Eyes on the horizon, feet on the ground: interview with Tim Hunt

Image courtesy of Ed Swinden

Tim Hunt

Professor Tim Hunt, winner of the 2001 Nobel Prize in Physiology or Medicine, talks to **Philipp Gebhardt** about his passion for science, the importance of pure research, the influence of enthusiastic colleagues – and the role of serendipity in scientific discovery.

In 2001, Tim Hunt was awarded the Nobel Prize in Physiology or Medicine together with Leland Hartwell and Paul Nurse 'for their discoveries of key regulators of the cell cycle'[w1].

Multicellular organisms develop from a fertilised egg by a process of many cell divisions. During the life of the organism, individual cells die and are replaced by the process of cell division. There are several events that must occur in a eukaryotic cell before it can divide into two daughter cells. This series of phases – including the replication of the genome, cellular growth and the segregation of the chromosomes – is the process known as the cell cycle (see images).

All the steps in the cell cycle must be tightly controlled to avoid damage and subsequent developmental abnormalities, such as the formation of tumours. Control takes place at 'cell cycle checkpoints', points at which cellular mechanisms can intervene if something goes wrong. Tim Hunt discovered that the passage through the cell cycle checkpoints requires cyclins, newly discovered proteins that are synthesised just before each checkpoint and destroyed immediately after the checkpoint has been passed. The cyclins themselves activate other proteins, kinases, that enable cells to pass into the next stage of the cycle. His work has major implications for biology and medicine, especially in understanding how cells form tumours. He currently works at Cancer Research UK[w2].

What made you want to study biology?

I think it was largely the influence of my school. I decided to be a biologist when I performed particularly well in a school biology exam at the age of eleven. We had a very good science teacher and I looked forward to science lessons very much; they were much more interesting than the Latin and Greek that we mostly did. I wasn't very good at physics, but biology required no effort. I also had a very good chemistry teacher later on, so going to university to study biochemistry – this is in the late 1950s – was very natural. I never really had to make any decisions; I was just doing what I liked and found fascinating.

It was quite a shock when I went up to university, because there I found there were people who knew much more than I did, who understood much more than I did and who were much cleverer than I was. *[Laughs]* Then I found that actually I could hold my own, and again I did well in the exams. I was able to take the courses I wanted: I explored a little bit and dabbled in psychology, for example. I found it interesting but I was no good at it. The whole point of education to me is to find out what you like and what you are good at. Then it doesn't feel like work any more – you just do it. It's fun!

All young scientists learn that well-planned experiments are crucial for successful research, but sooner or later we also discover that every

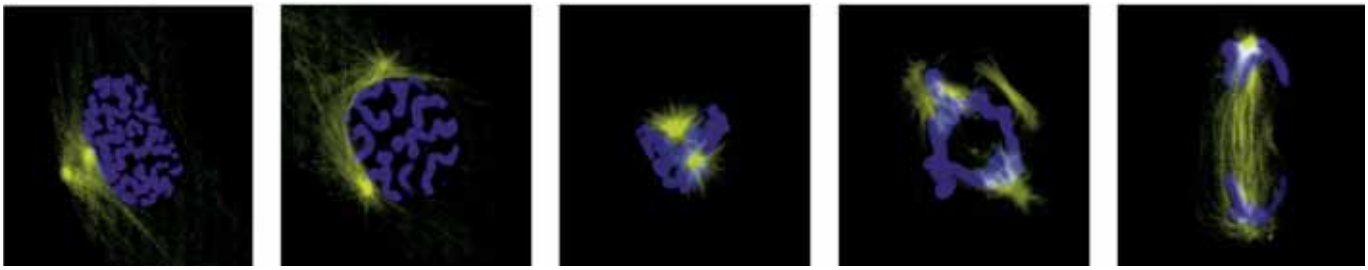

Image courtesy of Jan Ellenberg

A live mammalian (kangaroo rat) cell going through the different stages of the M-phase in the cell cycle. From left to right: prophase, prometaphase, metaphase, anaphase, telophase. DNA (blue) and microtubules (yellow) are labelled with fluorescent proteins or vital dyes respectively

experiment also needs good interpretation. Often the results are totally unexpected and that's where the real work starts…and often serendipity comes into play. What role did serendipity play in your research career?

Oh, a major role…again and again and again. The first real discovery I made when I was a graduate student, and some colleagues and I were trying to find out whether ribosomes were uniformly distributed on messenger RNA. This involved running sucrose gradients, experiments that took quite a long time. Once we went out for lunch while the experiment was running and stayed out a bit too long. But still, being lazy, we analysed the result. As a result of that piece of laziness, we discovered something new that we'd never have discovered otherwise! We found that there were fewer ribosomes on the messenger RNA making alpha chains than making beta chains. That was my first paper in *Nature*! In those days, there was no pressure to publish; we just thought it was an interesting result, so we sent it in. It was quite an important result, but it was complete accident, an utter piece of serendipity – just an experiment that was left a little bit too long.

I must say that we then misinterpreted the finding and did other experiments in which we didn't do proper controls, so we got the answer wrong. A good friend, Harvey Lodish, later corrected us and provided the correct interpretation. That was the big lesson: serendipity shows you something that you didn't suspect, you try to figure it out with 'well-planned experiments', you misinterpret the experiments, a colleague sets you right…. It's fun and it's a good learning experience.

How should a team leader preserve and foster the creativity of his or her co-workers?

I am not too keen on leaders, actually; I prefer a loose confederation of people. Sustaining people's morale and enthusiasm is tremendously important and I am not so sure how good I am at that. You have to be so critical of yourself and of the people around you; often they take that very hard. The truth is that it's very, very difficult to find things out. And unless you are extraordinarily self-critical, you get ideas that are wrong and because you love the ideas so much, you are not prepared to disprove them.

It's much easier when you are working with your peers. There's a famous interview with James Watson and Francis Crick – "Why did we succeed and the others not"; Francis Crick said that one of the reasons was that they could be really frank with one another and not take it personally: "That's a bad idea. It was your idea, but it's still a bad idea and you have to look for a better idea." But it can be very crushing when someone more senior tells you that.

How has your research career evolved?

Well, I suppose my career has evolved. *[Laughs]*. My friends and I somehow always had the money to carry on – but not very much money. When I returned from America to England, my salary dropped fivefold! We were very poor and had to worry about whether there was enough to eat, but we were having so much fun. We were in a wonderful, vibrant, intellectual environment; we were finding things out and that was more important than a career. The freedom to have a grant just to do research is a wonderful blessing. For about ten years, I never had more than three years tenure at a time and the same is true for some of my most successful friends. You have no responsibilities, you can go anywhere in the world, do anything you like. But you do have to find something out, otherwise people won't give you the next grant. Then I got a job and that was the end…. *[Laughs]*

I often say to people 'I am so glad I am not twenty-something anymore'. I think it's a lot harder now than it was when I started out. In my particular field, so little was known that almost any stone that you turned over had something interesting crawling out

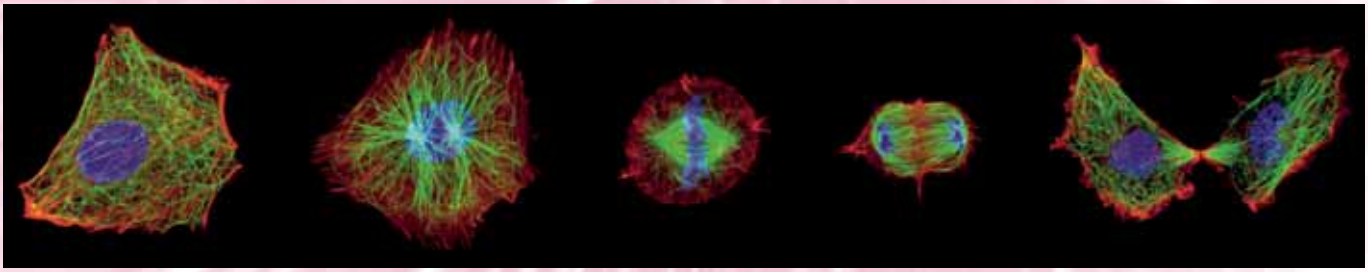

Image courtesy of Jan Ellenberg

Fixed mammalian (rat) cells in different stages of the M-phase in the cell cycle. From left to right: interphase, prophase, metaphase, anaphase, cytokinesis. DNA (blue) and microtubules (green) and actin filaments (red) are labeled by fluorescently labelled antibodies or dyes respectively

from under it. I think that's harder now in biology.

What are you researching now?

I am working on a couple of questions about cell-cycle control. We discovered that cell-cycle transitions are catalysed by protein kinases, but the question now is how many proteins do these kinases have to phosphorylate, and to what degree, for cells to enter mitosis? And what about the control of the phosphatases that reverse the process? That turns out to be a very difficult problem; we have been struggling with it for several years and I don't know whether we will ever come to a satisfactory conclusion. The other very interesting thing is that the protein that I discovered – the cyclin – is distinguished by an abrupt disappearance and we still don't really understand what the mechanism is.

It is a very competitive field but it's good fun. It's also difficult: it has been a decade since we found the underlying mechanisms but we still don't really understand how it works. I think I'll probably still be puzzled when I retire – whenever that may be.

You still sound very excited about your research.

It comes and it goes, I must admit. When I won the Nobel Prize, I thought that maybe it was time to stop. You know that it's exceedingly unlikely that you will ever make such a great discovery again, so why not just stop? Stop and try to help other people.

For a while, I involved myself in lobbying for the European Research Council, for example – something I am passionate about. Ultimately, though, I found that the only thing I am really good at is doing experiments, and the fun of working in a lab and finding things out came back. So that's what I am doing now.

Image courtesy of the US National Oceanic and Atmospheric Administration/Department of Commerce

Sea urchin

[Eggs and oocytes from the African clawed frog *Xenopus laevis* have become an important tool in biological research. These relatively big cells can be manipulated easily and are used for the study of developmental processes. In molecular biology they provide a controlled system for the expression of manipulated proteins. Tim Hunt and his colleagues used these frogs' eggs to analyse the proteins that play a key role in the complex network of cell-cycle regulation. They not only showed that this regulatory system, identified previously in the eggs of sea urchins

and clams, exists in the cells of vertebrates but also characterized the other molecules involved.]

Paul Nurse, with whom you shared the 2001 Nobel Prize, once said that "good science is carried out by creative individuals working within a scientific society which is socially interactive, with lots of freedom to follow their scientific ideas." The public supports this because they expect something back, such as improvements in health or wealth. How would you explain the social benefit of research on frogs' eggs to a non-scientist?

It isn't easy! I think one almost has to justify it as a cultural activity: it's better to know things and if you know things, it's very, very beautiful.

Also, the benefits of pure research are often quite unexpected. Apparently, Michael Faraday was demonstrating electricity to an audience in the 1830s and a woman asked him, 'Of what use is your discovery of electricity?' Faraday is supposed to have said, 'Madam, of what use is a newborn child?' I feel rather like that about my *Xenopus* research. When Faraday discovered electricity, the transformation that it has made to our society cannot have been foreseeable. He was just finding out about the way the world works, and I think it's the same with working on frogs' eggs.

Where do you see the strengths of the European research society compared with others, for example, in the USA?

I worry about the European research effort compared with the US research effort. Somehow, the Americans are so much more successful at engendering and sustaining a vibrant and creative research ethos. It's partly because they have tons more money – although people sometimes deny that. I think they have an amazing openness to new ideas and a kind of celebration of pure research in many quarters – not just by scientists. If you go to any American university,

Image courtesy of Tomasz Sienicki

Sea urchin

you will find that the buildings were put up by wealthy local people. That sort of thing doesn't happen in Europe so much.

European universities are in a very bad state of repair in general. It's a shocking thing that American universities seem, by any criteria, to be among the most successful: 15 out of the 20 top universities in the world are in the USA! You would expect to find the University of Paris and the University of Berlin up there in the top league – but they are not. I think we should ask ourselves very carefully why not and whether there is something that we can do to change that.

In your opinion, is the European Union taking the right measures to move European science forward?

I am very optimistic that the formation of the European Research Council will help. I think, in the past, the emphasis has been too much on practical benefit – with agriculture, with medicine, with technology and so forth. I am a great believer in having a vibrant pure research community because that produces bright, creative individuals who will be successful in whatever they ultimately do. I am not saying that all scientists should be pure researchers for their entire lives, or that the entire research effort should be pure research – obviously not. But I do think that, in Europe, there is not enough emphasis placed on having universities that allow creativity and fun, and value the importance of just understanding. We are too obsessed with the utilitarian justification for science and not enough with the joys of science for its own sake.

Please complete the following sentence: "The best place to do research…"

…is in a place where lots of other very smart people are doing research. I was very happy in Cambridge because it had such a strong tradition of excellence in research. It was a little bit intimidating – you were well aware you were no Newton. On the other hand, the fact that so many fantastic scientific discoveries had been made in this funny, rather boring, town was quite important: science was the most interesting thing you could do.

What advice would you offer people at the start of a research career or considering it as an option? What are important attributes to have?

I think, mainly, you just need curiosity and to enjoy finding things out. You've got to want to know. It is not an ordinary career and it isn't ordinary work.

Role models are important, too. When I started at Cambridge, there were many Nobel laureates around and they had been spectacularly successful at understanding the way that cells work. That was very helpful because you actually knew these guys, you sometimes sat at lunch with them, and you could see that they were the best you could possibly be at science and yet they were human beings. They could make stupid remarks; they weren't omniscient. It gave one some hope that one's own modest efforts might succeed.

Image courtesy of EMBL Photolab

Sea urchin

And one last sentence to complete: "Receiving the Nobel Prize changed my life in a way that…"

… I didn't foresee. I think the main difference is that I've become a much more self-confident person.

Web references

w1 – An overview of the cell cycle and details of Tim Hunt, Leland Hartwell and Paul Nurse's work is given in the press release announcing their Nobel Prize: http://nobelprize.org/nobel_prizes/medicine/laureates/2001/press.html

To learn more about the cell cycle, play the 'Control of the Cell Cycle' game on the Nobel website: http://nobelprize.org/educational_games/medicine/2001/

For more information about the Nobel Prize, including biographies of the Prize winners, see http://nobelprize.org/

w2 – Cancer Research UK is the UK's leading cancer charity: www.cancerresearchuk.org

Resources

The audio file of the complete interview is available here: http://onlinesymposium.predocs.org/media/career-development-session/timhuntinterview/index.html

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Philipp Gebhardt is a PhD student at the European Molecular Biology Laboratory in Heidelberg, Germany, studying proteins involved in the dosage compensation phenomenon. This is a process that ensures that the gene products of the sex chromosomes are produced at the same rate in males and in females. Otherwise, females (with two X chromosomes) would produce twice the quantity of gene products encoded on the X chromosome as males (with only one X chromosome).

REVIEW

Nobel Prize winner Tim Hunt shares his personal experiences and reflections on science, its utilitarian applications, its role in our developed society and especially its cultural value and beauty.

Isabella Marini, Italy