Our series continues in which Australian scientists describe their journeys of personal and professional development. Ian Smith describes his unforeseen foray into Australian research, and the peptides, personalities and restored cars he has encountered on the way.

HAVE PEPTIDES, WILL TRAVEL

Ian Smith

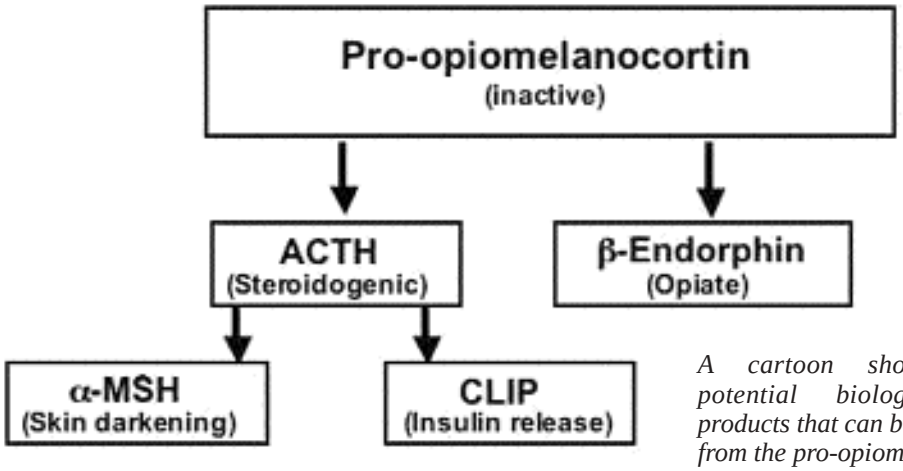
In the beginning

After a somewhat uneventful childhood, an interesting adolescence and spending my early teens in the Sixties (I must have been there because I can't remember them!), I embarked on a degree in Biochemistry at my home town university in Newcastle-upon-Tyne. My introduction to medical research came as a junior research officer at the Medical Research Council (MRC) Unit for Reproduction and Growth in 1974. I remember vividly that one of my first tasks was to measure glucose in urine taken from diabetic expectant mums. In those (good old?) days prior to automatic pipettes, everything was done by mouth pipette. Imagine my terror at seeing an air bubble slowly developing at the bottom of the pipette knowing that within microseconds, I was about to get a mouthful of warm fresh… !

1978 was a watershed year for me. I met my future Australian wife, I moved to the MRC Neuroendocrinology Unit (also in Newcastle) and I began a parallel love affair by restoring the car of my dreams, an MGB-GT. My great passion, other than my wife and family, is the restoration of old British cars and as I write this, there is an old, now partially restored Rover sitting in my driveway. Also in 1978, I discovered HPLC and neuropeptides. The late Seventies and early Eighties were an exciting time in peptide science, as the landmark discovery of the enkephalins, the natural opioid peptides, opened up a new and very exciting field of research. The discovery of this new class of neuroactive compounds, coupled with the development of high resolution separation technologies, allowed the almost weekly discovery of new peptide-based signalling systems. This period also saw the birth of modern molecular biology. These new molecular technologies, specifically cloning, coupled with the then-new sensitive technologies to both measure (radioimmunoassay) and characterise (HPLC) peptides, allowed unique insights into how peptides were made and processed.

Research in the lab focussed on the post-translational processing and metabolism of these newly discovered peptide hormones in the brain and pituitary gland. The discovery that multiple copies of the same peptide and/or different peptides were present in the same precursor molecule opened the door to the discovery of endless potentially bioactive peptide entities. My own research centred on the pituitary hormone precursor pro-opio-melanocortin (POMC) which we and others showed actually codes for a number of peptides that have quite distinct biological activities. For example, α-MSH is responsible for skin darkening, ACTH triggers the adrenal gland to produce glucocorticoids, and β-endorphin has powerful opioid activity. All these activities are associated with stress, and given that the pituitary is sensitive to stressors, the secretion of these peptides from the pituitary all made perfect physiological sense. Interestingly, our research showed that the POMC precursor was expressed in other tissues

The much-loved, fully restored MGB-GT



A cartoon showing the potential biological end products that can be generated from the pro-opiomelanocortin (POMC) precursor.

and surprisingly these different tissues handled the precursor quite differently to generate a completely different set of peptide end products. My research in Newcastle thus progressed to examine how and why these tissues expressed and processed POMC differently, as well as trying to determine the biological role of these different peptide entities.

The Antipodean move

In October 1983, Chris and I flew over to Australia to marry. We had no real intention of settling in Australia and both felt it would be a great opportunity to meet all of Chris's family and see some of this wonderful country. Indeed, we even took the in-laws on our honeymoon, as we knew our time in Australia with the family would be limited. As part of my trip I visited Prince Henry's Institute, where I met John Funder. I knew that he was also working on the POMC system and the involvement of the POMC-derived peptide products in endocrine signalling. Unbeknown to me, however, Funder was actively looking for someone (young and gullible) with HPLC/peptide biochemistry skills! I enjoyed a very pleasant day at Prince Henry's, meeting many of Funder's research team and discussing our many mutual research interests. I left in the evening and headed back to Warragul in West Gippsland where I was staying with Chris's family who farmed just outside the town. A day later Funder called and asked if I would be visiting Melbourne again to do some duty-free shopping and if I was, could I drop by as there were some things he would like to chat about. He also mentioned that he would like to meet my new wife (no, the alarm bells had not yet gone off!). So we drove down to Prince Henry's, and met up with Funder, who directed me to some colleagues

That very first HPLC run, October 1978.

The new Baker Institute building which opened in 2001.

while he chatted with Chris. I walked into his office about an hour or so later to say goodbye, casually mentioning how much I had enjoyed my visit and asking him to bear me in mind should any job opportunities arise in the future. At this point both he and my new wife looked up and in unison said, "Could you start in a couple of months!" So in early April 1984, I sold the beloved MG and Chris and I stepped aboard QF-001 to start a new life in Australia.

I have very fond memories of my time at Prince Henry's. I was made to feel very welcome and Chris and I remain very close to the many friends we made in those early days. I do remember a couple of days after we arrived in Melbourne and had moved into a small flat in South Yarra, Funder arrived at our door one morning with a beautiful Edwardian dining room setting. He said it was cluttering up his garage and we were welcome to use the set. It was nearly two years later when I glanced at the Prince Henry's noticeboard one day and saw an anguished plea from Zyg Krozowski, a returning Post Doc, asking if anyone knew the whereabouts of his precious dining room setting! Seemingly, Funder had agreed to store them while Zyg was overseas, but had forgotten what had happened to them!

As well as being a very warm and friendly environment, my time at Prince Henry's was very productive scientifically. Soon after I started I enrolled for a PhD at Monash University with Funder as my supervisor, my research still focussing on peptide processing, but more on the physiological regulation of these events. Inevitably, being in Australia I started working with sheep! The main reason was access to large amounts of tissue through the local slaughterhouses and also access to some very sophisticated experimental sheep models developed by Iain Clarke at Prince Henry's. One of the challenges for me, and later for all my new PhD students, was coming to terms with the blood and gore at the Werribee animal facility, where we conducted most of our sheep studies. This work resulted in a number of what I believe were quite important discoveries. Perhaps one of the most significant was the observation of quite profound differences in peptide processing patterns between abattoir sheep and those slaughtered on the farm. We went on to show that these changes were a consequence of the chronic stress that slaughterhouse sheep are subjected to as a result of transport to and from saleyards, exposure to dogs and constraint in sheep pens. It makes one think what the peptide profiles would be like in the sheep en route to the Middle East!

The Baker's dozen

In late 1990, Funder was appointed as the new director of the Baker Medical Research Institute and in early 1991, 13 of us (the Baker's dozen) moved with Funder from Prince Henry's to Prahran. The Baker was (and still is) very focussed on cardiovascular research and the Institute's clear strengths were in the areas of classical pharmacology, whole animal physiology with exquisite whole animal models and a very strong clinical interface. I believe the skills we brought from Prince Henry's, principally protein and peptide biochemistry and molecular biology, complemented and strengthened the existing Baker research programs. The move also provided me with space to establish the Peptide Biology laboratory and my research gradually moved from neuroendocrine peptides toward the peptidases that generate and terminate peptide signals, particularly those acting on peptides involved in regulating cardiovascular function. One ultimate goal of our current work is the design and analysis of novel specific peptidase inhibitors, which may ultimately prove to have therapeutic value. Indeed, in collaboration with Mibel Aguilar and Patrick Perlmutter at Monash University respectively at Biochemistry and Molecular Biology, and Chemistry, we have developed a novel platform technology to incorporate beta amino acids into substrate-based peptidase inhibitors.

Over the last 12 years since the move to the Baker, there have been many highlights for me. In 1995 I spent a fabulous three months doing a sabbatical in New York with Jim Roberts and Marc Glucksman at Mt Sinai Hospital. During this period I managed to acquire some

molecular biology skills, specifically site-directed mutagenesis. We lived in an apartment on the Upper West Side, about a 25-minute walk through Central Park to Mt Sinai on the Upper East Side. My wife and two boys loved New York; with our apartment overlooking Central Park and next door to the Museum of Natural History, it does not get any better for a shopaholic wife and two young boys, then aged seven and nine. As a family we managed to spend time exploring New York and the surrounding areas. I also spent many (probably too many!) evenings in the pub after work discussing science, the world, the universe and everything. Following these engrossing discussions, I would innocently set off for the walk home, often late at night, through Central Park. It was only toward the end of my stint that my horrified hosts realised this and pointed out to me the dangers of this exercise!

The last few years have been a particularly exciting time for both the Baker and myself. In 2001 we moved from our dark and dingy labs at the back of the Alfred Hospital into superb new purpose-built labs housed in the new Baker building which is part of the Alfred Medical Research and Education Precinct (AMREP). We were fortunate enough to receive a very generous grant from the Ramaciotti Foundation in 2000 to establish a state-of-the-art high throughput proteomics facility in my lab at the Baker. This facility not only meets my own and the Baker's requirements, but it also allows other groups on the site, and indeed beyond, access to sophisticated proteomic analysis.

The new precinct, brings together the Alfred Hospital, some sections of Monash University, the Burnet Institute, five biotech companies as well as the Baker Institute. AMREP now houses a critical mass of first-class scientists with a quite diverse array of skills, all seeking ways to interact and work more closely together. I believe the future for the Baker and the associated institutions and companies, is exciting. I only hope that the various funding bodies recognise and support this and, of course, the other Australian centres of research excellence.

My great expectations

What are my great expectations? I have indeed had a very fortunate and very privileged career in science. I think, perhaps more by good luck than my own good judgement, I have had an outstanding series of scientific mentors, colleagues and collaborators. I have also received fantastic support from my lab, with loyal supporters such as Cathy Hamilton, Becky Lew, Shane Reeve and more recently, Sam Smith and Mike Yarski, as well as some absolutely terrific students. The only way I can repay this debt is to try and offer the same levels of support and mentorship to those around me and, of course, to the next generation of scientists coming through.

I am a strong believer in the concept that science can only move as quickly as the technology allows and that great scientific breakthroughs often follow on from some significant technological advance. Technology is moving at breakneck speed and we scientists have to be prepared to take risks and invest in these new technologies if we wish to remain competitive. The costs are often prohibitive and the only practical way forward is to work in larger groups, submit joint across department / institute / discipline grant applications for large items of equipment and to take multidisciplinary, collaborative approaches to address complex scientific questions. This is particularly important in Australia where we have such a small research base, but do have some outstanding scientists and technologies.

Finally, I am a strong supporter of the growing biotech sector. To me, the biotechnology industry represents the best way Australia can capture the true value of the monies and intellectual investments made in the crucially important curiosity-driven research. Indeed, as I write this, a small biotech company with which I am associated, Cryptome Pharmaceuticals, is about to list on the Australian stock exchange. Although unlikely to make me a fortune, any money I do make will no doubt go toward funding the restoration of the next project car! My main hope however is that Cryptome Pharmaceuticals can successfully translate basic research into new drugs that can be used to treat one of our biggest killers, cardiovascular disease.

GREAT EXPECTATIONS

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