel*, a retroviral oncogene, which, at the time, had recently been identified as a member of the NF- κ B family of transcription factors. Tom Gilmore had become interested in that gene a few years earlier when he was a fellow in Nobel Laureate Howard Temin's laboratory. We now know a lot about the pathways, both upstream and downstream, of these important transcription factors, but at the time little was known and I decided to study the I κ B proteins, the upstream inhibitors of NF- κ B. My 4 years in Boston were really fantastic as I really discovered what research was really about: the excitement of a new discovery and the much more frequent disappointments of failed experiments. I had the opportunity to learn so much about the field of cancer research and got to enjoy Boston area's incredible scientific wealth. I, together with three or four other BU graduate students, frequently attended seminars at various institutions around town. Sometimes we would walk over to Harvard Medical School or across the bridge to MIT, and other times we would take the T to Brandeis or

Tufts. I got to attend great talks by luminaries such as David Baltimore, Walter Gilbert, Tony Hunter, Bob Weinberg, Paul Nurse, and many others. These years in Boston were truly exciting and inspiring, and I would encourage every young scientist to learn about the work of great scientists in various fields. Much of the information gleaned from these illustrious scientists turned out to be extremely useful later in my career.

After a 4-year stint at BU working on my PhD, I started looking at various laboratories for my postdoctoral work. My goal was to find a laboratory involved in the most exciting and impactful cancer research. I talked to several biology faculty members at BU, and one of them, Edward Loechler, suggested that I apply to Dr Bert Vogelstein's laboratory at Johns Hopkins Medical Institutions in Baltimore. Bert Vogelstein had just published a series of transformative papers identifying and characterizing mutations in mismatch repair genes in colorectal cancer. The work was just another step in a long series of breakthroughs that Vogelstein and colleagues had been intimately involved in since the early 1980s. Their work, using colorectal cancer as a model, basically suggested that cancer developed through a series of mutations in various cancer genes. It had been shown that the first gene to be mutated in colorectal cancer is *APC* and, for this reason, *APC* had been coined the gatekeeper of colorectal cancer. I found this concept fascinating and, when I interviewed with Bert Vogelstein and Kenneth Kinzler, the laboratory co-director, I mentioned my interests in the pathway and told them that should I be offered the job, I would like to work on *APC*. Perhaps because the 'hot' topic was mismatch repair at the time, they seemed surprised with this idea and offered me a position on the day of my interview. I still do not quite know how I managed to join such a competitive and high-profile laboratory. They later told me that they receive hundreds of applications every year, many of which I am sure were at least as good, if not better, than mine. I think it was a case, like many things in life and in science, of being at the right place at the right time. I certainly learned that luck plays a big role in scientific discoveries, and being accepted in one of the best cancer research laboratories in the world was certainly a stroke of luck that affected much of my future career.

In June 1994, when I joined the Vogelstein/Kinzler laboratory, little was known about the mechanisms by which *APC* exerted its role as a tumor suppressor gene. My first project was to generate colorectal cell lines with an inducible *APC* gene. After much effort, I was able to generate a cell line that contained the *APC* gene driven by the metallothionein promoter and that could therefore be

induced by zinc. The cell line was used to show that *APC* expression appeared to sensitize the cells to cell death, but again the mechanisms by which this happened were elusive. Paul Polakis' group had shown some time earlier that β -catenin could interact with the APC protein and that this complex reduced β -catenin levels. We started to consider the possibility that APC and β -catenin may be part of a pathway that is important in colon cell proliferation and survival. Interestingly, a paper by Randy Moon's laboratory showed that β -catenin in *Xenopus* contained phosphorylation sites that were crucial in targeting this protein for degradation. Mutations at these sites in *Xenopus* led to an increase in the stability and activity of β -catenin. Upon reading this paper, Bert Vogelstein called us into his office and predicted that β -catenin was going to be found mutated in human cancers at the same phosphorylation sites. Sure enough, a few days later, after sequencing several colon cancer samples, we identified β -catenin mutations in the phosphorylation sites and found that the mutations made β -catenin resistant to APC-mediated proteasome degradation, therefore leading to an increase in β -catenin-mediated transcriptional activity. The identification of β -catenin mutations in colorectal cancer was published in *Science* in 1997 and was the first paper, together with another paper on melanoma in the same issue, that identified mutations in this gene and also provided a mechanistic explanation for these mutations. As of January 2014, this paper has garnered over 3000 citations and β -catenin mutations have been found in many human cancer types.

Despite the high level of science in the Vogelstein/Kinzler laboratory, there was still time for some fun. During my second year there, we began a new area of exploration that was musical rather than scientific. Having played guitar in various bands since my teenage years, I was the catalyst in starting a band known as 'Wild Type', which eventually garnered a small cult following of fellow scientists. Bert Vogelstein was the keyboard player, Ken Kinzler, the drummer, Chris Torrance, the other guitarist, Bob Casero, the bassist, and Ellie Carson-Walter, the singer. All of us were part of the Vogelstein/Kinzler laboratory, except for Bob Casero, who was a Professor and cancer researcher with laboratory space right next to us at the Johns Hopkins Oncology Center. At first, we were hard pressed to find any fans, as we had a one-song repertoire (Johnny B Goode), which we practiced repeatedly in a small room at the Johns Hopkins Hospital. Perhaps one of Wild Type's lowest points was when a nurse from the methadone clinic next door came over to tell us that her patients would really appreciate it if we could learn other songs! With that impetus and after

many hours of practice, we built a song list varied enough to begin playing out, not only at scientific conferences, but also at various bars in the famous Fells Point area of Baltimore. Our original song 'The Grant-Writing Blues' written by myself and Bob Casero was less popular in Fells Point, but got heartfelt support at scientific meetings. (In this funding climate, I believe that it would now be a chart-topping hit...) Perhaps our best and most exciting gig was at the 1998 AACR annual meeting in New Orleans. The room was throbbing with several thousand people, all dancing and cheering. When Bert Vogelstein performed his signature move, playing the solo of 'Great Balls of Fire' behind his back, the crowd literally went wild. We felt like real rock stars! Unfortunately, a few years later, graduate students graduated, and post-docs moved on, and Wild Type continued to exist only in occasional reunions. The Wild Type episode was a great lesson for me. I learned that although working hard is important, and we all did, it is also important to find time for other activities, ultimately making us happier and more productive.

After about 4 years of research at Johns Hopkins as postdoctoral fellow, I was ready to start looking for a faculty position. I looked at various opportunities, but ended up choosing a position in the intramural program of the National Institute on Aging at the NIH. The NIH intramural program is an interesting concept. Initially, all the NIH-funded research was performed in federal laboratories, but when the NIH expanded after WWII and started funding extramural research, it was decided that a fraction of the NIH money would remain in intramural laboratories to fund scientists pursuing high-risk, high-reward research. The intramural research program accounts for just about 10% of the entire NIH budget, and the budget was approximately \$3.4 billion in the fiscal year 2013. Intramural tenure-track research positions typically come with laboratory space and research staff, as well as research funds. For example, I was offered one technician, two postdoctoral fellows, and a research budget sufficient to support the work performed by these individuals. In addition, access to all the core facilities (genomics, microarray, mouse facility, and biostatistics) is included. It is understood that the size of an intramural laboratory can grow over time, depending on successful evaluations by a group of external reviewers. This review takes place every 3–4 years. Poor productivity and/or negative reviews by the external committee can lead to the position of the investigator to be terminated or to the support being decreased. On the other hand, after a number of years, an NIH investigator who has done particularly well can be given tenure and promoted to 'senior investigator'. Intramural investigators are not

allowed to apply for NIH grants, as the NIH does not want to divert extramural money to intramural investigators and effectively increase the size of the intramural program. As I will discuss later, the inability to apply for extramural funding can unfortunately have a severe impact on the mobility of NIH intramural investigators.

My laboratory at the NIH focused on the study of ovarian cancer. I had two main areas of interest: i) identifying/developing new biomarkers for this disease and ii) understanding the mechanisms of drug resistance. Drug resistance is a major problem in ovarian cancer, and we hoped that a better understanding of what makes the ovarian cancer cell resistant may lead to novel strategies to circumvent drug resistance. Early in my time at the NIH, we used a technique that had been recently developed by the Vogelstein/Kinzler laboratory, known as Serial Analysis of Gene Expression, and identified claudin proteins as a family of proteins frequently over-expressed in ovarian cancer. This finding represented the first time that these proteins were implicated in cancer, and we focused on these intriguing proteins and their role in the pathogenesis of ovarian cancer. Our work suggested that these proteins, which normally function as tight junction proteins, have altered functions in cancer, where they can promote cell migration, invasion, and possibly angiogenesis, the formation of new blood vessels to feed the tumor. I was awarded tenure in 2004, making that year a banner year, as it was also the year that my wife Ashani Weeraratna, also a cancer researcher, gave birth to our beautiful daughter, Alina. At that time, I did not believe that I would ever leave academia or even the NIH.

Following a change in the leadership of the National Institute on Aging, I was told that cancer research was no longer a priority at the Institute on Aging (I was actually told that aging was not relevant to cancer!!) and was asked to re-orient my research priorities. I was shocked, as I had been performing cancer research for the past 20 years and had actually received tenure at the NIH based on that research. Because I was tenured, I did not have to leave the NIH, but the threat of cuts to my budget for cancer research was enough to lead me to reassess my situation, tenured or not. I started looking for opportunities in academia, but I soon realized that without independent funding, finding a position in academia in the USA would be difficult. I consulted with many scientists, including research directors at various institutions, and always received the same verdict: my prospects of finding a position in academia were not good. The combination of being a 'mid-career' investigator and having no grant support to take with me was a fatal flaw. I certainly had an active

research program and respectable CV with over 85 publications and an h-factor of 42, but none of it mattered: no grants, no job. That was when I realized that an investigator position at the NIH can be a dead-end position. I knew of a few people in my situation and they all faced the same problem. Some left science completely, while others, like me, took positions in science administration. For my part, I must say I was particularly lucky in the end as my current position as the director of the Grants Programs at the AACR allows me to remain deeply involved in cancer research and continue to have an impact on the field. I enjoy discussing the latest advances in basic, translational, and clinical sciences on a daily basis with leading scientists in the field. However, as I mentioned, not all NIH investigators who chose or had to leave had the same luck. I believe that the NIH should develop an RO-1-size 'bridge grant' that NIH investigators who decide to leave could compete for, so that they can be on a more level playing field when applying for academic positions for which other scientists who have their own grants are also applying. I did mention this idea a few years ago to a high-level individual at the NIH, but I am not sure that this idea will ever take hold. Until then, I could not, in all good conscience, recommend to a young scientist to accept a position as an investigator in the intramural program of the NIH.

Overall, I must say that things have worked out extremely well for me, in spite of the unexpected change in career direction. I had a chance to perform high-level cancer research for over 20 years as a graduate student, a postdoctoral fellow, and an independent investigator. My new career as the director of the Grants Programs at the AACR has been a huge change, but very interesting. Do I sometimes miss active research? Sure I do, but I need to embrace this change as nothing lasts forever and I am still able to use my scientific knowledge and continue to have an impact on the field of cancer research. In the end, isn't that what it's all about?

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this profile.

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