



The Kringle of Life

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If you are a scientist and you were born the child of a scientist—even more so the child of two scientists—then it will be generally assumed that you were greatly influenced by your parents. This was certainly the case for me.

I received my undergraduate degree in Chemistry from the same Department at Carnegie Mellon University (CMU) in which my father worked. Perhaps the toughest test (literally) during my undergraduate years was having to take Physical Chemistry III: Quantum Mechanics, taught by none other than my father. More than anything, this taught me how he viewed the world and how he approached his thinking about both science and life. In his view, most things should be able to be explained mathematically from basic principles.

My father had come to CMU in 1976 from the laboratory of Kurt Wüthrich at the Eidgenössische Technische Hochschule (ETH) in Zurich where he published the first ¹⁵N nuclear magnetic resonance (NMR) study on living cells [21] and explored the structure and dynamics of aluminum desferri-ferrichrome [24], [26, 27]. His interest in coming to CMU stemmed in large part from the Department of Chemistry's innovations in the area of NMR at that time. My father had a particular goal of applying state-of-the-art NMR technology to the structural analysis of proteins. At CMU, he pursued his studies in the company of Aksel Bothner-By, Joseph Dadok, John Pople, and others who became life-long colleagues and good friends of his.

In the mid-1970s Bothner-By and Dadok had collaborated to build the world's first 600 MHz NMR spectrometer. I remember spending Saturday mornings in my father's lab poring over the printouts of the spectra associated with the

NMR spectrometer and using the rulers on the drafting table to find the rectilinear positions of the peaks to extrapolate the data in 3-D. Of course this is all now done by computers. My father innovated by using NMR to advance our understanding of the mechanism of blood clot dissolution, by studying the structure–function relationship of the kringle domains from tissue plasminogen activator (tPA) and other fibrinolytic proteins [2, 4, 7–8, 11, 30–32, 35–40]. tPA is now widely used to treat blood clots in thrombolytic therapy.

Many years later, one of the highlights of being a Chemistry major at CMU was that we got to use this same NMR spectrometer for our lab course. This instrument was remarkable in its appearance. It was housed in a gigantic room, and it looked as though it was built from scratch using a bunch of Radio Shack parts, combined with odds and ends from a hobby store (both of which have gone extinct). Wires ran all over the room in what seemed like a chaotic mess. Despite its unusual appearance, the NMR spectra generated by this instrument were truly spectacular!

Undoubtedly my father influenced my career in many ways, both directly and indirectly. When I was fresh out of college he helped me to secure an internship with his colleagues Ulrich Kohnert and Stephan Fisher [9–10] at a protein production facility of Boehringer Mannheim (now Roche Diagnostics) in Penzberg, Germany which had a small research arm. Although I had pursued research in yeast genetics as an undergraduate student at CMU, it was at Boehringer that I had my first exposure to industry-level research by working as a full-time technician. Although these efforts resulted in my first scientific publication [13], the experience fully convinced me that I needed to go to graduate school so that I could define and lead my own independent research interests.

After spending a wonderful nine months living in the foothills of the Bavarian Alps, I was delighted to go off to UC Berkeley to pursue my PhD. Now I was really following in the footsteps of my parents who had first arrived in the USA to study at Berkeley in 1963. Everywhere I went on campus had ties to my family history and the tumultuous 60 s and 70 s, from the Free Speech Movement to the

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anti-Vietnam War demonstrations. My father had great stories about working in the lab of Joe Neilands, who was an ardent activist during the Vietnam war. He likewise told tales of working side-by-side in the lab with Kary Mullis, whose antics and late-night experimenting were novel to my immigrant parents [33]. It was at Berkeley working with Joe Neilands and Melvin Klein that he began his lifelong work using NMR to explore solution structures of peptides with a particular focus on ferrichrome, a cyclic hexapeptide siderophore [15–20, 22, 23, 25].

Many other friends and colleagues my parents had from their time at Berkeley were still in the area, making it an inviting place for me. During my time there my mother was awarded a plaque that now hangs in Cory Hall, honoring her for being one of the first women who earned their PhDs in electrical engineering at UC Berkeley [41]. Although my mother recalls that it was odd to be in class with only men, she found the scientific environment to be highly motivating.

For my PhD thesis, I chose to work in the area of biophysics and protein folding with Prof. Susan Marqusee in Stanley Hall, the old Biochemistry and Virus Laboratory building. My doctoral work also employed NMR, which I used to measure protein stability and dynamics by hydrogen deuterium exchange in the recombinant scrapie prion protein [14] and T4 lysozyme [3, 28]. To do these studies, I worked in the famous round and open Calvin Lab, where my father had done his work on ferrichromes decades earlier. This work also led me to a series of wonderful collaborations with the lab of the renowned protein NMR spectroscopist Rick Dahlquist, who was then at the University of Oregon.

As my research interests turned away from protein biophysics during my postdoctoral years at UC San Francisco in the laboratory of Prof. Joseph DeRisi, my father was enthusiastic about my new interests in transcriptomics (further advancing the, then-new, technology of DNA microarrays) and the basic molecular underpinnings of the biology of the malaria parasite [29]. This work ultimately earned me an assistant professorship at Princeton University in 2005.

Since my father had begun his early training in medicine, he was delighted that I was focusing my research on a pathogen of major global health impact and applying modern tools of molecular biology and genetics. However, my training in chemistry continued to impact my research interests. I became fascinated by the metabolism and biochemistry of the malaria parasite, and my research group began to explore emerging methods in the area of metabolomics. Over the years, we developed approaches to quantitatively measure global intracellular metabolites using a combination of mass spectrometry and NMR spectroscopy [5, 12, 34, 1, 6]. These research directions continue to thrive in my current lab at Penn State University. In the end, not only did my father influence my work, but I physically came full circle to live within reach of my hometown of Pittsburgh, Pennsylvania,

which facilitated visiting him frequently during the last years of his life.

Anyone who knew my father knows that he was a purist and a self-proclaimed “expert” on a wide range of topics. This certitude extended beyond his passion for science to his tastes in music, food, wine, travel, and art. I would like to think that many of the things he valued have contributed to who I am today. In his work and in his daily life, my father pursued his idea of perfection. While life isn’t perfect, we can remember him for seeking this ideal in himself and others, and for encouraging us to always strive to achieve our best.

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