



Jill
Trehwella.

Our series continues in which Australian scientists describe their journeys of professional and personal development. Jill Trehwella describes her career, including heading the high-profile Bioscience Division in Los Alamos, USA, and what convinced her to return to her roots in NSW.

Exploring the Horizons

Those of us who are passionate about science, and who have the good fortune to be able to pursue that passion, have remarkable opportunities to explore diverse worlds; from the intricate details of our specialists worlds to the greater issues of how science impacts society and vice versa.

When I look back on my career as a scientist, the thing that stands out for me is how science broadened my horizons – and not just geographically. I had the very good fortune to be presented with what I realise now were unique opportunities to experience science on a world stage that went beyond my own specialist interests in biophysics and structural biology. My retrospective here brings home to me how important it is to make the most of the opportunities at hand and not be overly focused on designing the perfect opportunity; after all, none of us really knows what lies over that horizon!

The Beginnings

I grew up about 50 miles north of Sydney on the Central Coast, surrounded by old orchards and bush. Narara Primary School was across the road at our back fence and because I had to hear the end of the radio soap that was on every morning – 'Portia Faces Life', I recall, was one of my favourites – most mornings would find me diving out the back door, over the fence, never to arrive at assembly or class before the bell and constantly in trouble for it.

When I think about how I ended up a scientist from this somewhat dodgy attitude to formal education, I go back to these same days, when I would follow my father around as he made his way through the canyons formed by the racks of electronics that made up the telephone exchanges he built and maintained – their chattering relays carrying messages from one part of our community to another. Messages that might be urgent and life saving, social, or just simple information, but together they formed a network that helped bind a community and facilitate its functions. I was fascinated by the magic of this communication – today I study how the molecules of life form networks and communicate in order to accomplish the essential functions of life.

Like my mother, my favorite subject at school was Maths because it required little in the way of memorising. Armed with my secondary education from Gosford High School, I headed for 'the big smoke' – Sydney – to attend the University of New South Wales and complete a Bachelor of Science with a double major in Applied Mathematics and Physics, and then

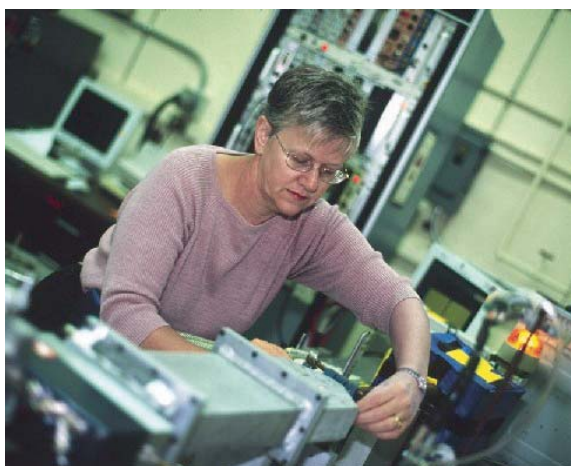
begin a PhD in Physics studying the structures of small molecules using crystallography. The arrival of my son Graham interrupted my university studies for two years, during which time I enjoyed motherhood, tinkered with my piano, and wrote up a Masters in Physics while enjoying the country life back on the Central Coast. When Graham turned two, it was decided that our little family would move back to Sydney and, having lost my country life, I decided to use what remained of my postgraduate Commonwealth scholarship to take up PhD studies again. This time I chose the University of Sydney and the School of Chemistry as the place to pursue what was an emerging interest in structural biology.

An Emerging Interest in Structural Biology

My crystallographic studies had included an anticancer drug that bound to duplex DNA and prevented its unwinding and hence replication – I found the architecture of DNA and its relationship to the molecule's role in the cell fascinating. At the time, everyone was flocking to the new and trendy world of molecular biology and genetics, and so I found myself swimming against the tide. There was a new lecturer in the school, a bright, young rising star fresh from Oxford called Peter Wright, who was just embarking on what would become an extraordinary career studying protein structures using NMR. It seemed like an interesting thing to do. Australia had one high field NMR instrument then – a 270 MHz instrument in Canberra. Peter and I would fly to Canberra on weekends to sit up 36 hours at a time taking data. Multidimensional NMR methods were only just being developed and my work on the haemoglobin found in the root nodules of leguminous plants was done largely using one-dimensional proton NMR methods, with a heavy dependence on the hyperfine shifted resonances of the porphyrin ring and 'heme tickling' experiments aimed at identifying resonances of side chains in the heme pocket where the ligand binding action occurred. I would pore through large rolls of paper with printed NMR spectra, all measured by hand using ruler and square, in order to glean some clues about the structure of the heme pocket or the protonation state of specific residues that could influence ligand binding and kinetics. A paper in *Nature* on the heme propionic acid acting as a pH-dependent gate keeper to the ligand binding site was the biggest news from my PhD work. I learned that my colleagues would only be interested in what I was doing if my structural results could explain how the protein worked – the joy of solving the structural puzzle that sustained my interest would not, by itself, sustain a research career.

Neutron Scattering and Biophysics: Unanticipated Promise!

The US beckoned after my PhD with postdoctoral opportunities at Yale and a project that aimed to use two-dimensional neutron diffraction to determine the first structure of a membrane protein – bacteriorhodopsin. A colleague in the protein crystallography group in Sydney, Mitchell Guss, said "If this [neutron diffraction approach] works, it will be a very important result," so I set off to see what I could do. In this work, I continued what was to become a career-long mode of having my major research infrastructure a long way away and with restricted access. This time, I had to go a little further than from Sydney to Canberra – crossing the Atlantic and navigating my way to Grenoble, France, and the Institut Laue Langevin, where they still have the world's most powerful facilities for neutron scattering. My skills at planning, preparing, anticipating and adapting to the unanticipated were honed, as we only ever had a few times a year to do our key experiments – so they had to work. Bacteriorhodopsin proved a recalcitrant target for study, and with much effort, we managed only to assign a few of the helical sequence segments to locations in the two-dimensional projection of the seven-helical bundle that we could see with our neutrons. Eventually, bacteriorhodopsin would reveal more of its structural secrets to the electron diffractionists and ultimately to the X-ray crystallographers; its main gift to me was an increasing understanding of how to use neutrons and contrast variation to study biomolecular structures.



Jill working with Nell – her homemade small-angle X-ray scattering instrument (photo by Graham Ollis).

Los Alamos and the Land of Enchantment

Hunting for a place to land toward the end of my postdoc at Yale, a series of chance happenings brought me to a unique place that would help shape me as an independent scientist and a citizen. My postdoctoral advisor made a passing comment that "Los Alamos is looking for a biological neutron scatterer," just a few days before I was embarking with my parents and son for a holiday in the Rocky Mountains. This adventure was to begin with a car trip from Denver to New Mexico to visit a graduate student colleague who had just taken a position with the GenBank project at Los Alamos, an initiative led by a nuclear physicist, Walter Goad, who had the then revolutionary idea to create a

searchable DNA database for biomedical research. "I'm a neutron scatterer," I said, and soon I was driving with my family on a southern route along the Rockies to the Land of Enchantment – northern New Mexico. All the way, I rehearsed in my mind what I would say when I meet Mark Bitensky, the Life Sciences Division Leader at Los Alamos. Six months later, as a blizzard was whipping up in Connecticut, I set off for what would become a remarkable 20 years of science in an environment where freedom to pursue ideas was a primary cultural value, but in a 'big science' environment where researchers thrived on collaboration – we were not constrained by concerns about who got the most credit, in part because we did not have the US academic tenure system at play in our halcyon world.

Faced with a developing neutron source that was not working to specifications yet, I had to get going on something and I chose a technique I had never used before: small-angle scattering. I thought that neutron small-angle scattering and contrast variation would allow us to study the structures of complexes that could not be crystallised, but were important – and the challenges in structural biology were fast moving beyond the chemistry at the active sites of enzymes and increasingly concerned with the interactions of biomolecules in complexes and assemblies. With my colleague Phil Seeger, we set out to build a small-angle neutron scattering instrument. I purchased components for a small-angle X-ray scattering instrument that would be used to develop systems for neutron scattering studies and also provide data in its own right. This decision was one of the most important I made in those early days. When I look at the 20 years I did science at Los Alamos, as much as three quarters of it was produced primarily by this homemade instrument – affectionately known as 'Nell' after my grandmother for her reliability and character. With Nell, I started studying calcium-binding proteins that had interesting shapes in solution that changed upon interactions with their binding partners. My early work on calmodulin and troponin C set me on a path for structural studies of regulatory proteins in solution with the aim of understanding the essential signaling mechanisms that underpin healthy function. This work complemented what could be learned from crystallography and NMR, allowing us to study complex systems in a wide range of states. I continued to develop this line of investigation using X-rays and neutrons, as well as spectroscopic techniques occasionally, as I became increasingly aware of the larger Los Alamos.

High Stakes on a World Stage

Los Alamos is a controversial place; where Oppenheimer led the project to develop the atomic bomb that changed our world forever and today the Lab Director has responsibility for verifying the safety and reliability of the US nuclear arsenal. While this central part of 'the Lab' was remote from my work, it did mean that even though we were perched on an isolated mesa top in the American South West, we all shared a sense of being on a world stage. And the world came to visit us. This sense of being part of a world stage was brought home to me most strongly

GREAT EXPECTATIONS

during my last five years at Los Alamos when I led the Bioscience Division. During this intense period, my division was involved in projects that brought me to meet powerful world leaders and talk about the role of science and technology in solving real world problems. I would often have the chance to deliver my favorite message: that the technology we have today to fight infectious diseases or sequence the entire human genome, for example, comes primarily from investing in curiosity-driven research and a culture of freedom to enquire.

My five years as Bioscience Division Leader were a constant adrenalin high as I found my way through this fascinating world with significant victories, such as the successful completion of our role in the sequencing of the human genome that was announced by Bill Clinton and Tony Blair on the 50th anniversary of the publication in *Nature* of the structure of DNA by Watson and Crick. But there were also a series of crises that changed our world – including Los Alamos – in fundamental ways. The events of 9/11 were just one set of the crises, with the anthrax letters to follow, which engaged me and my division directly because of our expertise in microbial forensics. Another was our town being ringed by wildfire that destroyed 450 homes and charred our beautiful mountainsides. I was launched into situations I had never imagined: the spotlight of national and international media, while giving high stakes advice to national leaders on possible technology solutions when the nation had been traumatised and was fearful; the sudden evacuation of our town, which found us dispersed in hotel rooms or anywhere we could find a bed, staring at TV screens showing footage of our neighbours' homes being engulfed in a firestorm and then returning to pick up the pieces and go about the business of managing the safe restart of the lab. These times tested me, and I value them greatly for all that I learned.



Prince Andrew (right) visits Los Alamos and the Bioscience Division entertains! Jill and fellow scientist Andrew Bradbury in animated conversation with HRH; looking on is the Lab Director Pete Nanos (left).

At Home on Two Sides of a Great Ocean

In 2004, with a rich store of precious memories of our years in Los Alamos, my physicist husband, Don Parkin, took his retirement from the lab and I had the chance to consider opportunities beyond Los Alamos. I had often thought I would like university life, and for largely personal reasons, I chose to explore possibilities at the University of Sydney and the University of Utah. After 25 years in the US, I felt at home there, but Australia also had its pull on me, so it was not an easy decision. A few key things ultimately shifted the balance to Sydney. Australia offered me a Federation Fellowship and an extraordinary opportunity to focus entirely on research for long enough to do something significant. And ANSTO (Australian Nuclear Science and Technology Organisation) was building a research reactor (OPAL) and wanted someone who knew how to use neutrons to study biological molecules. What a gift! There were also family considerations – Australians are great world travelers, but we do seem most often to come home eventually.

In my three years back at University of Sydney, with my colleague, now Professor Mitchell Guss, I have been able to put together a diverse team that includes outstanding molecular biologists, biochemists, physical chemists, biophysicists and physicists, who have come together to do some wonderful research. I continue my focus on regulatory proteins and signal transduction, but now with a team with the full breadth of capability needed to most effectively pursue the difficult experiments that are needed to work on these demanding systems. I regularly travel to the US – mostly to the University of Utah, where I developed a number of important collaborations during my year there after leaving Los Alamos and while deciding my future. The US will always be a second home to me – and every so often, we return to our Land of Enchantment to remind ourselves of the intensity of those turquoise blue skies over sparkling snow-capped mountains that stand guard over the beautiful desert valleys. In the meantime, Sydney Harbour, with its gardens and icons, is pretty nice, too!



Jill at her desk (photo by Graham Ollis).

