From Beach to Bench and Back Again

After 30 years doing science, I think I've figured it out: I should have been a builder. Or maybe an engineer. Or stayed someone's postdoc. I was just too 'hands-on' to end up running a lab, or at least to survive in the system.

Rohan Baker.

Childhood

I was born in Townsville in 1962, a year after my parents moved from Brisbane for my father to start the Chemistry department of the fledgling university that is now James Cook University. I had a fairly normal childhood, pretty carefree and plenty of love and support at home. Dad was a rugby league player – he played for Queensland in 1959 – but his regular injuries encouraged me into a less-contact sport, basketball, which I played through primary school, high school and university. My first building job was a treehouse in our mango tree, which caused two problems: falling out of the tree and badly twisting an ankle; and getting into trouble when I stayed in the tree one night to frighten the fruit bats away without telling Mum and Dad where I was. But my overall memory is growing up with a chemistry professor as a Dad, going to his lab, and playing with glassware, chemicals and Bunsen burners; what more could a boy want?

Move to Sydney

After year 6, we moved to Sydney, when Dad became Director of the new Roche Research Institute of Marine Pharmacology (RRIMP) in Dee Why. The best part was our house at Bilgola on the northern beaches; imagine that, going swimming at the beach any time of the year without worrying about box jellyfish! I went to the local high school, where the back gate opens onto Avalon Beach, but I never took up surfing – too much fair skin and red hair – yet spent plenty of time in the water bodysurfing, skin-diving and surf-skiing. I spent some time at school as well; I enjoyed maths and the general science subjects, but I also really enjoyed woodwork and was much in demand for more treehouse building! In year 11 and 12, I did Chemistry and Physics, but left Biology aside for then. I worked a couple of summers at RRIMP and discovered what research was all about. I was in the organic chemistry group, purifying isomers of some long-forgotten compound by differential crystallisation techniques, which would then be screened for biological activity in cell and animal models. I can still remember my sense of achievement when a technique I had worked out was successful in separating the isomers. These experiences of the hands-on nature and teamwork involved in scientific research got me hooked. I should have taken more notice of the role of the group leader stuck behind his desk, though...

At the end of year 12, the career question was pretty easy after my summers at RRIMP: I wanted to be a researcher in organic chemistry. So, in 1980 I set off to UNSW, starting as a double major in organic chemistry. I couldn't give up the northern beaches, so it was quite a trek, but I car-pooled with a few mates from high school who were studying engineering. I also did biology in first year, which was very interesting, and took some biochemistry classes in second year to fill up my units. Biochemistry was a nice middle ground, blending organic chemistry and biology, and somewhere along the line I took microbiology, which seemed like a great system to study biological processes, all bundled up in a neat little self-contained package. So I added a fourth year to my BSc and ended up with a triple-major in organic chemistry, biochemistry and microbiology. That year, I took a new subject called 'molecular biology', run by Tony Mackinlay and Tom Stewart, and I was hooked – I was particularly fascinated by restriction enzymes; how could an enzyme be so specific (obviously I didn't pay enough attention in enzymology lectures) AND give you the ability to join pieces of DNA artificially? At about this time, my father gave me a book, *Genetic Engineering* by Ananda Chakrabarty, the first person to patent a living organism (a genetically-modified, oil-eating *Pseudomonas*). So, that settled it: I could be a genetic engineer and combine my love for making things with genetics and molecular biology. This led me to doing Honours in Molecular Biology with Tom Stewart and my first foray into cloning and DNA sequencing (in this case, a bovine seryl tRNA gene). I had to argue my case with the HoD, Professor Thompson, because my worst grades from my three majors were in biochemistry, but luckily my high distinction in molecular biology, and Tom Stewart's support, swayed him.

On to a PhD

After a fully enjoyable Honours year, it was time for a change from UNSW. I had proposed to my high school sweetheart Chelsey, and we'd set a wedding date, so we had to decide where to go. We were both keen snow skiers at the time, so Canberra seemed a logical choice. However, I was also interested in combining molecular biology and marine biology, so we visited Townsville to check out options at James Cook, but decided we couldn't live in that heat and humidity, so we were Canberra-bound. After a week's honeymoon on Lord Howe Island, then another week walking in Kosciusko, we stopped at ANU

to talk to labs at the John Curtin School and the Faculty of Science. Of the few labs working on molecular biology, I was most impressed with Philip Board at JCSMR, who was working on human glutathione-transferases (GSTs) and had started a program to clone and sequence their genes. Luckily I brought the Sanger-sequencing techniques and reagents from Tom's lab, and got Phil away from Maxam and Gilbert sequencing; a bit too much chemistry for me! My project began with screening a cDNA expression library with anti-GST antibodies. I sequenced the most promising immunopositive clone I had, which, when translated, didn't give the sequence we had expected. With Ian Young's help, and after a FASTA database search that took two days, the sequence came back as – ubiquitin! It was very novel at the time, and we decided to switch my PhD project to look at human ubiquitin genes. I am continually grateful to Phil for taking on a project that really had nothing to do with his research interests! I am also lucky this was the 'good old days' when you could sequence and map a few genes and get a PhD out of it; these days you could do my whole PhD in five seconds online!

On to the USA for a Postdoc

After a lot of gene sequencing (and many ski trips), I was getting interested in the function of ubiquitin. From what little was known at the time, it had a role in protein degradation, including some cell-cycle regulatory proteins. I received a Fulbright Fellowship to go to the lab of one of my PhD examiners, Alex Varshavsky at MIT, who was using yeast as a model to look at ubiquitin function. Chelsey had relatives on the US east coast, so we had a support base there. I was invited to speak at a Cold Spring Harbor Banbury Centre symposium on ubiquitin, which probably had 30 people there; pretty much the world's collection of ubiquitin researchers at the time. We ended up in Boston for three years for my postdoc. This was an incredible experience in a strong, intellectually stimulating lab; about 12 postdocs and six PhD students at any one time, many of whom have become leaders in the ubiquitin field. Here I learned yeast genetics and added to my molecular biology skills, working on two main projects: understanding how some proteins are targeted for ubiquitin conjugation and trafficking to the proteasome for degradation; and cloning the first members of what turned out to be a large family of deubiquitinases, enzymes that cleave ubiquitin, either from the ubiquitin polyprotein resulting from ubiquitin gene expression or from proteins destined for proteasomal degradation. Using ubiquitin-fusion proteins and deubiquitinases, we also worked out methods to increase yield and purity of recombinant proteins. These techniques led to several patents and an effort to spin-off a biotech company, of which I was to be Research Director. But the venture capital didn't come through, and Phil Board lured me back to the JCSMR with a different commercial venture: discovering novel vaccine antigens for sheep liver fluke and using our ubiquitin fusion techniques to produce recombinant vaccines. In the end, I was happy to come back to Australia; I don't think I have the personality to survive the US biotech industry, and Australia is the best place in the world to live.

Digging out the car during a Boston winter in 1989.

Back to Canberra

The sheep liver fluke project was going well, with lots of novel proteins cloned using expression libraries and antisera from infected sheep. Chelsey and I bought a little house in Curtin that we renovated, allowing me to indulge my 'builder fantasy'. As opposed to some days in science, with building you can see a reward for your efforts at the end of the day (or week or month…). After a couple of years, the commercial partner pulled the funding on the project, but Phil Board supported me as a Research Fellow in his group, so I was back in the glutathione-transferase fold, isolating the mouse genes as a precursor to making knockout mice. In 1994, I applied for a QEII fellowship from the ARC, with the aim of starting an independent group full-time on ubiquitin. This application was successful, and I started my own group in 1995 to study the function of novel yeast and mammalian deubiquitinases. This work was greatly helped by a steady stream of Honours and PhD students. Supervising higher-degree students was one of the most satisfying parts of having my own group; I enjoyed the one-on-one interaction with other motivated researchers, and have supervised 24 students over 14 years, plus a few postdocs.

The Baker family at Avalon Beach, 2008. From left: Rohan, Chelsey, Merryn and Jackson.

The mosh pit rocks as the Zinc Fingers play the OzBio2010 Conference Dinner in Melbourne. Band members from left: Rohan Baker, John Lee (obscured), Chelsey Baker, Dave Roberts, Glenn Skarratt and Russell Baker.

We also started our family at this time, with our daughter Merryn born in 1997, and son Jackson in 1999. I was very lucky to have Chelsey put her career on hold, stay at home and do the bulk of the early years while I worked full time; I greatly admire any woman who can have children and a career, especially in science. Watching children grow up is a wonderful experience, and puts the rest of your life in perspective.

My older brother was a part-time musician and had taught me guitar in high school. I put the guitar aside during my postdoc years, but took it up again post-children and started a rock-and-roll covers band. Variously called 'The Major Groove' and later, 'The Zinc Fingers', it had several line-up changes over the years and we've played at many ComBio dinners, most recently, OzBio2010; maybe you've had a dance to us.

Moving Away from the Bench

One problem I have is that I can't say no, so I ended up doing too much work outside the lab. This can be OK if you have an ulterior purpose in mind, but I was always an innocent altruist, so the end result was a lot of time spent away from the main focus of the lab. This included organising committee roles for the ASBMB 1996 and ComBio 2001 Canberra conferences, several Lorne Genome conferences, and Council/Board roles for Lorne Genome, ASBMB, and ASMR, as well as departmental and university committees. All very valid causes, but very time consuming for me as I believed in the importance of them and put the effort in. So before you say yes, decide what's in it for you, and work towards that goal. If there's nothing in it for you, or it's not the right time, then say no!

I chose a career in research because I enjoyed doing experimental work at the bench; I need to get my hands dirty. So, I didn't spend enough time writing grants, writing papers, and managing people. All these things took me away from what I love, and what I'm good at – bench science. Presumably some people like this transition, but I certainly didn't. I also never got the knack of networking, so I wasn't good at promoting my research among my peers – and grant reviewers! I don't have an ego, and I wasn't good at stroking other people's egos. My grant support dwindled, numbers in the lab shrank, and it was too hard to sustain the research effort to fuel the papers and grant applications. This led to much soul-searching about whether this was the career for me. I knew I still loved doing science, but I wasn't good at running a lab. It was a very depressing realisation.

Back to the Beach

Around this time we began formulating our escape plan: back to Avalon to Chelsey's grandmother's old house. I needed a break from academia, and it had always been our long-term plan to go back to the beach someday, so the kids could grow up there. JCSMR Director Judith Whitworth was accommodating in negotiating a redundancy for me, so I left in early 2007, 22 years after I started my PhD. Back in Avalon, I became an owner-builder: we drew up plans for extending the house, got them through Council, got our construction certificate, and I became a full-time builder. In all I had 40 months off work, an incredible indulgence for me, and I will be eternally grateful for Chelsey's support and patience, as well as her house and garden designs, and paintbrush skills. We've transformed a two-bedroom cottage into a five-bedroom house that we absolutely love, and while there are still a few things to finish, it's almost there. It was also a chance to recharge my batteries, swing a hammer, and think about what I was good at, not good at, able to change, or not willing to change. I was good at building – but too slow to make a living from it, and probably too old to get a licence. I missed the lab bench – but not the office. I needed a focussed research project with a direct application, not an esoteric academic project.

Back to the Bench

The answer arrived as we were running out of money for the house – biotech! I first worked with Human Genetic Signatures, a small biotech in North Ryde developing *in vitro* diagnostic kits for human bacterial and viral pathogens. This was my first exposure to real-time PCR and DNA methylation techniques, and I got a successful assay up and running. However, HGS soon moved to Randwick, and I couldn't face the Avalon-to-Randwick commute again. But I am grateful to John Melki and Doug Millar at HGS for letting me get my foot back in the door.

When that door closed, another one opened next door; another small biotech called Clinical Genomics, who were developing a blood test for bowel cancer, initially looking at protein biomarkers, then RNA markers, and when I joined, about to switch to DNA methylation markers, developed in conjunction with CSIRO and Flinders Medical Centre in Adelaide. After an incredibly exciting 17 months developing assays for as many candidate genes, we are now entering a clinical trial with two DNA methylation markers, after pushing real-time PCR to the limit, to detect the small amount of methylated DNA that 'leaks' from cells

in the tumour into the bloodstream. Apart from developing assays, I have focussed on optimising DNA extraction from plasma and optimising recovery after bisulfite conversion of the DNA, and am now moving these techniques onto automated platforms. It has been a wild ride, great fun, and right up my alley: a focussed project with a clear goal, 100% hands-on bench science, no grants, no committees. Pure heaven! My eternal gratitude to Larry LaPointe and Susanne Pedersen for giving an old guy a go.

What have I learned after 30 years in science? There is life in science outside academia; don't be afraid of change, even if it's a big one; make something good out of your mid-life crisis! You can't fight the system, so if it doesn't work for you, or you can't make it work for you, then get out into something better. But most importantly, don't let it get in the way of the people you love, and who love you.

Rohan as owner-builder, fiddling on the roof, 2009.