

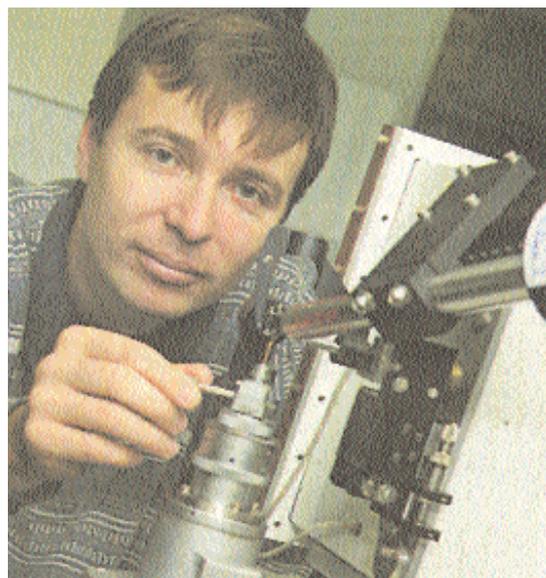
# GREAT EXPECTATIONS

Our series continues in which Australian scientists describe their journeys of personal and professional development. Bostjan Kobe describes the winding path that led him from his beginnings in Slovenia to become a structural biologist and an Australian citizen.

## STRUCTURAL BIOLOGY AMIDST WORLD POLITICS

### Slovenia

I grew up in Ljubljana, the capital of Slovenia, which is a small European country of two million people. At the time, Slovenia was a Republic in the Yugoslavian federation (in the news recently for ceasing to exist), and had been an independent country since 1991. My early school days were characterised by lots of missed classes and bleary-eyed mornings, spending time on skiing slopes instead. Alpine skiing is the Slovenian national sport, and I could never quite work out why my parents would steer me towards the most competitive sport around. My life could have been very different if I had ever made it into the National Team.



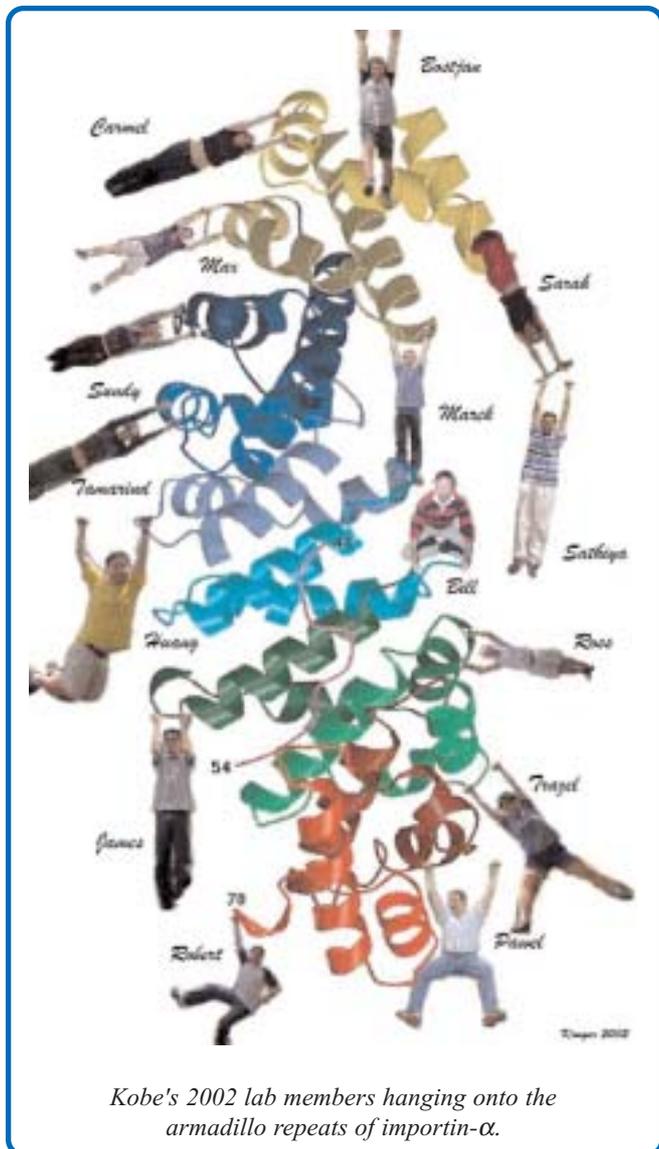
*Bostjan Kobe with the X-ray equipment at the University of Queensland.*

My dad is an organic chemist, and I guess the continuous discussion of science in our family contributed to the fact that both I and my brother ended up scientists. Despite (or perhaps because of?) my father's efforts to persuade me not to study chemistry, I did exactly that. I was fascinated by the beauty and logic of chemical structures, and ended up working on the crystal structure of a bio-inorganic molecule for my diploma project (equivalent to Honours in Australia). I did not like biochemistry as an undergraduate student; the teaching approach emphasised memorising too much over logic. The revelation occurred during my diploma project, when I discovered that people studied structures of proteins. That is when biochemistry suddenly became the most interesting topic.

### The United States

There was no macromolecular crystallography research going on in Slovenia at the time, and I may have even been the first person to set up a protein crystallisation experiment in the country (lysozyme of course, as a side project to my diploma work). However, to do real protein crystallography I had to go abroad. Several European countries would have been a possibility, but it turned out it was simpler to get a PhD studentship in the US. After doing the TOEFL and GRE exams, I applied to a few American Universities with structural biology labs. My score for the verbal part of GRE was quite miserable, but surprisingly I did get offers from a few places I applied to. I chose the University of Texas Southwestern Medical Center in Dallas, which had four crystallography groups at the time, one of them led by a Nobel Prize winner. They also waived the international fees for graduate students.

The US and UT Southwestern turned out to be an excellent choice. For someone with basically no background in biology, the coursework in the first two years of the PhD program allowed me to



*Kobe's 2002 lab members hanging onto the armadillo repeats of importin- $\alpha$ .*

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*Ski touring at Mt Howitt, Victoria.*



*Near the finish of the Host City Marathon, Sydney.*



*Sea kayaking with Trazel Teh around the Antarctic Peninsula.*

cover a few holes in my knowledge. The qualifying exam of writing a research proposal in the second year might have been the hardest, but was also the most useful educational experience I have ever had. The US wasn't easy at the start; while I had always thought I had solid English skills, I realised that the combination of spoken English and unfamiliar subjects was a bit too much at times. But lots of reading and hard work got me on track.

The first year of the PhD program practised at UT Southwestern involved at least three lab rotations involving three-month projects in different labs. This allowed the students to learn different

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techniques, try out prospective PhD supervisors, and make sure they choose what they really want to be doing for the following few years. I tried out two crystallography labs, an NMR lab, and a molecular biology lab. In the end, I chose the JD (Hans Deisenhofer) lab for my PhD work, both because of the nature of the project available and the fact that the supervisor turned out to be a very nice guy. The US system as practised at UT does not impose any time limit on the PhD project. While there may be disadvantages to this approach, it also has some obvious advantages: a student can take on ambitious projects, and it allows the student to be awarded a PhD when they are really ready for it, that is, when they are reasonably independent and mature.

Looking back, the project I chose was extremely risky. For almost two years I tried expressing a protein in various systems without success. While I was aware it was possible to purify the protein from certain tissues in reasonably large quantities, it was my PhD committee who really persuaded me to give this option a go. Owens Sausage near Dallas made my PhD project a success by supplying me with pig livers. From then on, things went relatively smoothly, and I finished my PhD after about four and a half years.

I was in the US when Yugoslavia fell apart. While there were some indications in 1989 that things were not going too well, I never would have anticipated what happened to the country. People tell me I was lucky that I avoided all the events that took place in the 90s, but I am not sure if it was easier or harder to be in another part of the world at the time. Slovenia was the first to prepare for separation from the Federation, and together with Croatia jointly declared independence in 1991. It was on the very first day after the celebrations that the Yugoslav Army (dominated by Serbian generals) launched a surprise takeover of Slovenia. Fortunately, the Army did not expect the resistance organised by some clairvoyant Slovenian individuals, and the Army pulled out of Slovenia after only three weeks, leaving it a peaceful place ever since. It was hard for me not knowing what was going on during this time; the American media paid very little attention to the events, and what they reported turned out to be false. The only reliable news I received was by phone and email from family, friends and an unofficial email news service organised by another Slovenian student in the US. I will never forget one phone call, when my brother told me he couldn't talk because they were being called into the shelter to avoid air bombing.

## St Vincent's Institute, Melbourne

My choice to come to Australia was only partly scientific. At the time I was finishing my PhD in 1994, I was convinced I would return to Slovenia or at least somewhere in Europe eventually. However, it was the combination of the realisation that this was the perfect opportunity to experience something new, and the mystique of a country that was in a completely different part of the world, that led me to Melbourne. It was Bruce Kemp at St Vincent's Institute who offered the type of job and project that I was looking for, as a structural biologist in a lab not only dedicated to crystallography, but also working on protein kinases, which I have always been fascinated by. So I ended up flying around the world to a country I had never visited

before, not knowing what to expect.

The Australian community accepted me really well. I was invited to talk about my PhD work at various institutions, I was awarded fellowships, I was introduced into the system through reviewing grant proposals, and I was even given a couple of awards. This experience was completely opposite to my native country Slovenia; whenever I enquired about possibilities to join its academic institutions, I learnt of new obstacles preventing scientists to return to Slovenia from abroad.

In particular, the Wellcome Fellowship scheme in Australia provided exceptional opportunities for young investigators to establish themselves independently. The recent termination of that scheme in Australia and New Zealand seems to have left a gap not covered by other currently available initiatives. In contrast to Australia, the New Zealand government has already funded a scheme analogous to the Wellcome Fellowships to fill that gap.

One of the most memorable projects pursued at St Vincent's Institute was certainly the structure determination of the enzyme phenylalanine hydroxylase (PAH), a rewarding and very educational experience. The PAH crystals resisted revealing their structure in numerous ways. I collected over 150 diffraction data sets to try to advance towards the structure of this protein, with very little progress. Then in 1996 I discovered a poster at a meeting in the US that described the structure of one domain of the related enzyme tyrosine hydroxylase. Because that structure could help us solve the structure of PAH, I decided the most sensible thing to do was to ask the authors of the tyrosine hydroxylase work if they wanted to join forces and work on the structure of PAH in a collaborative effort, and they agreed. However, after returning to Australia, months and months passed, and the coordinates they agreed to provide never arrived. It turned out these people were simultaneously competing with us by working on the structure of the catalytic domain of PAH. The structure we solved in the end was very interesting, but this was not yet the end of the PAH curse; it took submissions to six different journals before the paper was finally accepted for publication.

I had an early introduction to the reality of scientific publishing when my diploma work was published in *Acta Crystallographica* without any mention of my name. The experience with PAH in particular prompted me to do a lot of further thinking on the topic. It is clear that the anonymity of reviewers but not the authors during peer review creates an unfair situation, and the system should either be all closed or all open, but not somewhere in between. A description of contributions by individual authors could eliminate much authorship misuse. Perhaps my efforts did contribute to one little change, because soon after publishing a note where I drew attention to these issues, *Nature* did in fact start encouraging authors to list the contributions of individual authors to the papers they publish. But more changes should take place. My view is that instead of authors submitting papers directly to journals (and risking wasting lots of time if their work is not accepted, by having to start all over resubmitting to another journal), authors would submit to a

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central repository and peer review resource. It would then be the job of the journals to then bid for the papers they were interested in. This would ensure that the paper would be published in a journal of a suitable quality without unnecessary delays. There are certainly some practical issues to be solved before this idea could be translated into practice, and if anyone has any suggestions of how to make this happen, please let me know.

## University of Queensland, Brisbane

Many people have asked me why I chose to move to UQ in 2000. The amazing Brisbane weather and the distance from the mountains and skiing clearly cancel each other out for me. Perhaps I was a bit idealistic perceiving a major difference between the territorial and self-sufficient tendencies of Melbourne institutions, and the comparatively cooperative tendencies in Brisbane. At St Vincent's, I was surrounded by many excellent people, but at UQ, there is a much greater breadth of science at close reach, and access to students can be a very rewarding part of research.

One of the deciding factors was also the receptiveness of UQ researchers to cooperate in taking non-traditional approaches. Much of the world has recognised the significance of the comprehensive, functional genomics approaches to biological problems, and it seems they are funding these extensively. However, in Australia, the reverse appears to be true. Two successful projects of this nature that we have been trying to get going in the lab and have already led to publications, continue to fail to attract funding.

## Conclusions

What do my experiences teach me about being a structural biologist and a scientist? It can be an extremely

rewarding, but also an extremely frustrating career. If you want to make money quickly or with little effort, this is not a career for you. If there are many aspects of being a scientist that you do not enjoy, this is not a career for you. If you are content being mediocre, this is not a career for you. But there are so many rewarding aspects. Where else can one explore areas where nobody else has set foot before? Seeing the electron density of a new protein crystal structure for the first time can definitely cause some serious goose bumps. There are plenty of opportunities to travel, and you can have a very flexible lifestyle and make enough money to get by. I don't think you need to devote every moment of your life to science to be successful, but I think you need to make it a high enough priority. I know many successful scientists that seem to be able to fit much more than science into their lives.

I am hooked on being a scientist, but there are a few things that I would like to change, for example the scientific publishing process. Although online publishing is changing things rapidly, traditional journals will persist and could do with some change. The Australian postgraduate system could be improved; there are several aspects of the American system that could be implemented even within the restrictions of the Australian environment. And finally, there will always be scientists who think they can gain by restricting the opportunities of others; I think this is a very short-sighted attitude and one that can only bring temporary gain. The funding situation puts some severe restrictions on the science one can do; you cannot always pursue what you think is the most interesting and the most significant topic, but you should be ready to fight, at times compromise, and keep pursuing those great expectations.

