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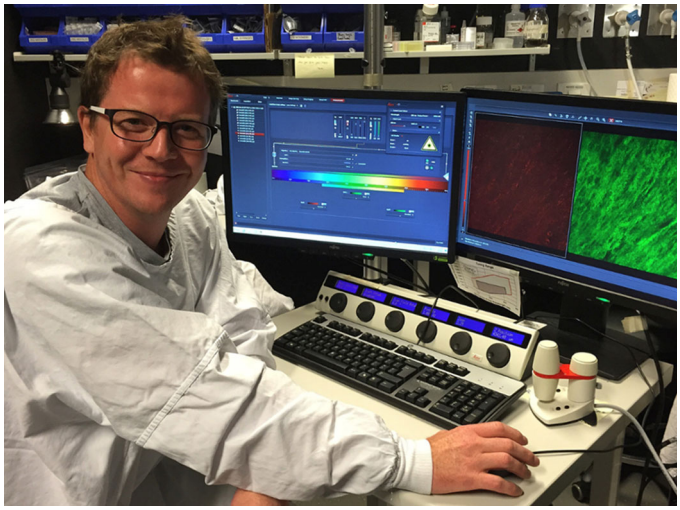
CELL SCIENTISTS TO WATCH

Cell scientist to watch – Paul Timpson

Paul Timpson received his bachelor's degree from the University of Strathclyde, UK and completed his PhD under the supervision of Margaret Frame at the Beatson Institute for Cancer Research and the University of Glasgow in 2002, working on Src kinases and Rho family GTPases in cancer cell invasion. He then moved to the Garvan Institute of Medical Research in Sydney, Australia to work with Roger Daly on the actin-binding protein cortactin in several cancer models. Paul returned to the Beatson Institute in 2007 with the aid of an AstraZeneca postdoctoral research fellowship. He worked with Kurt Anderson on the development of multi-disciplinary live-cell imaging techniques to investigate the molecular dynamics of cancer cells *in vivo*. In 2012, he started his own research group at the Garvan Institute, assessing cancer in the context of its surrounding environment with the use of advanced intravital imaging technology. His aim is to target distinct hallmarks of cancer progression and to reduce resistance pathways to improve anti-cancer therapeutics.



Paul Timpson

What inspired you to become a scientist?

When I was younger I competed with my school against other schools in engineering and problem solving. It was great for me to travel around the country and to get to leave school. There were no rules and no correct answers to the problems and I liked that. Later, I did biology as a side course and when I was at university to study engineering, much to the shock of my parents, I dropped out of university a year later and made the switch to life science the following year.

You're now working on cancer invasion and metastasis. How did you end up in this field?

For my PhD, the Beatson Institute in Glasgow was top of the list. I worked with Margaret Frame and Valerie Brunton on the cell biology of cancers. Cell biology sits very well with me because I'm a visual person and like to see how things move and work together. By using microscopy, I looked at the actin cytoskeleton and the movement of cells during metastasis in my PhD. Afterwards I went to the Garvan Institute and worked with Roger Daly to get out of my comfort zone and to increase the breadth of my knowledge, doing more biochemistry and work based on signal transduction. Next, I combined the latter with cell biology. I thought intravital imaging was a really exciting area because I was interested in looking into native 3D tissue and at the cellular processes in real-time to recapitulate the behaviour of cancer, and this is what we're doing now. We now apply intravital imaging to look at pancreatic cancer, which is highly aggressive and rapidly metastasises.

What are the projects you're working on right now?

We have three main projects in the lab. The first one is to target the surrounding tissue or fibrosis, particularly for pancreatic cancer. I think the hammer and nail idea to ablate and smash away the stroma might not be the best approach because you're going to have tissue damage, immune infiltrates and lots of normal cell function problems using this approach. We think mechanosensing is the key; to target and relax the stroma and the feedback to the tumour, to make the tumour more vulnerable to subsequent therapy. The second area is to target the early invasion events in cancer. If you can predict early events in cancer metastasis spread, then you can treat with an anti-invasive drug on top of standard-of-care therapy and maximise cancer cell killing, while minimising spread. For example, we recently used a fluorescent E-cadherin–GFP mouse model and fluorescence recovery after photobleaching (FRAP) to look at early cell–cell dissolution events preceding metastasis in pancreatic cancer. We also study RhoGTPases and the actin cytoskeleton to look at early cell movement and local invasion events, and we're creating more biosensor mice strains for other hallmarks of pancreatic cancer. These strains are freely available for anyone to use so that other researchers can apply them to different cancers and diseases and maximise their impact. As a third stream, we develop technologies in-house for these projects and questions. We work on new mice strains and imaging techniques in an effort to improve or 'fine-tune' response to therapy – it's a holistic approach, because once we have created these imaging tools or biosensor mice, we use them to assess how best to target (1) tumour growth, (2) survival and (3) progression to metastasis.

"…it's really positive and very important to show true translation of the work to the public."

What are the methods that inspire you and experiments you'd love to do?

I like work using optical windows and longitudinal imaging to look at the single-cell to subcellular level in organs deep within the abdominal cavity. We have recently combined this approach with

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A Timpson family selfie with Paul's wife Haley, daughter Ella (13) and son Lewis (4).

our biosensor mice to look at drug targeting efficiency, and this reveals multiple zones of poor drug delivery and heterogeneity that we had not seen before. Another idea I'm excited about is the use of biosensors in pancreatic cancer samples from patients, making patient-derived xenografts (PDXs). That's a real translational effort based on imaging and we are working closely on this with Marina Pajic here at Garvan.

Speaking of translating research towards patients, do you think your work is particularly well suited to showcase science to the general public?

Yes, here at the Garvan Institute we manage to do quite a lot of outreach. Our work is very visual and appealing to the public and we've been lucky to have had multiple TV appearances. The most difficult part actually is my Scottish accent, but what they do is they voice over the movies [laughs]. Some of our films show quantum dots in the blood vessel, and people can see the chemotherapy moving out into the tumour. By combining this with our biosensor mice, we can then see where and when the chemotherapy is working. It's almost like a traffic light – these biosensor mice change to one colour when the cancer's been attacked, and another if it hasn't. I think it's really positive and very important to show true translation of the work to the public. Those who engage with our research may have experienced cancer themselves or may be a relative of someone with cancer – so we owe it to them to convey our research in an accessible and accurate way.

What challenges did you face when starting your own lab that you didn't expect?

I did not know how ever-present you have to be as a group leader. Also, when you're buying expensive equipment like a multiphoton microscope, you have to decide not only what's best now, but also what will be top level five to ten years in the future to get the most out of your investment. Having an adaptable system is key. As for hiring people, I took a long time to hire the people I have now, but it was worth the wait. It's one of the most important things to get the right people, otherwise there's massive downtime if you don't have the right skill sets and team in your group.

Such a hiring approach – is that advice you received yourself?

I had great advice from the late Arthur Alberts. I had won an award to go and work in his lab as a PhD student, and I loved working with him. He told me "hire people that are smarter than you". Now of course everyone says this, so it's easy to say; although for me it's not that hard to hire people that are smarter than me! [laughs]. But what you have to do is hire people that are diverse in their skills, for example image-analysis experts, geneticists for the biosensor mouse work and cell biologists for example. When I'm talking to these people, the marriage of those two minds means we can do things that no one discipline can achieve. At the end you have a team with common goals but diverse skills and when you look at it as a whole, it's larger than you could have ever imagined and I think that's key.

Are you still doing experiments yourself?

I think my lab would love for me to pretend I'm at the bench. We have a swipe pass to get into the microscopes and I think I only go there to give tours! I taught my lab at the beginning how to do organotypic cultures and I think it took five or six weeks and then I was told, "Paul, I can do it better than you, your way's wrong and can you just please leave." I love being in there but I think if I look at the group as a whole, it's way more efficient that I stay out of the lab these days. You want to still be in there, but leading the group, developing ideas and concepts and getting the money is my job now and actually, there's nothing greater than when someone does the experiments and has the results you dreamed of, and your theory has borne fruit.

> "…hire people that are smarter than you".

How do you achieve a work–life balance when you're trying to establish yourself as an independent investigator?

For the first six to twelve months, I was like a deer in the headlights because I didn't know the grant management structure of the Australian system. The work–life balance is something that everyone is aware of but you don't realise how much establishing a lab consumes you. I think my social life got absorbed; I still went out but I was constantly talking about science, so my wife – a scientist as well – told me often that I needed to change the subject! When I came here my wife was pregnant and we had our older daughter already, so that was obviously a stress in both respects. The balance is always tough as a young scientist, but if you take time to do the things you love, then it works. Our group has expanded recently and I have senior postdocs and a larger team now working well together, which takes the weight off your shoulders a bit in terms of daily workload.

What is the most important advice you would give to someone about to start their own lab?

Like the advice I received – don't jump in and hire the first person, don't think that numbers matter. Related to that, you have to put serious effort into your students and postdocs – invest in your staff and they will invest time in you and your lab. You have to try and see through the apparent naivety and the young age of researchers at a junior level – these people have serious potential, they're just a young future group leader. I think that if you instil that in them, then it's going to be there for the rest of their life and they might be the one who will do the next big thing. I guess looking after people is something that I'm reasonably good at and I've done well so far, so I think I'm going to keep that up and then your students and postdocs become your colleagues.

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What is your advice on establishing good collaborations?

If you create a tool that's useful for the community, there is nothing to lose by giving that to someone in neuroscience, embryogenesis, development or the cancer field for that matter. That way you can help in many areas beyond your own direct interests. We get a lot of requests and we're very open in sharing tools and biosensor mice. I also think it goes both ways – the more you collaborate, the more you get back. It was Heidi Welch (Babraham, Cambridge) who opened my eyes to the idea that you can give stuff to people and it doesn't affect you – it's actually really good for the whole field! However, when I was a postdoc I probably collaborated too much; however, as long as you have good core projects as a group leader, you can quite easily collaborate on side projects.

How do you get the most out of the meetings you attend, particularly in the early stages of your career?

I think you've got to be available for people to talk to you at meetings; treat it like a privilege, especially if you get a chance to talk. I always love the poster session. You can see the top scientists in the world skimming and flying around the poster session because that's where you find raw, new science, new collaborations and talent. I also think that if you go to multi-disciplinary meetings you can actually quite easily help people in different fields, or get their help, and it makes a world of difference to their work or yours with sometimes minimal effort. And don't just go to a conference and go home at night; you need to socialise at lunch, dinner etc., because it's those tiny discussions that make a big difference.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

Ok, this is for all potential postdocs out there. My institute is four kilometres away from Bondi Beach and this is where I learnt to surf. I feel if you're going to do a postdoc, do it somewhere where the science is great but also a place that is exciting and an adventure! My home is just 100 m away from water, so life is not exactly hard. I love to surf.

What great advertisement for postdocs – I'm sure they'll bombard you with emails after reading this!

Yes, all postdocs come with free surf lessons… by a Scotsman. Maybe I'll make that a clause.

Paul Timpson was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.