BACR Interview #3: Professor Len Seymour (Hybrid Systems)

*In the third of our series of interviews with BACR personnel who are commercialising their research, Dr. Nick Miller interviews Professor Len Seymour, whose research is being commercialised through Hybrid Sytems Ltd (www.**hybridsystems**.co.uk). Professor Seymour is Professor of Genetic Therapies in the Department of Clinical Pharmacology, University of Oxford, Head of the Cancer Research UK Gene Delivery Group, President of the British Society for Gene Therapy, and Supernumerary Fellow of Wolfson College, Oxford.*

NM: Leaving aside the contract research and reagent provision aspect of Hybrid Systems, I believe the company is focussing on commercialisation of an enabling technology based on the polymer poly(hydroxypropylmethacrylamide). In particular, the company is looking at applications of the polymer in terms of coating recombinant virus particles in order to shield them from the immune system and from interactions with other non-target cells. This is anticipated to prevent clearance, increase serum half-life, and allow lower titres of virus to be used in a therapeutic context. In particular, Hybrid Systems expects the polymer coating to facilitate use of recombinant viruses in two distinct but related areas, namely virotherapy (treatment of cancer by injection of a replication-competent lytic virus in order to cause a spreading infection that would eliminate disseminated cancer) and cancer vaccines (recruitment of an immune response against the cancer, by expression of an appropriate antigen in an appropriate host cell).

LS: Yes, that's right, although I should also say that the Hybrid Systems approach in fact is applicable to a very broad range of vaccines, not just cancer vaccines. It turns out that much of our early work is directly applicable to vaccine development, and the vaccine side of our business is becoming increasingly important. In addition, we are refining a number of different polymers, not just one.

NM: Can you tell us a little about how you came to discover the potential for the Hybrid Systems polymers in viral masking applications?

LS: The trigger was the discovery of unexpected activity in preparations of polymer-coated viruses. The anticipation had been that coating a virus with a synthetic polymer would kill it, but our work showed that if you introduced a novel ligand into the polymer coating, the coated virus could infect cells via new ligand-receptor interactions. This raised the possibility of constructing stealth viruses that could enter cells by ligands of our choice. We have since discovered that the adenoviral protease activated after cell entry retains its ability to cause shedding of the viral capsular proteins, along with the polymer bound to the capsular proteins. So the polymer system provides the ideal combination of features, in that it shields the virus while it is outside the cell, but does not interfere with viral functions post-cell entry, such as nuclear translocation and gene expression.

NM: What happens to the polymer in the body – for example, is it metabolised, excreted unchanged, or accumulated in tissue? How much clinical or animal safety data is there?

LS: The polymer is essentially non-biodegradable, so pretty much nothing happens to it in the body. In any case, we make the polymer chains small enough for them to be rapidly excreted. In terms of safety, this polymer has been through Phase I and II clinical trials with patients receiving gram doses of polymer with no apparent safety issues, and we are using quantities of polymer far smaller than that. We don't anticipate any significant safety concerns with this system.

NM: Could normal stealth / targeted liposome technology compete with your polymer?

LS: The problem with most systems that seek to deliver a drug cargo by targeting particular receptors is that the therapeutic effect may be limited by the number of receptors. Usually the numbers of cell-specific receptors are just not sufficient to internalise a dose of cytotoxic agent in quantities great enough to mediate a therapeutic effect, at least not with current cytotoxic agents. Our virotherapy approach has an intrinsic amplification step – once the virus enters a cancer cell, it replicates and provides a spreading lytic infection. Approaches which provide this type of amplification have obvious advantages over approaches which are limited by the numbers of available receptors on target cells.

NM: Is Hybrid Systems limiting itself to commercialising the polymer coating as an enabling technology for virotherapeutic or vaccine products developed by other companies, or is there any intention to generate intellectual property in, for example, proprietary targeting ligands for a virotherapy, or novel antigens for a vaccine?

LS: No, we are focussing on refining the enabling polymer technology for application to therapeutics or vaccines developed by other companies. It's a bit like wheels for sports cars – manufacturers of sports cars need good wheels to get optimal performance from their products, and some businesses focus on making the wheels. Hybrid Systems products are analogous to wheels, not the complete sports car.

NM: So the commercial potential of your technology is linked to that of virotherapy and vaccine products developed by other companies. How would you go about putting a relative value on your polymer technology vis-à-vis the various components of a virotherapy, for example, the vector backbone or the targeting ligand? I ask this because one of the problems that dogged the commercialisation of gene therapy technologies in the 90s was the royalty stacking issue, whereby if you need several disparate technologies to make a gene therapy work, and if each technology comes from a separate commercial source each of whom demands a royalty on product sales, you may get a stack of royalties that makes the end product commercially untenable.

LS: A virotherapy product will need our delivery technology for intravenous administration, or it will be rapidly cleared by the innate immune system; and our technology will only form part of a therapy in conjunction with a virus. Both components are necessary, and once there is the opportunity to turn a combination of the two into a product, people will have to discuss and agree on commercial terms. I would say that at present the major problem to overcome is

demonstration of proof-of-principle of virotherapy in a clinical context. Once that happens, everything else will rapidly fall into place.

NM: Moving away from technology issues, I think a lot of BACR members would be interested in learning about how you started your company, and what made you want to commercialise your academic research.

LS: It was largely precipitated by a PhD student who was capable and commercially motivated. Prior to that I had been writing patents on my own from time to time, but it really needed a team of two to make things happen. Our first point of contact with the commercial world came when we entered a BBSRC business plan competition – disappointingly, we only came third, but it was still very helpful, because it opened our eyes to the opportunities and problems involved in the commercialisation of science. Going down the commercial route seemed like a big step at the time – I felt like I was sullying myself in some way, almost compromising my academic principles. I think this is a peculiarly British idea, that academic research is done for the love of knowledge and that money is somehow distasteful – but this is misguided, because if you don't patent and protect your research, it will be difficult to exploit it and use it to make a difference in the real world. And if you patent your research and take it forward commercially, there is a chance that you might see some reward from it – which seems appropriate, because scientists are not paid that well, and why should they not enjoy some return from their discoveries? I think that every group leader should make efforts to foster and exploit commercial links.

NM: What advice would you give other BACR members who might wish to get involved in technology commercialisation?

LS: I think that one of the problems in UK biotech in the past has been that a few scientists have overstated their data. This has resulted in a number of commercial failures and disappointments, and has damaged the credibility of the sector as a whole. In addition, it has called into question the integrity of some scientists. So one piece of advice would be, don't be tempted to overstate data and compromise your academic integrity. Another would be to stand up for yourselves in discussions with VCs. I have come across some investors who demand that the scientist puts his or her house on the line in return for business finance. That is ridiculous – the relationship is that the scientist contributes his time, expertise and inventions, while the VC contributes some of the fund that he is paid to manage. The scientist's house or other assets do not enter into the equation. Finally, although of course you hope that your business will make a major breakthrough and provide significant financial rewards, don't underestimate the value of a smaller additional income source, which may be a more realistic goal for many business propositions.

NM: What would you have done differently if you had to do it over again?

LS: Our model has been different from that of most other biotechs, in that we have only ever accepted about £250,000 investment money, which was from a seedcorn Challenge fund. Instead, from the beginning we have looked to raise financial support through commercial partnerships. Our reasoning was that commercial partnerships are a valuable source of expertise, market intelligence, route to market, and so on, which you just don't get from VCs. We entered into a relationship with Schering early on, which has been very useful to us. We have also got various monies through competitive grant applications, applications for EU funds, and similar sources. This is a slow method of growing the company, but frankly it suited the pace of development of the technology. However, we are now getting to the stage where we may consider looking for investor money. I think

that our model has been correct and appropriate for what we were trying to achieve, and I would not change the way we went about things. The only thing that might have been done better would perhaps have been to get a high-profile, experienced CEO, even on a part-time basis, to help us steer the commercial development of the technology faster and earlier in time. Also, having the company in closer physical proximity to my academic lab would have helped, but on the other hand the current location allows the business to take advantage of bioincubator facilities, so there are pros and cons to both locations.

NM: Do you have any regrets?

LS: No, none. Hybrid Systems has not got in the way of my academic research, in fact it has helped it, in that it provides pointers on how things should develop.

NM: Are you seeking collaborations with other BACR members? Do you have any job opportunities in Hybrid Systems for BACR members?

LS: Yes, we are looking for people with vaccine experience. Although historically Hybrid Systems has focussed on virotherapy, the vaccine arm of the company seems likely to grow in importance, and we need somebody to lead that part of the business. We would be very interested in hearing from anybody with experience in developing antibody-resistant, cell-selective viral vaccines.

NM: Are there any final comments you'd like to share with BACR membership on the topics we have discussed?

LS: I suppose my experience suggests that when scientists step into the commercial arena, at first they don't know how much they don't know. We had to learn a lot of things that perhaps we would rather have learnt in a different way, rather than by learning from our mistakes. So I would say that it is advisable to talk to people with appropriate experience early on, and get advice on issues like tax credits and so forth. Learning from mistakes is not always the best way to go about things.