Interview

Enriching the pore

Professor Hagan Bayley speaks to Hannah Stanwix, Assistant Commissioning Editor

Professor Hagan Bayley received his Bachelor of Arts degree in Chemistry from the University of Oxford (Oxford, UK) in 1974. He holds a PhD in Chemistry from Harvard University (MA, USA) and completed a postdoctoral fellowship at the Massachusetts Institute of Technology (MA, USA). In 1981, Professor Bayley moved to Columbia University (NY, USA) as an Assistant Professor of Biochemistry. He subsequently worked at the Worcester Foundation for Biomedical Research (MA, USA) and in 1997, Professor Bayley moved to Texas A&M University (TX, USA) to become a Professor of Chemistry and Head of the Department of Medical Biochemistry & Genetics. Professor Bayley returned to the University of Oxford in 2003 and is currently the Professor of Chemical Biology. Professor Bayley is a Fellow of the American Association for the Advancement of Science, a Fellow of the Society of Biology (London, UK) and a Fellow of the Royal Society (London, UK). He has received numerous awards including the Royal Society of Chemistry 2009 Chemistry World Entrepreneur of the Year. Professor Bayley is the founder of Oxford Nanopore Technologies Ltd., a private company based in Oxford (UK). Professor Bayley has authored over 150 peer-reviewed papers, over 40 book chapters and review articles, as well as numerous patents.

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■ Your undergraduate studies and subsequent PhD were in chemistry. What took you from this background to researching the properties of nanopores and their potential for DNA sequencing?

First of all, I think chemistry is a very good degree to have in science. It's different to some other subjects because it is quantitative and also requires qualitative and creative thinking. Chemistry is a bit like chess as it involves both analytical and intuitive thinking. So I think an undergraduate degree in chemistry is good, not just for doing chemistry but for doing all types of science. Of course at the cutting edge of science, it is sometimes impossible to define whether you are doing chemistry, physics, biology or engineering. While I was studying chemistry at Oxford University (Oxford, UK), I was always interested in biology and when I did a PhD with Jeremy Knowles (formerly Harvard University, MA, USA) I worked with membrane proteins and I have stayed interested in membrane proteins for my whole life. I did a postdoctoral fellowship with Gobind Khorana at the Massachusetts Institute of Technology (MA, USA) on

bacteriorhodopsin, the first large membrane protein to be sequenced. So the connection with nanopores is a basic science connection. When I began as an Assistant Professor at Columbia University (NY, USA), I looked for a model protein system where I could answer the question of how do membrane proteins get into membranes, assemble and become functional. In the literature, I found the α -hemolysin protein, which is a toxin secreted by *Staphylococcus aureus*. It performs the amazing trick of being a monomeric water-soluble protein that assembles into lipid bilayers to form a pore that has seven subunits and makes a hole through the bilayer. Initially, I set out to study that as a basic science problem. But at the time, in the late 1980s and early 1990s, there was a lot of work on engineering enzymes and antibodies for applications in biotechnology. So, I wondered if membrane proteins, which are often much more difficult to handle, could have applications in biotechnology as well. There were a lot of things that we considered, including killing tumor cells, permeabilizing cells to get cryoprotectants in to store them, making filters, all sorts of things. The sensing applications turned out to be

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the most interesting. Combining protein engineering with the ability to record currents passing through single copies of a pore enabled us to develop a new form of sensing, which we called 'stochastic sensing'. You use a sensor, a single element, in this case a pore, to detect individual molecules. Originally this was developed for detecting a wide variety of analytes. We started with metal ions and then we moved onto organic molecules and fragments of DNA, proteins, sugars and so on. It was only later in 2005, after the NIH had started their 1000 genome project, that we really got interested in turning the pore into a DNA sequencer, an idea which had been suggested many years earlier by Dave Deamer (University of California Santa Cruz, CA, USA) and Dan Branton (Harvard University).

■ In 2005, you founded the company Oxford Nanopore Technologies. What led you to establish this company?

While I was in the USA, we had been trying to establish a company based on stochastic sensing, not just DNA detection, but a whole sensing platform. I came back to the UK in 2003 and we continued to try and do this for a year or so after I got back. This company was based in Germany and we couldn't get adequate funding to get started. I came to Oxford University in 2003. There is an excellent environment for starting companies in Oxford, it is not frowned upon by the University, and they have a very good technology licensing office called Isis Innovation. Most importantly, the University has an association with a company called IP Group, which specializes in university start-ups. Having met with IP Group in 2004, in 2005 I went to them and said that we really wanted to get the company going, can you help us? They said that the best thing to do was to start a new company; they liked the technology and it went from there. The first person we brought in was Gordon Sanghera as CEO and shortly after that Spike Willcocks came to join us. They have remained key players ever since.

■ As the Professor of Chemical Biology at the University of Oxford and founder of Oxford Nanopore

Technologies, you have successfully combined academia with business. How do the two compare and what have you learnt from the experience?

I've not run the company; I still remain very much an academic. At the very most, I spent 20% of my time on the company. The company has been run by Gordon Sanghera, the CEO, and the many other excellent people he has brought in. The company right now is five- or six-times bigger than my own laboratory. I haven't done the two things in parallel. I started the company and spent a fraction of my time on the board and advising the company. The company certainly uses the technology we developed and continue to develop in the laboratory, but I do not spend half my time at the company and half my time at Oxford University.

■ At the time, did you realize the impact that the nanopore technologies being developed at the company would eventually have on DNA sequencing?

No, and I am still guarded about that. Technologies come and go but I think we knew it would be a very useful platform sensing technology. Not just for DNA sequencing, but for sensing many analytes that might be important, for example, in medicine, food safety or chemical warfare. Stochastic sensing has a huge number of applications. So we felt this was a technology with a lot of potential, but at the start you can never tell where things will go and how far they will go. I think that is quite impossible to say.

■ The company has recently announced a portable device for DNA sequencing. Do you envisage these devices having a use in the clinical setting?

Yes, definitely. Possibly the only thing that will slow down such applications will be regulations. I think such devices could be used in a GP setting but obviously general practice in the UK remains incredibly primitive (about the only technology GPs have today is a stethoscope), and adoption will be an issue. I think the technology certainly has the potential to be used in big clinical centers, where you could sequence

entire genomes and compare them with those of other patients. The nanopore technology, not only the sequencing but other things that we can detect, could be performed by GPs, but it could also be performed by the patients themselves. We've heard a lot about a massive IT infrastructure for medicine, a big computer that will hold everyone's medical information, but I think we are going to see a movement back towards individual patients with measurements stored on devices like iPhones®. In this regard, miniaturized, basically disposable, medical testing technology could be very useful.

■ **What do you think the other potential applications of nanopore-based sensors could be?**

In some ways, as an academic, I am less concerned about where things will be used or what the market will be. We have shown the potential to detect just about anything you can think of. Certainly at airports there is a need for very rapid real-time screening, which nanopore technology is capable of. You can't be pulling every other person out of the queue and keeping them for 2 h while you do a test on them. So it has to be quick and this technology is quick. It has the potential to detect explosives or chemical weapons, or could even be used with ill people, sequencing the viruses they carry very quickly.

■ **Aside from DNA sequencing, what other areas of research are you and your group working on?**

We're particularly interested in artificial tissues, and we are moving towards working in the synthetic biology field. We've been interested in membranes and membrane proteins and they would be critical towards building artificial tissues that may be used as implants in the body for example. That's one area we find quite interesting.

■ **Is there a particular area of your research that you are most excited about?**

I have to be careful here, there are lots of different people in my laboratory! I'm excited about everything that is going on in the laboratory but if I choose one area it would be the artificial tissues. We are

also looking at chemical reactions, bond-making and bond-breaking, at the single molecule level, using the nanopores as detectors. I think that is a tremendously interesting area. There are quite a few things that we are doing in the laboratory, sometimes they are just at the level of one person beginning something to see if a new line of research will work. The synthetic tissues and the single-molecule covalent chemistry are two areas where we have substantial efforts.

■ **The last decade has seen some incredible advances in the field of nanomedicine as a whole. In your opinion, what do you think the most interesting developments have been?**

Certainly, DNA sequencing has revolutionized the way we look at genomic medicine. Less than 10 years ago it cost GB£70 million to sequence someone's genome and now it really is down to the US\$1000 level. That is going to be absolutely revolutionary in terms of genetic disease and cancer. There are many other areas that I find exciting. I think tissue engineering, for example, is going to be revolutionized by all the new things we have learnt about stem cells in the last few years. To grow tissues *in vitro* in 3D, you need scaffolds, which involves nanotechnology to develop the scaffolds. I think imaging is another incredible area in which chemistry can have a huge impact. All of these new technologies will affect medicine in the western world, but we also need to think about technologies that will affect all of our population of 7 billion. That's a bit of a different matter. Who will be able to afford these technologies and who won't? I think then that the so-called e-health revolution will be critical. The ability to convert an iPhone into a device that can record an ECG, for example, is going to be massively important in countries like India where you can take a cheap mobile phone, record an ECG in a village and transmit it to a medical center in 2 min. That is going to be huge.

■ **Throughout your career you have collaborated with numerous scientists and other research groups. What are the advantages of**

such collaborations in terms of scientific progress?

My philosophy has been more if we can do it ourselves, let's do it ourselves. I have a highly multidisciplinary group with chemists, biologist, physicists and engineers. I wouldn't say that we are the best in the world at any of these things but bringing all these people together in one laboratory has an incredible synergistic effect. On the whole, we have tended not to collaborate as much as some other groups. But we have had vital collaborations, for example, in crystallography; the structure of the hemolysin pore was solved by Eric Gouaux (Vollum Institute, OR, USA) and Howard Hughes Medical Institute (MA, USA) in the 1990s and that was really critical to the success of our later work. We recently had a collaboration with Cees Dekker (Delft University of Technology, The Netherlands) to put our protein pores into apertures in solid-state membranes to get rid of lipid bilayers altogether, and I think that is going to be very important indeed. I do understand collaboration is useful in some areas and encouraged by the research councils, but I also think there is a role for large multidisciplinary research groups, where you can have all of the people in the same space at the same time. There are advantages to having a group that is like a think-tank, where we can just have a go at new things and have the expertise in place to do that.

■ Your career so far has been varied and successful. Are you able to pick one specific highlight?

That is also very hard. Certainly one highlight was the discovery of the molecular adapters that you can put inside nanopores. We can put cyclodextrins, cyclic oligosaccharides, inside the pores where they can bind organic analytes. That was a discovery that really came out of the blue and moved the field forward. Then in 2006 we published the first paper that showed you can identify all four DNA bases using a single pore; I believe that was very important for us and for pushing

the field forward. More recently, about 5 years ago, the discovery of the ability to make networks of artificial droplets was an important step forward for us towards making artificial tissues.

■ Finally, where do you see yourself and the field of DNA sequencing in 5 years time?

It's hard to say. DNA sequencing at the protein nanopore level, I would say, is finished as an academic pursuit. I think people, including me, are going to have to move onto other areas. Because a protein is used to drive the DNA through the pore, protein nanopore sequencing is limited to a sequencing speed of a few milliseconds per base. If solid-state sequencing, which I think is 5 or 10 years away, works as expected, it may be possible to sequence DNA 1000-times faster, at a few microseconds per base. That would be tremendously exciting. Furthermore, it is how you use the sequence as well as generate the sequence that is important. Say you have the sequences of 100,000 humans, how do you compare those sequences and use that information to predict disease and diagnose patients? Clearly the DNA field is going to turn into a highly informatics-driven area. Areas that will remain interesting for academic experimental scientists in the medical sciences will include imaging and tissue engineering.

Financial & competing interests disclosure

Hagan Bayley is the Founder, a Director and a shareholder of Oxford Nanopore Technologies, a company engaged in the development of nanopore sequencing technology. Work in the Bayley laboratory at the University of Oxford is supported in part by Oxford Nanopore Technologies. Work on this Interview was not supported by Oxford Nanopore Technologies. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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