interview

Peter Ghazal talks about his vision for the Scottish Centre for Genomic Technology and Informatics

Interviewed by **Ulrike Knies-Bamforth**

Peter Ghazal
Director of the Scottish Centre for Genomic Technology and Informatics, University of Edinburgh Medical School

Peter Ghazal was educated in the UK and did his PhD at the University of Edinburgh. Then, he did a postdoctoral fellowship at the NIH and, after that, moved to a faculty appointment at the Scripps Research Institute in California, USA where he worked for many years.

To start off, can you tell us a bit about yourself and your career?

My present position at the Medical School is the first time I have had a university job. As a result, there have been some interesting challenges from moving into the academic setting of a university.

However, I had the good fortune of being in San Diego at the time when the biotech and pharmaceutical industry was very small and only five or ten companies were in the area. As many hundreds of companies and big pharmaceutical companies moved in, I had the opportunity to closely interact with industry there, which was a very productive way of working. In terms of the science, I was trained as a geneticist when I was at the NIH – doing biochemistry and molecular biology.

At the Scripps Research Institute, infectious diseases and pathology became an interest and a passion and that led me onto microarrays and biochips. Pretty early on, we were involved in developing some viral microarray chips and that then led me in to the genomics area. Measuring multiple factors and working with that type of data set the stage for where we are at now with our thinking around pathway biology, which is more of a systems computational approach to understanding what you might call high-dimensional biology.

What projects are you currently focusing on in your own research?

We have two main thematic thrusts. One is about developing a methodology around pathway biology. We are interested in the interferon pathway because it is essential for establishing anti-infective states, as well as anticancer states inside the cell. In particular, we are interested in looking at host–pathogen interactions. Interferon was one of the first protein therapeutics and is currently used in a range of different therapeutic modalities from multiple sclerosis to anti-infectives and oncology. By using the virus as a tool for uncovering some rules and principles of the pathway we want to gain a deeper understanding that will allow us to either manipulate the current treatment or to use new diagnostic tools.

The other area of interest is trying to move basic science into clinical practice, the area we call biochip medicine. At the moment, most clinical diagnosis is done using single parameter measurements. However, multi-parameter measurements might actually be better for the treatment and management of patients. This involves looking at different computational methods on how to present the symptom issue, and also some of the hardware aspects, for example which biochips you might want to use. We also have activities trying to make sense of technology, for example using electrochemical detection methods, enabling real-time fast monitoring. Looking to the future, we have a programme on developing DNA sensors that can also work as logic sensors. This is closely allied to the basic science of pathway biology, which is to understand the logic of pathways. The ultimate aim is to have logic sensors that can 'talk' to the biology and those sensors themselves 'talking' to the electronics.

'The patient needs to understand how this technology can actually help them get better treatment.'

The next logical question would be what do you consider the biggest challenge for bringing microarray technology to the point of care?

We think that if you really want this to work it has to be seen as being of value in the treatment of the patient by the physician. At the same time, the patient needs to understand how this technology

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.03.006

can actually help them get better treatment. To my mind, those are the key challenges.

How does that translate into something tangible? For example, if you currently study biochips and you look at the complexity of the data, your eyes glaze over and ask yourself what does this all mean? So you have to think of smart ways of presenting the information. You also need to work out simple readouts, answering questions such as what is happening to this patient, and should I be using this drug or not? At the same time you need to be able to show and discuss the results with the patient. These present key challenges that I think are currently under appreciated. At the moment, diagnostics relies on single parameters but things are not that simple, which is why you have so many repeat visits to the doctors. Our idea is to short-circuit that and to have a better and more-efficient treatment.

So you think that technological progress has actually, at the moment, outpaced the intellectual progress so we have to match these two up again?

Yes, this is because a lot of the biochips have been deeply rooted in the research environment and in order to translate this, to help the physician and benefit the patient, you need to really de-skill the chip side of things.

A recent report by the Royal Society states that personalized medicines will not become a reality much sooner than in 10 years time. Would you think that this is the right timescale looking at pharmacogenomics and pharmagcogenetics?

I think that the issue is whether personalized medicine is the model for the current pharmaceutical industry. Personalized medicine challenges the way the industry thinks about how it might use or capitalize on that. At the moment there are two schools of thought, one is simply that if you take a market and you start to segment it, as personalized medicine is interpreted to do, then this raises the question from the current industries point of view – if the smaller market justifies developing a drug. Ultimately, you might decide not to make a personal drug for a specific individual. This type of model doesn't fit with where industry is at the moment. The other school of thought is, can personalized medicine be used to help reducing costs? Making sure that, instead of doing extremely large clinical trials, you can select the responders from the nonresponders early on. Again, this segments the market but there is greater justification for this because the costs of developing a drug are reduced. So, how does an industry look at this? How do they move forward? What are the types of models? We will see. Historically this might be something that is not championed by the pharmaceutical companies. Maybe this is more something for the biotech sector, which has been a little bit more willing to look at smaller markets.

You are the Director of the Scottish Centre for Genomic Technology and Informatics (GTI), can you tell us a bit about the GTI?

Yes, I suppose this has evolved from the realization in the mid 1990's that to maximize the use of high-dimensional microarray data you need different disciplines: you need skills in engineering, in the actual computational side, and a lot of other disciplines. The GTI as an academic model very much seeks to cross the different disciplines to link basic fundamental science with clinical practice. How do we actually do that? If we want to bring advanced science and technology closer to clinical practice, the collaboration of mathematics, physics, chemistry and biology are required. For this, we are using T-structuring, an approach that was not invented by us but that is well suited for our science. Instead of taking individuals that only represent 'I' structures with a great depth we are interested in expanding at the top in terms of breadth into other disciplines. Doing so, we end up with individuals that, for example, understand a little about engineering or the computational side but don't have depth of knowledge in those areas. Of course, that individual is an expert in their own field. As a result, if you put all the T's together then you create a situation where you have depth and breadth – and that is what we try to do around the various specific projects that we have.

'We have a healthy portfolio of funding from a variety of funding bodies.'

How is the GTI funded and how do you think it has benefited the development of this area of science in Scotland as a whole?

We have a healthy portfolio of funding from a variety of funding bodies, including the Wellcome Trust and the Research Councils in the UK, to European-based funding. Industrial sponsorship has been lacking to date. In the beginning, we were seed-funded by the Scottish Executive with the aim to enable microarray technology throughout Scotland, which we have done and obviously have moved on, focusing on our research programmes in pathway biology and biochip medicine. Over all, I am pleased with our funding base and resources.

'We are seeing an incredible explosion of knowledge and information catalyzed by the human genome project.'

Could you outline the short- and long-term goals for the GTI as an institution?

In basic science, we are seeing an incredible explosion of knowledge and information catalyzed by the human genome project. Historically, medicine is a very conservative industry, and it has to be. The danger is that we have an exponential growth of knowledge from basic research, however we only have a linear growth of medicine and the problem is that as you go into the future, the delta between the two gets larger and larger.

Our long-term objective is to shorten that delta, which is why we want to help bring a lot of fundamental science closer to the clinical practice. The short-term objective is really to do excellent outstanding science, and to have fun doing it. For example, some of the work we are doing around the pathway analysis is so fascinating because you start to look at a biological response in a different way, you start to see the behaviour of networks and subnetworks and the interactions of those, and it teaches you almost a different way of looking at a biological system, which is fascinating.

Systems biology is very much en vogue at the moment and some people now voice their concerns and ask whether it has actually delivered particularly in drug discovery. What is your opinion on that?

We have to remember that it is still early days. I am not aware of any examples in which systems biology has had any use in drug discovery. However, we actually don't even know if our basic science is going to be of value. This is why we make the distinction between systems biology and pathway biology, which you could call a subarea of systems biology. Systems biology, for example, models a whole organ or an *in silico* human being. From my perspective, neither is very tangible. However, if you take a more pragmatic view and ask can we actually just get our heads around a subsystem within that system, like the interferon pathway, and understand

its behaviour, is that tractable? Can we then generate the right computational model and can this be informative for us in terms of being able to understand patient responses or to improve drugs?

Pathway biology is a more pragmatic approach and might give us the opportunity of showing more tangible benefits. Having said that, the idea of systems biology really sets the landmark for a greater use and understanding of computational science and how it can be applied to biology and chemistry. Coming back to your question, I think that it depends on what the expectations are. I would say from having an increased computational capability and understanding how to use it, that it is already happening in the industry and will have a very real impact in a few years.

'Other opportunities might arise from the commercialization of ideas.'

How do you think one could improve the commercialization of findings made in academic research?

Let me talk from a European perspective. When you have two communities that rarely talk to each other then it is very difficult to see how you might link the commercial side of a community with academics, who are solely there to understand and do their science. As a consequence, if you want to create links between the communities, there need to be more physical interactions, so the first part then is really having better interactions between large pharmaceutical R&D departments with academia. This does happen in a very selective way but this is certainly an activity that could be encouraged more.

Other opportunities might arise from the commercialization of ideas. You can have many ideas but those ideas are nothing unless you convert them into a product that sells and actually makes a real world impact. So the question is, how you do you get academic innovation tied with commercialization of a product? You can take two roads, one is to say we are going to organically grow this from university as spinouts, the other way is to actually attract people from industry to identify areas where we can actually synergize for doing that, so they are spin buys if you like. We've been involved in two companies, one is Arrayjet using inkjet technology for improving the quality and production of microarrays. This came about through interactions between Howard Manning, a physicist from the inkjet technology world, and ourselves, discussing how inkjet technology could be applied in microarrays and we came up with the concept behind Arrayjet. The other example is a company called Lab 901, which involved interactions between two ex-Motorola engineers and ourselves to develop a microfluidic concept of a lab on a tape, where you can do operational microfluidic operations on a tape device. Those are ideas that one can patent and, therefore, commercialize but you also have the seasoned industrialists, who are also part of making this a success, which, again, is following a T-structuring model.

'I think that the Europeans tend to be a little bit more open to the collaboration model.'

You returned to Scotland after 16 years in the United States. First of all why did you return?

The US is a land of opportunity with great science and, yes, there was the thought of never coming back. Returning to the UK was, in part, a personal decision, but from a scientific point of view there was this particular disconnection on the clinical side. To be more specific, in the US it is very difficult to stimulate interaction between the clinic and academic research. The primary reason is because of the cost model operated in the US for hospitals to undertake research.

This is not to say that it doesn't happen in the US, but it's not very frequent. In the UK, however, I think that there is a lot more opportunity to do that. We are able to have interactions that would be fairly difficult to establish in the US. Also I think that the Europeans tend to be a little bit more open to the collaboration model. This might be because there has never been the amount of resources in funding and, therefore, people have had to collaborate to achieve their scientific objectives. From this point of view, the move has been very successful and I think that what we have established with GTI could not have been established in the US.

Is there something that you would say is specifically good about the location, in Scotland, of Edinburgh – or would you say there are advantages UK or even Europe wide?

The medical school in Edinburgh is very good. It has always been at the forefront of medicine. The school itself about five or six years ago, had started to change its organizational structure, which has provided an opportunity. We were relocated to this new site, which, at the moment, is an ~100 hectare development and there is still another 400 hectares to develop. It is a billion Euro investment, which is an opportunity for a lot of co-localization, bringing in opportunity for new structures, new interdisciplinary, cross-disciplinary types of activities – so all of those combined, I think, really make it quite a unique setting. If we were stuck in an historical part of the town, I think it would be more difficult to get the same type of interactions that we have here in Edinburgh and Scotland.