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BACR Interview #4: Professor Paul Workman (Piramed Pharma / Chroma Therapeutics)

*In the fourth of our series of interviews with BACR members who are commercialising their research, Dr. Nick Miller from Beremans Ltd (www.**beremans.com**) interviews Professor Paul Workman, who has been instrumental in the formation of two biotechnology companies, Chroma Therapeutics and Piramed Pharma. This interview focuses on Piramed, which was acquired by Roche in 2008; Chroma Therapeutics will be the subject of a later discussion. In his academic life, Paul is Director of the Cancer Research UK Centre for Cancer Therapeutics at The Institute for Cancer Research, Sutton and Harrap Professor of Pharmacology and Therapeutics there.*

NM: As background to this discussion, it seems fair to say that abnormal cell signalling pathways in cancer cells may constitute a rich source of druggable targets. For example, there may be up to 1000 kinases in the human genome and kinases are the most common class of cancer genes, suggesting an abundance of cell signal drug targets. Furthermore, there is now substantial proof of concept in that a number of oncology drugs that target signalling pathways have reached the market, such as Iressa, Erbitux and Herceptin. Piramed focussed on the PI3 kinase / Akt pathway. Could you expand a little on the rationale for this approach?

PW: Clearly, in a situation where there are over 300 cancer-associated genes, you have to decide very carefully where to apply your resources in drug discovery. Good target validation is key. My feeling is that one should prioritise a pathway that is frequently deregulated genetically in cancer and that is hijacked in a variety of ways, as these characteristics would suggest that the pathway is of critical importance in the oncogenic process. P110α, the catalytic subunit of PI3 kinase, is the most commonly mutated kinase in cancer, leading to activation of the pathway in a wide range of human malignancies. And the PI3 kinase pathway is also activated by overexpression or mutation of upstream receptors, increased expression of the downstream kinase Akt or PKB, loss of the PTEN tumour suppressor, and so on. So this oncogenic signalling cascade really stands out. As further validation, mutated p110α is oncogenic in preclinical models and the other related "class I" PI3 kinases, although not mutated, are also oncogenic. And importantly we knew that kinases are druggable with small molecules. So, overall PI3 kinase is a rational and important target. Given the genetics and biological data, we might anticipate that inhibition of PI3 kinase could be beneficial in many different cancers. You could envisage single agent activity or you could combine PI3 kinase inhibitors with other molecularly targeted agents or with cytotoxic drugs. For example, in one type of cancer that we are interested in my academic lab – brain tumours known as gliomas which have truncated, hyperactive EGF receptors, PI3 kinase mutations and PTEN loss – you could think about using a PI3 kinase inhibitor in combination with the currently used drug temozolomide. We recently published a paper showing increased therapeutic activity of the prototype PI3 kinase inhibitor PI-103 combined with temozolomide in an animal model of glioma.

NM: Obviously, PI3 kinase has normal functions in normal cells, so unless you are developing drugs specific to mutant p110α, then side-effects seem likely. What kind of toxicities would you expect to be associated with the PI3 kinase inhibitors?

PW: It is very difficult to predict toxic outcomes. The likeliest mechanism-based side-effect would probably be the induction of some degree of diabetes, as both p110α knock-in mice and chemical biology studies indicate an effect on insulin signalling and glucose uptake. However, with PI3 kinase inhibitors like PI-103 we can achieve profound effects on tumour growth in animal models with doses that do not cause any significant weight loss or major changes in blood glucose. In any case, if diabetic effects were induced these can be managed and would be acceptable in the treatment of a serious disease like cancer. I think what is most important here is that we are exploiting the "addiction" of tumour cells to the PI3 kinase pathway, which should result in a therapeutic window between cancer and non-malignant cells.

NM: You specified the applicability of the PI3 kinase inhibitors to gliomas. I wonder if one might also expect specific neural toxicities. For example, it is often said that cancer patients are prone to strokes, and it is known that stroke results in an ischaemic penumbra around the primary lesion, the stressed cells of the penumbra having the potential to survive or die according to whether or not they are tipped into apoptosis. If apoptosis is encouraged in neural tissues by compounds which target this pathway, then stroke lesions might be made larger, which would have implications for disability and recovery.

PW: Actually, although there was an expectation that the PI3 kinase inhibitors will push cells into apoptosis, this is often not the case. We have shown that PI3 kinase inhibitors do, as you would predict, decrease phosphorylation of Akt and other critical molecules in the PI3 kinase pathway – however, this mainly results in a strong cell cycle arrest, usually in G1 phase, but without in general causing apoptosis. In cancer cells we have to combine a PI3 kinase inhibitor with another stress, like the temozolomide treatment in glioma cells as I mentioned earlier or taxanes in the case of ovarian cancer, before we see major cell death. And there is oncogene addiction to provide the basis for a selective effect in cancer cells. In any case, my experience in drug development is that we need to be aware of – but not frightened by – the possible side-effects. For example, it was not really predicted that skin rashes would be the primary side-effect with Iressa, which I helped to develop when I was at AstraZeneca – many people thought that GI toxicity would be a bigger problem. So attempting to predict toxic outcomes is problematic. Nevertheless, we need to be on the look out for both predicted and unpredictable side-effects during preclinical development and early clinical trials and be prepared to manage the consequences if they arise.

NM: Publications state that the PI3 kinase inhibitors work by competitive inhibition at the ATP-binding site of the kinase, and that you can get high specificity for PI3 kinase by targeting this site. I seem to recall some work indicating that there is high sequence homology between the ATP-binding sites of various kinases, making it difficult to develop kinase-specific inhibitors. I think this was particularly exemplified by work aimed at developing Rho kinase inhibitors, which turned out to be very difficult. Against this background, how was the PI3 kinase specificity built into the Piramed compounds?

PW: Once you get crystal structures of kinase-inhibitor interactions – which we now have for PI3 kinase – it becomes very clear how you can obtain varying degrees of selectivity with kinase inhibitors. For example, there is a 'specificity pocket' around the ATP-binding site of kinases for which you can design in functional groups to modulate binding affinity. Also, although the ATP binding site structures of activated kinases may be very similar, they differ considerably in non-activated kinases, so you can use the inactive form as a target for specific inhibitors. We now use large panels of kinases which allow inhibitors with unwanted interactions to be screened out. In our work over the years we have identified compounds that are not only specific across the important class I group of PI3 kinases and which appear to hit very few protein kinases, and there are also inhibitors which show selective effects between the class I isoforms of p110 which are the α, β, γ and δ flavours. This may be of particular interest given that although only p110α is mutated in cancer, the other isoforms are upregulated in various malignancies, and appear to have a role in transformation. I should

also say that it has become clear from the protein kinase field that you can develop drugs which are relatively non-specific, that is they modulate several kinases, and which still are well-tolerated and achieve good antitumour effects, so a very high level of specificity may not always be essential. There may even be advantages in a degree of “polypharmacology” and Gleevec, Sorafenib are Sutent are good examples of this. A range of PI3 kinase inhibitors that have different selectivity profiles are now under development by several companies. Some, for example, inhibit the downstream target mTOR as well as class I PI3 kinases, giving a double hit on the pathway. It will take time figure out the optimal spectrum of kinases to hit in the clinic and there may be several combinatorial kinase inhibition options. It’s going to be very interesting to see how this works out.

NM: A sub-text of the Piramed approach is the idea of personalised medicine, in which patients have therapies tailored according to the set of oncogenic mutations they possess. We are seeing this happen with gefitinib, which somewhat serendipitously seems to have a better response among patients with mutations in the intracellular domain of HER1. Is this the way you see cancer therapy developing in the future?

PW: Absolutely. I am strong proponent of getting the right drug to the right patent according to the molecular make-up of the target cancer cells. It’s interesting that high-throughput genome sequencing studies have shown that patients often have 10-20 or more kinases mutated in the one tumour, and so successful therapies are likely to require a cocktail of drugs personalised to the patient in question. It may be necessary to target more than one signalling pathway, and to hit a given signalling pathway in more than one place, in order for example to stop positive feedback activation and to reduce the opportunities for drug resistance by kinase mutation or kinase switching. I’ve talked about the need to create a “perfect storm” in the cancer cell. At the moment in the field we still don’t fully understand the best settings in which to use PI3 kinase inhibitors but cancers with various types of deregulation in the PI3 kinase pathway are clearly prime targets. Looking at the cancer problem more broadly, it seems likely to me that in 10 or so years time personalized medicine in cancer will involve drug combinations tailored to the genome sequence of individual cancers and I think PI3 kinase pathway inhibition will be an important part of these future treatments.

NM: There is a feeling in some quarters that stratifying the patient population by mutation analysis will result in patient populations that are too small to justify the ~$800 million investment required to bring a drug to market. How would you respond to this?

PW: Experience with drugs such as Iressa and Tarceva, which appear to have particularly good activity in patients with EGFR mutations, is changing that attitude. Also, remember that Gleevec is used to treat a small group of patients but since it is dosed chronically and is very effective it generates over a billion dollars of revenue annually. Furthermore, some mutations will be found in a wide variety of cancers, and so the patient population for mutation-specific drugs won’t necessarily be that small. This is particularly the case for PI3 kinase pathway mutations, which are found in many different tumour types, including some very common kinds which are poorly treated at present, for example hormone-refractory prostate cancer and subsets of bowel, lung and breast cancer. In addition, even if you are dealing with a smaller number of patients overall, you will be treating a selected subset who are highly likely to respond, so a company can make a stronger pharmacoeconomic case that will allow it to recoup its investment. It’s also important to recognize that by focussing on patients with a particularly responsive molecular profile in clinical trials, you can significantly reduce the overall size and length of time of clinical trials and thus reduce the cost of getting to market. So there is a sound economic rationale for proceeding in this way. In any case the science and the unmet medical need are driving us inexorably in this direction and that’s good for the patients as well as the industry in the long run.

NM: There might be a hidden cost to that approach, in that a smaller, faster clinical trial would be less likely to pick up serious adverse events, which often are only detected in trials involving large numbers of patients. So regulatory bodies might require you to carry out onerous Phase IV studies and post-marketing surveillance.

PW: That is a fair point, but cancer is a serious life-threatening disease, and the regulatory bodies will recognise the advantages of getting an effective drug to market as fast as is compatible with safety, so that many patients benefit. I think this what cancer patients want.

NM: What can you tell us about the clinical progress of Piramed compounds?

PW: The programme directed at discovering inhibitors targeting the PI3 kinase p110α was licensed by Piramed to Genentech and the first drug, called GDC-0941, has now been taken into the clinic. We are all delighted that years of hard work in the laboratory and involving a great team of people may now start to benefit patients.

NM: How and why was Piramed formed?

PW: It's an interesting story! The three scientific founders, Peter Parker, Michael Waterfield and myself, were convinced that PI3 kinase signalling was important in cancer, and were initially working with Yamanouchi Pharma (now Astellas) in this area. During this time the team found many inhibitors of p110α and optimized these to achieve inhibition of tumour growth in animal models. It was also discovered around this time that p110α is often mutated in cancers, which provided additional biological justification for developing PI3 kinase inhibitors. After the Yamanouchi collaboration finished we kept the drug discovery work going in our institute while we went out on the fund-raising trail. I think we had an unusually strong package as we were armed with patents covering screening against p110α in addition to strong composition of matter patents on a wide range of chemical inhibitors. We attracted very good investors, JP Morgan and Merlin, and recruited excellent management and scientific staff to join Piramed. The project then moved very quickly, leading to the licensing of the p110α inhibitors to Genentech who then had the resources to expedite progression to the clinic. The Genentech deal provided very significant independent validation of our approach. Of course the ultimate validation of the technology for a biotech company these days is usually acquisition by a large pharmaceutical company, and the purchase of Piramed by Roche clearly provided that and really maximizes the likelihood that patients with cancer – and other diseases in fact where PI3 kinases are also involved – can benefit from the PI3 kinase inhibitor technology.

NM: You make it sound as though you had a smooth ride – was this the case?

PW: Only if you think a rollercoaster ride is smooth! We had a lot of ups and downs, went down a few blind alleys, and there were some difficult times requiring a lot of hard work by a large group of talented people. Drug discovery is difficult and high risk. Getting external investment is probably never easy, and certainly we all had to put in a huge amount of effort on that in addition to the challenging science. But it was great fun.

NM: What motivated you to put in all this effort? Why did you want to see your laboratory research translated into the commercial world?

PW: In addition to the exciting science, the thing that motivates me really is patient benefit; from this there follows the recognition that at some point the drug must be marketed if patients are to benefit widely and quickly. Academics can take drugs to Phase I studies and perhaps small Phase II studies before partnering, but you must bring in a commercial partner if you want to take the drug any further than that. The real questions are: when is the best time to bring in a commercial partner and who is the best partner for the project at that time? There is the option to initiate a research collaboration with a company or to go down the start-up route – and in fact we have do both with projects in our Centre. Usually, it becomes obvious when a project needs extra resources. By working with Yamanouchi, then with Piramed and finally with Genentech and Roche, the programme benefited from big injections of resources that could not have been accessed if the project had remained in the academic labs. And yet at the same time the academic scientists were able to stay involved with the project which I think is very important and satisfying.

NM: Do you have any regrets? Would you do anything differently if you were starting over again?

PW: No regrets really, in fact many happy memories and certainly exciting times! We have had a fantastic team of people involved throughout the history of the PI3 kinase inhibitor project and we have made some good friends along the way. I believe that through all the inevitable ups and downs in the life of the drug discovery project – and of Piramed – we have made the right decisions at the right times, moving the project along quickly but with good science at the forefront. So no, I don't think I would change anything. Of course, the real validation of our approach will be a PI3 kinase drug that has a major impact on the lives of patients with cancer. But with the resources of Genentech and Roche, and the progression of our lead drug into the clinic, I think we are heading in the right direction.

NM: What advice would you give other BACR members who are contemplating a similar step?

PW: I would say that academics should think carefully before getting involved directly in drug development and certainly before taking the biotech start-up route. This is probably not for everybody. If you do get involved directly in drug development you should have a taste for interdisciplinary collaboration – which I think is really great – and also an appetite for working with multiple uncertainties. On the science side, you will find that you are not just focussing a single parameter, for example finding the most potent inhibitor – instead you must optimise many other properties at the same time, like selectivity, solubility, stability, tolerability, metabolism, tumour uptake, and so on. So it's not like pure academic research where you are often testing a single primary hypothesis. Similarly, with a biotech company you must be happy working to milestones, under pressure, keeping to tight deadlines, participating in frequent meetings and so on. Additionally, you must be aware of the business dimension, as it is often the case that the most attractive and interesting option scientifically is not necessarily the best solution in business terms – you need to be able to marry the scientific aspects, the commercial elements and most importantly the potential for the patient. Of course you have to create value for the investors who have funded your R and D activities. So you need to be able to tolerate different complex and uncertain environments. If you enjoy this type of complex challenge, then getting involved in biotech will enable you to achieve things that otherwise you could not do – but it involves a lot of hard work and stress as well being very rewarding.

NM: Finally, do you have any thoughts about the biotech industry in the current difficult financial climate?

PW: This clearly a tough time. Its harder to get investment, the initial public offering route is closed and even trade sales are difficult at the moment. Having said that I think good companies with excellent science, experienced management and effective products will survive. A thriving biotech sector is really important for UK science and is essential to help plug the productivity gap that big pharma is facing as many drugs come off patent. The government wants to see scientific innovation and I think really needs to provide as much support as possible for the biotech sector, particularly now. It's exciting that there is currently an increase in academic drug development initiatives which I think is very important, especially in these difficult times for biotech and big pharma. These things are cyclical of course and I am an optimist. I think that good science and creative entrepreneurs will always find a way a way forward.