



Justine Hill.

Getting Started in Science

My journey into the world of science was a gradual process. At school, my favourite subject was maths, but literature and reading were a passion and I spent much of my spare time immersed in books. This led to some early thoughts of studying professional communication at university and becoming a print journalist. I was also fascinated by ancient history and contemplated becoming an archaeologist. When it came time to enter university, I decided on the Bachelor of Applied Science degree at Queensland University of Technology (QUT) because it offered a wide range of courses and kept my options open. During my first year, I was rather surprised to discover that what I enjoyed most was chemistry. I particularly liked the practical classes and even the preparation of lab reports, which was fortunate, as this comprised a significant component of the chemistry program at QUT. Unfortunately, I didn't like biochemistry at the time, largely because the teaching approach emphasised memorisation. Although later on, I often wished that I'd persevered, as it definitely would have helped to smooth my journey through the postdoc years.

The spark to pursue a career in research was ignited during an industry placement between the 2nd and 3rd year of my undergraduate degree. QUT's Cooperative Education program provided an opportunity to take a break from formal study following 2nd year to gain some valuable work experience. Excitedly, I set off on my first overseas trip to work at Rhône-Poulenc Chemicals in the UK. The company was located in the rather unglamorous Avonmouth docklands of Bristol, and the site comprised several chemical plants manufacturing small organic intermediates for the pharmaceutical industry. While at Rhône-Poulenc, I was part of the Research Analytical Laboratory, whose primary role was to provide technical support for the research groups working to optimise or develop new synthetic strategies for compounds of interest. My job performing gas chromatographic analysis of organic compounds was not particularly challenging, but it afforded an opportunity

Solving Protein Puzzles with NMR

Justine Hill describes how perseverance and on-the-job training has led her to NMR success and running her own lab.

to interact with the neighbouring research groups and to learn more about their work and the research process. The ability to explore your own ideas and design your own experiments sounded ideal, and it inspired me to undertake further study and to ultimately pursue a research career. It was during this year that I also realised the great potential to combine science with travel. Bristol and the nearby spa town of Bath were lively and fun places to spend the weekends, and I made trips to several other cities, including London, Oxford, Edinburgh and York, throughout the year. I also managed to squeeze in that once rite of passage for many young Australians, a bus and camping tour throughout Europe, before returning to Australia with a renewed sense of purpose to complete my undergraduate studies.

Bitten by the NMR Bug

As my undergraduate degree at QUT progressed, I found that what I enjoyed most was physical chemistry, particularly spectroscopy. I was fortunate to choose John Bartley as a supervisor for both my undergraduate and Honours research projects. John's interests included structure elucidation of natural products and he shared his enthusiasm for NMR spectroscopy with me. John was also interested in NMR of macromolecules and had undertaken a sabbatical visit to work on triplex DNA with Andy Lane (then at Mill Hill in London), and discussed with me advances that were being made in the study of nucleic acids and proteins. The first three-dimensional protein structures using NMR had only recently been determined, and the triple-resonance NMR methods that we use routinely today were just being developed. Exciting times to be involved with NMR, and they still are today with new developments continually being made!

My Honours research focused on optimising the large-scale synthesis of glyphosate, a herbicide more commonly known as Zero or Roundup. Monsanto's patent on glyphosate synthesis had recently expired, and a small chemical company just north of Brisbane was interested in commencing manufacture. My syntheses in stirred batch reactors were conducted in a large tin shed under experimental conditions that proved difficult to control. As temperature was an important factor for the reaction, this was quite challenging, and rather than high yields of glyphosate, I succeeded in creating several previously unreported by-products! On a brighter note, I established an HPLC method to nicely separate the reaction products and characterised them using NMR. I found that I really enjoyed piecing together the NMR data to reveal the molecular

GREAT EXPECTATIONS

structure of a compound, in much the same way as you solve a jigsaw puzzle. This foray into chemical synthesis also served to highlight my strengths in physical chemistry.

As an Honours student in chemistry at QUT, mixing the obligatory coloured liquids for the camera. Photo courtesy of Inside QUT.



Cone Snail Toxins and a PhD

After a short break following Honours and a trip to Egypt, Israel and Jordan to satisfy some of my historical and archaeological interests by visiting some places that I'd read so much about, it was time to take the next step. I was very fortunate that the beginning of my PhD in 1994 coincided with the relocation of David Craik from the Victorian College of Pharmacy (now part of Monash University) to the Centre for Drug Design and Development (3D Centre) at the University of Queensland. So I moved to UQ to study the structure of conotoxins, small polypeptide toxins from marine cone snails, using NMR spectroscopy. During my PhD, I worked within two groups at the 3D Centre, performing peptide synthesis under the guidance of Paul Alewood and NMR with David. Cone snail venoms were just beginning to be explored for compounds of potential pharmaceutical benefit and it was an exciting field to work in. Working on conotoxins also provided opportunities to become involved in field trips to the Great Barrier Reef for collection of cone snails and was a motivating factor for several of us to obtain our scuba diving certificates. Truth be told, I didn't actually find any cone snails while diving as walking around the reefs at low tide formed the majority of collections, but it was a great excuse!

Over the next few years, I synthesised and determined the structures of several conotoxins. Our workhorse was a 500 MHz NMR instrument (still going strong in David's lab) and later we also had access to a 750 MHz instrument housed in the Centre for Magnetic Resonance at UQ. This enabled us to determine high-resolution structures and glean new insights into conotoxin interactions with their ion channel receptors. My time as a PhD student was not only productive, enabling me to receive postdoctoral fellowships from the NHMRC and the Human Frontier Science Program, but highly enjoyable. Both David and Paul granted me a lot of intellectual freedom and encouragement to lead my project, thus also equipping me with fundamental skills in project design and time management, and giving me the confidence to go on to become an independent researcher.

Postdocing in New York

With my enthusiasm for NMR still intact and a desire to apply this to proteins, I looked for a postdoctoral position to enable me to obtain skills in both protein biochemistry and protein NMR. Towards the end of my PhD, I had seen a growing number of publications describing the identification of signal transduction pathways that regulate programmed cell death (apoptosis). This was a rapidly developing field that offered lots of opportunities for structural biology to contribute to the understanding of these newly identified proteins and pathways. Milton Werner's lab at the Rockefeller University in New York provided me with the opportunity to work on apoptosis, but also to obtain a new skill set in molecular biology and protein biochemistry. When I first arrived at Rockefeller, it was incredibly exciting, but I faced a steep learning curve. Not only was I starting work on a new project area for the lab, but I was a complete novice in the majority of techniques used. During the first few months, I was often met with looks of incredulity that I'd never done a PCR reaction, run an agarose or SDS-PAGE gel, or expressed and purified a protein. The list seemed never-ending! However, with generous help from Milton and other members of the lab, and armed with the Sambrook and Russell molecular cloning manuals, I soon found my feet.

My main project at Rockefeller was to study the structure and function of Fas-associated protein with Death Domain (FADD), the central adaptor protein in death receptor-mediated apoptosis. FADD proved to be a recalcitrant target for structural studies. The full-length protein had been reported as unsuitable for structural analysis, but I naively thought that it couldn't be that difficult... Several years later, after expressing a range of protein constructs with numerous different tags and introducing point mutations to improve solubility, we managed to identify a suitable form of the protein for NMR and determined its three-dimensional structure. Although it was demoralising at times, I thrived on the project because of its challenges. Working on FADD gave me a thorough education in molecular biology and recombinant protein production, as well as a few other lessons along the way. You learn far more about research and yourself by conquering a difficult problem than from solving several easy ones, and the ability to persevere has stood me in good stead.



Rockefeller colleagues and friends after a Sunday brunch. From left: Lester Lambert, Anja Wille, Justine Hill and Laurel Glaser.

Perhaps most importantly for my career development, Rockefeller provided a vibrant and inspirational environment to learn about biology. I hadn't studied biology at high school and only introductory courses in biology and biochemistry as an undergraduate, so I soaked it all up like a sponge. In addition to weekly seminars by distinguished visitors, there were numerous internal and local seminars where I was able to expand my knowledge. Rockefeller was full of outstanding researchers with a passion for science, which enabled us to feed off each other's ideas and learn from one another. Upon reflection, I probably couldn't have chosen a better place to broaden my scientific horizons. I also enjoyed myself hugely exploring the non-academic activities on offer in New York. My colleagues became good friends and we worked long hours, ate and played together.

Returning to Australia

After four years in New York, I decided to return to Australia and UQ in 2003 to begin building an independent research program. I was welcomed back into David Craik's group, now at the Institute for Molecular Bioscience, to complete the return leg of my CJ Martin Fellowship. Initially, I built upon my overseas work by embarking on structural and functional studies of complexes that regulate death receptor-mediated apoptosis. It was exciting to be awarded my first Project Grant a couple of years later to continue these studies. I also established a new project to investigate the structure of the inflammasome, a caspase-1 activating complex that plays an important role in innate immunity and inflammation. The inflammasome and death receptor signalling complexes share common protein interaction domains that mediate their assembly, so lessons learnt from one system are proving very useful to understand the other.

Returning to UQ has had several advantages for my career. Excellent existing facilities, together with plans to purchase a 900 MHz spectrometer (subsequently installed in mid-2006), meant that UQ was an ideal place for me to establish projects and build a group. It has also been invaluable to have the support of colleagues that I've known for many years. Without their wealth of advice and generosity in sharing equipment, setting up my own projects would have been a far more arduous task. In 2006, I was awarded an RD Wright Fellowship and shortly thereafter was offered the opportunity to move to the School of Molecular and Microbial Sciences (now known as the School of Chemistry and Molecular Biosciences, SCMB) to establish my own group. I happily accepted, and in early 2007, moved a couple of buildings across campus to SCMB.



Hill group at the end of 2009. From left: Ruth Mirams (PhD student), Parimala Vajjhala (Research Officer), Justine Hill and Sebastian Kaiser (Research Intern from Germany).

New Beginnings at SCMB

The past few years establishing a group at SCMB have been an exciting time in my career. The progression from organising just my own research to coordinating a research team, teaching undergraduate students, and becoming increasingly involved in administration has been challenging but also very rewarding. I still try to spend time in the lab and at the spectrometer, mostly helping students with experiments and occasionally doing some of my own. I am enjoying sharing my love of protein structure and function, and of course NMR, with postgraduate and undergraduate students. It is particularly fulfilling to have undergraduate students in the lab to give them their first taste of research and get them enthusiastic about science. I have been privileged to have an outstanding series of mentors throughout my career, and I hope to provide the same levels of support and mentorship to the next generation of scientists coming through.

As we inevitably spend long hours striving to do interesting and significant research, it is important to also have fun and enjoy what you do. A mentor at Rockefeller often said to me "Do good science, and science will be good to you." I am incredibly thankful for the experiences and opportunities that science has given me thus far, including a great group of colleagues, collaborators and friends. I look forward with anticipation for what is next to come on this unforeseen and exhilarating journey.

