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Simon Campbell on the ups and downs of drug discovery and development

Interviewed by Jayne Carey and Samantha Barton

Simon Campbell,
President of the Royal Society of Chemistry (UK)

Simon Campbell received his BSc and PhD from the University of Birmingham in 1962 and 1965, respectively. After completing postdoctoral research at the Santa Maria Technical University (Chile) on natural products, Campbell moved to Stanford University (USA) in 1968, where he remained for two years. In 1970, he accepted the position of visiting professor at the University of Säo Paulo (Brazil), where he established a synthetic organic chemistry laboratory. In 1972, Campbell returned to the UK to take up a position with Pfizer (Sandwich) as a medicinal chemist, where he went on to become head of World-wide Discovery. In 1997, Campbell became the first non-American to receive the prestigious E.B. Herschberg Award for Important Discoveries in Medicinally Active Substances from the American Chemical Society. On his retirement in 1998, Campbell was Senior VP at Pfizer for World-wide discovery and Medicinals R&D in Europe (World-wide Discovery encompassed the UK, USA and Japan; Medicinals R&D Europe encompassed not only discovery but also development). While at Pfizer, Campbell co-authored over 110 publications and patents and was a key member of the research teams that discovered doxazosin, amlodipine and sildenafil (more commonly known as Viagra™). In 1999, he was elected Fellow of the Royal Society, a scientific honour that is relatively rare for industrialists.

Regarding your postdoctoral experiences in Chile and Brazil, could you tell us a bit more about working in these countries in comparison with working in the UK? What did you gain from your time there?

Well, the first thing that I gained from working in Latin countries was to appreciate different types of personal interactions and a greater focus on the family. I derived great personal benefit from working in those countries and I recently returned to Brazil for the 60th birthday of one of our University football team players. In general, the labs were pretty well-equipped. I think the major difference between South America and North America then would be the speed with which one could order and receive chemicals. Whereas it's almost the same day in Europe and the USA, shipping-in chemicals to South America in those days was a slow business. But, with planning, we overcame most problems. So, I think the facilities were pretty good for synthetic organic chemistry research.

You were inaugural chairperson on the expert scientific committee for the first ever public–private partnership set up to tackle malaria, the Medicines for Malaria Venture (MMV). Can you tell us what you learned from working at MMV?

Well, I chaired the expert panel for four years. First of all, I really appreciated how devastating malaria is. It is endemic over a large part of sub-Saharan Africa – it afflicts ~300 million people and there are millions of deaths every year, mainly children. Also, I realized how poor current drugs are, in that resistance has developed to most of the drugs presently available and the treatments are largely ineffective. I realized that there was a desperate need for new drugs for the treatment of malaria, which were unlikely to come from the pharmaceutical industry because of the limited commercial opportunities. We were extremely grateful that the Gates Foundation and others made donations that enabled us to build up our research programme.

What types of incentive do you think could be offered to companies to encourage them to work more in neglected diseases such as malaria and African sleeping sickness?

I believe it is difficult for pharmaceutical companies to work in these areas given the limited commercial opportunities. But, if pharmaceutical companies develop a drug for another indication that could also be used

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for malaria or sleeping sickness, I'm sure they would be very pleased to make supplies available. For example, Pfizer made its antifungal drug fluconazole readily available in South Africa and Merck donated one of its compounds for river blindness. So, I think the pharmaceutical industry will be generous, if the agents it develops for other uses can be used in tropical medicine. Commencing work in these areas, I think, would be difficult for commercial reasons.

So, in that respect, would you say that it is more up to the academic researchers to investigate the current drugs to try to find the potential of existing drugs in the treatment of parasitic diseases?

I think the way MMV was constructed was an excellent way to go! We had academics collaborating with scientists from industry and biotech, and the pharmaceutical companies offering their advice and skills. They work together in multidisciplinary teams and there are several drugs going through the pipeline towards the clinic. I think that the MMV partnership and the partnership on TB [tuberculosis] are the way to go for these neglected diseases.

'What we try to do is to influence the government and funding agencies to recognize the importance of chemical science in the UK…'

What does your current role as the President of the Royal Society of Chemistry (RSC) involve?

There are full-time executives at the RSC who run the society, and the role of President is an honorary position that one serves for two years. What we try to do is to influence the government and funding agencies to recognize the importance of chemical science in the UK by providing proper financial support. You probably know that Exeter [University] has just closed its chemistry department on the basis of costs and others will go the same way unless urgent action is taken.

What about the Campaign for Chemical Science? How was that set up?

What we tried to do at the RSC was to bring together a whole series of initiatives that were being conducted independently – we integrated them, if you like, under an overall umbrella, which we labelled the Campaign for Chemical Science. It's a very useful way of pulling our initiatives together, to communicate with members, to give them an idea of what the Society is doing, and also to communicate with government and others. We just pulled our headlines, our initiatives under one umbrella, which I'm leading.

'…commercial companies should increase their expenditure on R&D.'

Talking about working with the government, in your recent speech to the Scottish Parliament, you mentioned the 'ten-year Science and Innovation Plan'. Could you explain what this plan is?

This is a plan that the government has published which stresses the importance of science and technology for the future of the country, as well as the importance of having a well-funded science base and increasing spend on R&D. Also, it emphasizes that commercial companies should increase their expenditure on R&D. Basically, this is a ten-year plan for science and innovation from which the Chancellor hopes that the UK will become the most attractive country in Europe for business R&D. If you look up the Treasury on the web, you'll find the ten-year Plan there and there's a useful easy-to-read summary (http://www.hm-treasury.gov.uk/media/D13/9D/science_406.pdf).

How do you think the UK compares with the rest of Europe and the USA in terms of education and funding?

I think the UK comes out very well when compared with Europe, but sits behind the USA, largely because the USA is more generously funded. But, in terms of value for money, and various studies have shown this, the UK comes out very well.

As long as no more chemistry departments are closed?

Well, if more departments are closed then we will really see a significant impact on science-based industries. The chemicals industry has a turnover of UK£50 billion per year and a positive balance of payments of UK£5 billion. We simply cannot allow that to erode and wither away.

What do you think can be done to try to reverse this trend?

The main factor, in my mind, is cost. Chemistry is an expensive subject. Chemists require laboratories that cannot be used for much else but chemistry, as well as specialized reagents and equipment. On the other hand, Vice Chancellors have to balance their books and have to make sure that they do not run into a deficit. If you have a chemistry department that is expensive and running at a deficit, then the easy way to solve the problem is to close that chemistry department. I think that a more logical way to solve the problem would be for the government to increase funding for chemistry and to recognize its true cost with respect to classroom-based subjects.

'…industry already makes a significant direct contribution to funding academic research…'

What about company sponsorship?

Companies already sponsor quite a lot of scientific research in this country – I don't have the figures, but certainly when I was at Pfizer we sponsored PhD research, postdoctoral research and individual collaborations with academia. So industry already makes a significant direct contribution to funding academic research in the UK. Of course, we also make an indirect contribution via the taxes that we pay.

You are on the scientific advisory board of several biotech companies, including Astex and Inpharmatica. What did you find to be the main difference between working for a global pharmaceutical company like Pfizer and the biotech industry?

I think both roles are equally satisfying but in different ways. In the pharmaceutical industry, I was very pleased that we discovered major drugs and that we had the money and the resources to advance them to the clinic, and then finally to commercialize them. In biotech, you're operating in a much smaller environment – it's easy to get to know everybody and the work that they do, and that enables one to make an impact. Both roles are stimulating but probably the main difference is the scale. The smaller scale of biotech enables more

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personal interaction, whereas the larger scale of pharma ensures that if you do discover something you have the means to drive it forward and to commercialize it.

Looking back on your career, who do you think has had the greatest influence on you?
I think there are several people. Obviously, there was my chemistry teacher at school, who influenced me to take up the subject. When I worked for Bill Johnson at Stanford, he was a great influence, particularly in stressing the importance of recognizing the contributions of collaborators. At Pfizer, there were several people, Ken Blackburn and Mike Davey had a great influence on me, with respect to pharmacology, biology and drug discovery. Peter Leeming had a significant influence with respect to personal development, teamwork and that kind of thing.

And what would you say is your greatest achievement to date?
I find it very difficult to single anything out. I think I'm most proud of working with my colleagues – chemists, biologists, drug metabolists and pharmacologists – in the pharmaceutical industry and very proud that we discovered three major new medicines – doxazosin, amlodipine and sildenafil. Pfizer is often known as the Viagra™ company, but in fact Norvasc™, and I'm co-inventor on that patent, is the fourth best-selling drug in the world. Although I wouldn't use the term greatest achievement, it is incredibly satisfying when I meet people who tell me 'Well, we've taken this drug, we've taken that drug, we really can feel the benefit and have had no adverse events at all.' I can't single out a greatest achievement, but this kind of feedback provides immense satisfaction.

As you have just stated, you've been involved in the development of at least three successful drugs for cardiovascular disorders – α1-adrenergic antagonists, dihydropyridine L-channel blockers and phosphodiesterase inhibitors. Which programme gave you the most satisfaction and which one provided the greatest challenge?
They were all quite different. When we discovered doxazosin, we had some experience at Pfizer with similar compounds and we had a flash of inspiration and said – why don't we make this compound? We rationalized the reasons for making it and we discovered doxazosin very quickly. When we worked on the amlodipine programme, there was a lot of competitor activity, hundreds of compounds in the literature, and that took us some time to think our way through. In the end, we made a very innovative decision, we placed a substituent in the molecule that nobody had done before and it dramatically improved the properties of the compound. We started with something that was administered three to four times a day and we ended up with a compound that could be taken once a day, with a very slow onset of action, which was great for patients' tolerance and safety. Then, we went on to sildenafil, and I wrote the research proposal with David Roberts and started off the project. The chemistry was picked up by Dave Brown and his colleagues and they are the inventors on the Viagra™ patent, but I was involved with the project right from the start and I was also present in New York (USA) on 27 March 1998, which happened to be my birthday, when Viagra™ was launched. So, I started the project and I was there at the launch. Those three experiences are all quite different. Of course, we started the Viagra™ project looking for a compound for angina and hypertension. It was only when we got to the clinic that we found that the compound had other uses!

'…the data deluge is not helping us.'

Viagra™ was developed after observations that zaprinast, an antiallergy compound caused vasodilation. Do you think that nowadays such information would be picked up from scientists working in different therapeutic areas as a result of the massive increase in data production?
Well, we did start the Viagra™ programme with zaprinast, and we noted its structure and modified it rationally. I do share your concerns to some extent in that I think we are producing scientists who are more and more specialized and who concentrate very much on their own field, which they know in immense detail. It may well be that what we're lacking now are people who are not only experts in their field, but can also scan the horizon and pick out inspiration from other disciplines. I am concerned about that and I do think that the data deluge is not helping us.

In 1998, you mentioned that 'scientists should rely less on streamlined assays and more on animal models'. Considering that animal models are not predictive of human responses to drugs, is this still your opinion? Or do you think the new technologies such as computational modelling and simulation can replace animal models?
I'm happy to use any technique that will get us to a new drug – I don't rule out one in favour of the other. What I was trying to say is that we are whole animals and if you do your experiments on isolated cells, where the cells can't 'talk' to other cells and the tissues can't talk, then you tend to get results that may not be representative of the whole animal. I think whenever one designs a pharmacological experiment, we should remember that we are treating whole animals and that's where the new medicines will be used.

Do you think that scientists who work in drug discovery and development are losing the ability to react to serendipity?
I think there are many more pressures on the pharmaceutical industry today – we've just seen that with the withdrawal of Vioxx™ – and it may well be that the pressure to deliver, the pressure to meet timetables may cause people to put the unexpected observation to one side. As a general point, I feel that the industry should be concerned about increasing pressures and time constraints that could result in too much focus on the task and allow less scope for innovation.

'…there is still a great place for the chemist staring out of the window and letting his/her imagination wander…'

What is your opinion on the changing role of synthetic and medicinal chemists in drug discovery and development considering the advances made in technology?
When I started out in chemistry, we had hand-held plastic and wire models comprising ball-shaped atoms that were of the appropriate relevant size. We played around with them, but we thought in 3D. What a computer does is to put the molecules on the screen, rotate them

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around, dock them and make them interact with each other. I think the computer enables us to act on a larger scale and is more accurate than before, with respect to the number of molecules we can deal with. Of course, we can now put protein structures on the computer, which again, when I started, we hand built and they were held together with wires. I think the computer is a great aid, but I would still use hand-held models, and I feel that there is still a great place for the chemist staring out of the window and letting his/her imagination wander – and given time to wander!

'…drug discovery is a personal experience and not a mechanical event.'

Do you think that scientists today rely too heavily on HTS and automation? Do you think they are losing basic 'bench' skills?

I don't think they're losing the basic bench skills, but I think there has been an assumption that if we crunch numbers, we'll win the game. If we have more compounds in the file, and if we run more screens, then we're bound to get a result. Well, that hasn't happened. I like to say that drug discovery is a personal experience and not a mechanical event. I think that over the past few years there has been an expectation that it could be a mechanical event and we could automate the process. I come back to it being a personal experience and the personal intervention of scientists on the project is very important.

In your opinion, who is doing really exciting, innovative research at the moment?

Well, I think there's some very nice work going on around protein structure and particularly ion channels. Ion channels control many of the processes in the body and these channels can be modulated. Norvasc™, as you pointed out, is a calcium-channel blocker that is effective for angina and hypertension. There's been some nice work done on ion channels by MacKinnon, who shared the Nobel Prize for Chemistry in 2003. It's been difficult to find specific ligands for ion channels but, I think with the X-ray work that's now being published, we might be able to understand how the channel functions and we may be able to understand how we can intervene and how we can design new drugs.

What do you envisage as being the next big break through in medicinal chemistry research?

In medicinal research, I very much hope that we can come up with a vaccine for AIDS and malaria. I've actually been hoping that for the last 20 years and we are probably still 15 years away. But, if one could have a wish, vaccines for AIDS and malaria would be top of the list. There's quite interesting work being done around RNA interference (RNAi) – you can knockdown the gene function with RNAi. The problem is with delivery. We've just seen that you can in fact deliver the RNAi with cholesterol tags to mice – I'm not sure what would happen in humans. But, I think if one could deliver RNAi to humans then that would be very exciting and would have great potential.

Going back to your role at the RSC, what would you like to have accomplished by the end of your Presidency?

By the end of my Presidency, I would hope that the government will have taken on board our message of the importance of a strong science base in the UK, that it will have listened and understood that we have to be properly funded, and it will have understood that an internationally competitive chemical sciences section is absolutely vital for the future prosperity of the country. Also, I hope it will understand that if we want to address major challenges such as climate change, energy efficiency and new medicines, then chemistry is fundamental to solving all those problems. Really, I think it would be good to get a mind switch from chemicals being the heavy industry to chemistry being the solution

'…to get a mind switch from chemicals being the heavy industry to chemistry being the solution to some of the pressing problems that we're facing.'

to some of the pressing problems that we're facing. I think that would be a great achievement. We have to work hard to get these messages over. When the government takes on the Presidency of the G8, climate change and Africa will be hot topics. And, as I've just mentioned, if you want new medicines for Africa and the rest of the developing world, then chemistry is vital. If we want to improve energy efficiency and reduce CO_2 emissions, then again chemistry is vital.

In that respect, is improving the image of chemistry a matter of changing public perception and not solely related to encouraging more people to study chemistry at higher education?

I think you're right, but influencing on a national scale is very difficult. I think one way to tackle the problem would be to encourage our teachers, help them with career development and enable them to be as up-to-date as possible with chemistry development. Then, if they influence the pupils and the pupils go on from there, to pursue science or other subjects, then at least they've understood science in the classroom and that stays with them for the rest of their lives. To undertake a national advertising campaign would be very expensive and, I don't know about you, but I'm not influenced by adverts. So, I'm not sure how useful it would be! The RSC invests over UK£1 million per year in supporting science education in schools, which is a significant investment.

As a demonstration of faith in pharmacology and championing a hypothesis, it would be difficult to top Giles Brindley's demonstration of 1983. Have you come across any observations in other scientists who have shown such zeal in their beliefs?

This is where he took his trousers down? Well, I wouldn't go as far as that, but what I would say is that when we're developing medicines the first thing that one does is to test them in normal healthy volunteers. I certainly volunteered to take doxazosin and my colleagues took other new medicines before anyone else was exposed to them. I think that does show a major commitment, with perhaps a more significant impact than Giles' demonstration!

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