Paul Workman on the challenges of cancer drug development

Interview by Katharine E. Pestell

Paul Workman, Director, Cancer Research UK Centre for Cancer Therapeutics.

Paul Workman has been Director of the Cancer Research UK Centre for Cancer Therapeutics at the Institute of Cancer Research (ICR; http://www.icr.ac.uk/cctherap), Sutton, UK since 1997. He is Harrap Professor of Pharmacology and Therapeutics at the University of London and became a Fellow of the Academy of Medical Sciences in 2002. He has been involved in setting up the biotech companies Chroma Therapeutics and PIramed. From 1993 to 1997 he held a senior cancer research post at Zeneca (now AstraZeneca) and before that was Cancer Research Campaign Professor of Experimental Cancer Therapy at the University of Glasgow and a researcher at the Medical Research Council Clinical Oncology Unit in Cambridge. Throughout his career he has been interested in the discovery and clinical development of cancer drugs and his various positions have given him a unique insight into this area of research.

What are the major criteria that make you select a target?

For me, the major criterion for selecting a new molecular target is whether there is genetic deregulation of that pathway, although the target we select is not necessarily mutated or overexpressed. There is clearly a familial component but on the whole most of the abnormalities that create and drive a cancer to a malignant state are somatic mutations. The identification of these mutations allows us to shine a spotlight on the abnormality in that particular cancer. For example, you can show that a particular receptor tyrosine kinase is overexpressed or that a particular signal transduction protein is mutated. This might implicate that particular protein as a good target or, alternatively, indicate that the pathway is worth attacking. However, it is not only the genetics and other molecular evidence, such as overexpression and knockout by RNA interference, but also the tractability and druggability of the target. A few years ago many people thought that kinases would not be good targets. I was involved from the earliest stages of developing kinase inhibitors and there was a strong view at the time that kinase inhibitors would not work. People questioned how you could selectively inhibit one kinase versus another, how you would compete with millimolar levels of ATP, and whether you would get severe side-effects. Yet it is now clear from Gleevec®, Iressa® and other drugs that these are very good targets.

The culture has changed over the past few years; we now know that cancer genome-based molecular therapeutics work, so the concept that we will carry on making old-fashioned cytotoxics because the new approach is too risky has gone. Also, cancer drug discovery is speeding up because of new technologies such as genomics, HTS and combinatorial chemistry that can be applied.

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There is a major intellectual challenge in the genetics of human cancer that has a distinct bearing on the development of new molecular therapeutics. Some of the genes you discover in cancer cells could represent the molecular archaeology of the cancer, but are no longer crucially important. Cancer arises via clonal development from a cell that builds up a series of mutations that are selected for. The resulting tumour cell is highly invasive and rapidly proliferating, and might have ten or more genes that are involved in the cancer process. The Achilles' heel is that the cancer cell has become highly dependent on those oncogenic mutations. We call this 'oncogene addiction'. If you can block those pathways that the cell relies so heavily upon, it is more sensitive than normal cells to those inhibitory drugs. This explains why Gleevec®, Iressa®, Herceptin® and other similar drugs are fairly effective. However, we also know that resistance to Gleevec® can develop, that only a proportion of non-small-cell lung cancer patients benefit from Iressa® and that only ErbB2-positive breast cancer patients benefit from Herceptin® – and then often become resistant. Combinatorial oncogenesis, where many genes combine to cause a cancer, can be considered in two different ways. One is that you will need to block all, or at least several of the key pathways at once with combination or cocktail therapies or with drugs that have multiple effects. The other is to envisage the cancer as a house of cards, built on a series of mutations. Correct one of the early mutations and then the cancer would collapse like a house of cards.

What do you think will be the best way to treat cancers with multiple molecular abnormalities?

There are two problems with the single-agent approach. The first is that blocking one target or pathway will not be sufficient, because the cancer does not behave like a house of cards and there are other redundant pathways or alternative oncogenic mechanisms that can immediately kick in. The second problem is that using a single drug would increase the chance of resistance developing. Cancer is already genetically unstable and you would be inviting the cancer to activate another pathway. Getting combinatorial effects from a single drug is an attractive notion. Some kinase drugs hit several kinases at once, such as Gleevec® and the VEGF receptor kinase inhibitors. The other drugs that are attractive because of their multiple effects are inhibitors of chromatin-modifying enzymes such as histone deacetylases (HDACs), and also drugs that block the molecular chaperone Hsp90, for

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example 17AAG, and proteasome inhibitors such as Velcade®. Another strategy is to use cocktails of targeted drugs. Being pragmatic, oncologists always end up using drug combinations in the clinic. That will probably continue I would guess, but the combinations will get smarter and more tailored to the genomics of the individual patient's cancer. That is my prediction.

You have talked a lot more about mechanism-based strategies rather than focussing on a particular cancer. Is that what the Centre prefers?

The Centre does prefer to take a target-based approach. By definition, as part of a cancer institute, we only work on the cancer therapeutic area and that is one of our strengths – an in-depth focus on cancer. But we do not particularly work on any one cancer type. I think the interesting challenge we have to face is that cancer is still currently treated anatomically by location so there are multidisciplinary clinical teams that work on breast or lung cancer. I think the future will be somewhere between the two – combining anatomy with genomics.

The Centre is nearly ten years old and has had many collaborations, for example with AstraZeneca and also with smaller biotech companies. What do you think has been learnt about how best to run these collaborations?

One of the things we rank very highly in selecting a target or strategy is collaboration. Although at the Centre we have a lot of expertise in drug development, in cancer models, in translational research and in taking drugs into the clinic, neither we, nor anyone else, can expect to be the sole source of all knowledge about cancer or its treatment. In deciding when to collaborate with a partner I have some very simple guidelines. On the one hand, we argue that if we can develop a drug internally and have enough expertise and fire power to take the drug through to completion of a Phase I clinical trial, establishing proof of principle, doing pharmacokinetics and pharmacodynamics studies and showing some therapeutic value, there is no need to collaborate. The advantage is that, as an academic institute, we keep control of the project, which can be very important because it means we are not subject to commercial pressures at too early a stage in the project. We can take the initial risk and partner the drug with a company at the end of Phase I trials. The later efficacy trials are, of course, much more expensive. In some cases we might take the initial drug into the clinic ourselves and then partner to develop a follow-up drug. That is exactly what happened with Tomudex®. From the Centre's work with thymidylate synthase (TS) inhibitors we took the first compound into the clinic and showed that this was a target that worked and gave a clinical benefit. But we also identified a side-effect. The project was partnered with AstraZeneca, or ICI as it was then, and the project went back into the lab. The compound was refined and it was approved as Tomudex® for colorectal cancer. Alternatively, we might partner a highly competitive project relatively early, perhaps at the point where we are optimising a lead. We look for an organisation with similar objectives but complementary skills to our own, as well as an overall increase in resources. Speed to the clinic and patient benefit is paramount.

Which companies are you collaborating with at the moment?

We have had a very active collaboration with Cyclacel to develop inhibitors of cyclin-dependent kinases (CDKs). The idea here is that a CDK inhibitor will restore the negative control on the cell cycle that is lost in cancers. With Cyclacel we have taken a drug called CYC202 into clinical trial. We have a great collaboration on Hsp90 molecular chaperone inhibitors with RiboTargets. They are extremely skilled at high-throughput crystallography and other methods of lead generation, including virtual screening. We are working on protein kinase B with Astex, who also have lead generation and crystallography technologies that are very valuable. Those are examples of collaborations with UK-based biotech companies. These have become very productive collaborations because there are a lot of synergies between a relatively large academic institute like ours and a small biotech company. The Centre has also started some spin-out companies. Chroma Therapeutics is a company I founded with Tony Kouzarides and David Allis to build on the chromatin-based fundamental work from Tony and Dave and the early development work we did on inhibitors of chromatin enzymes in the Centre. PIramed is a company that was founded by Mike Waterfield, Peter Parker and myself. PIramed will build on the discovery of PI3 kinase inhibitors carried out by our academic labs, in collaboration with the Yamanouchi pharmaceutical company. In that particular project we had not built up the chemistry in the Centre and Yamanouchi provided the original medicinal chemistry. Then there is Caroline Springer's work, in collaboration with Richard Marais, on a gene therapy approach called gene-directed enzyme prodrug therapy or GDEPT. This is an attractive targeted tumour cell killing approach. This work led to what was actually our first spin-out from the Centre, a company called Proacta.

We also work with a variety of companies through our Phase I clinical trials unit, which is one of the strengths of the Centre. This work is led by Ian Judson who works closely with Stan Kaye, Professor of Medicine at the Institute. The clinical trials are carried out in the Royal Marsden Hospital, who are our close partners. Many different companies come to work with us for Phase I clinical trials because of our expertise in this area. Of course, we also take our own drugs into clinical trials as well. I should mention that in the past the big successful collaborations were with Bristol-Myers Squibb for Carboplatin® and with Zeneca on TS inhibitors.

One of the missions of the centre is to go rapidly from bench-to-bedside, with researchers ranging from molecular biologists and chemists to clinicians and research nurses. What are the major strengths to this approach?

I think it is what we tend to call 'joined up thinking' – a fully integrated translational research activity. This particularly helps with the fact that translational research is no longer a linear process. We all know drug discovery is an iterative process and that you make a potential drug and then a progressively better one in the lab. In fact, this refinement applies all the way through to the clinic as you might find there is some limitation and so you go back into the lab to solve the problem. If you are fully integrated as an organisation it means you can go quicker at each stage in the process because there is no hand over to a different organisation to be dealt with. Another major advantage is that we not only have capabilities in molecular biology, HTS, medicinal chemistry, PK/ADME, tumour models and Phase I trials, but we are also integrated strongly with the genetics, cell and molecular biology and X-ray crystallography expertise in the rest of the

Institute. Molecular imaging as well. And the close link with Cancer Research UK provides formulation and toxicology resources. It is a powerful integrated package.

What do you see as the bottlenecks?
Finding targets and validating them, and finding drug leads are, of course, very important. But the bottleneck lies in finding a compound with good pharmacokinetic properties, and pharmacokinetics is very strong at the Centre. We also need to show that compounds hit the target – so finding assays that provide good molecular pharmacodynamic endpoints is important. I think this is a real strength of the Centre.

What do you think are the most exciting advances in treating cancer at the moment?
I think the revolution that has happened in the last five years is the demonstration that you can intervene with either biological agents or small-molecule drug acting on particular targets that are genomically deregulated in cancer. So Gleevec® is the prototype. Herceptin® was the first drug to be approved against a particular molecular abnormality so we only need to treat patients with ErbB2 overexpression. And then there is Iressa®, which I worked on at Zeneca, which inhibits the epidermal growth factor receptor tyrosine kinase. So those are the first three post-genomic cancer drugs, which show activity in patients in chronic myeloid leukemia (CML), breast cancer and non-small-cell lung cancer. Gleevec® is also approved in gastrointestinal stromal tumours (GIST). These are not yet magic bullets but are extending survival and improving quality of life. Now we are running into issues such as resistance and incomplete responses and are finding that in some cases (such as Iressa®) you do not always have the molecular marker that allows you to identify which patients should benefit. That was a real lesson for us. The really exciting thing is that the proof of principle that this new approach works has been conclusively demonstrated. Angiogenesis inhibitors, such as drugs acting on vascular endothelial growth factor (VEGF) receptors look very promising. Personalised medicine is the way we are all headed; identifying the patients who will respond and having a therapy that matches their particular molecular requirements. My personal list of the most exciting targets for future drugs would be the PI3 kinase pathway, chromatin enzymes, Hsp90 and BRAF. PI3 kinase is genetically deregulated by the loss of PTEN, which is a phosphatase and a tumour-suppressor gene, and is the second most common genetic abnormality after p53 across a range of tumour types. With PIramed, we are developing some inhibitors that are very active and selective for PI3 kinase and I think they will be exciting both as single agents and probably in combination with chemotherapy. With Chroma we are developing drugs against a range of chromatin modifying enzymes. As with drugs that act on chromatin abnormalities, and also PI3 kinase/Akt inhibitors, the Hsp90 drugs we are developing with RiboTargets should have broad spectrum activity in many types of cancer. Inhbitors of BRAF, the first target from the Cancer Genome Project that we are working on with the Wellcome Trust, might be very specific for cancers such as melanomas that have mutant BRAF. I call this genomic 'salami-slicing' of the cancer market.

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Drug development very often follows the hottest area of biology, and the time window is getting shorter. A future wave of drugs will probably act on apoptosis pathways. Although many of the potential targets are protein–protein interactions – Bcl2 for example – I do think that specific apoptosis modulating drugs will come through.

What do you think the three main achievements of the Centre have been?
First, over the past decade we have put one new drug into clinical trial every year, either alone or with collaborators, which is a considerable achievement. Second, in the previous incarnation of the Centre before I took over, the regulatory approval of Tomudex® and Carboplatin® were great achievements and these drugs are now benefiting patients with cancer. Third, since I came here, I am proud of the progress we have made in establishing many new molecular target projects and in putting in place all the new technologies required to move those projects forward towards the clinic.

Where would you like to see the Centre in five years' time?
This is dangerous to predict but I would like to think the work that we have done establishing techniques, and the leads we have discovered (Hsp90, PI3 kinase, chromatin, cell cycle, BRAF, apoptosis and so on), will be translated into Phase I trials. I would like to see at least one drug doing well in Phase II trials as this would be a real measure of success. I would like to see clever drugs in the clinic and benefit for cancer patients. Also, alongside the new agents, I would like to have produced important translational knowledge. For example, using drugs for clinical hypothesis tests that demonstrate the importance of oncogenic targets and pathways in human cancer.

What achievements in your career are you personally most proud of?
First, it was very satisfying to have taken on the Centre and, with huge support from my colleagues and collaborators, to have moved it on to become a modern centre capable of taking on the challenge of drugging the cancer genome. As a result, we now have a lot of exciting new leads coming through preclinical development. And second, there are three drugs I am particularly proud of my role in. The first is my involvement in Iressa® while at AstraZeneca. Seeing Iressa® approved for lung cancer in three countries, including the USA, and the beneficial consequences this has had for patients is very pleasing. Also, there is SR4554, our hypoxia detection agent, co-developed with SRI International. I have worked on tumour hypoxia throughout my career because hypoxia drives genomic instability and is also an important cause of the resistance of many cancers. I began the hypoxia work while in Cambridge, starting developing SR4554 while in Glasgow and am now involved with the first clinical trials here in Sutton. It has been a long haul but the clinical results look very promising. The other drug I have enjoyed being involved with is 17AAG. I think our Phase I trial of this Hsp90 inhibitor has been the most sophisticated to date in terms of molecular endpoints. This trial has not only demonstrated proof of principle, but has also shown clinical benefit in patients. The combination of doing creative, intellectually satisfying translational work, alongside achieving benefit for our cancer patients, is incredibly rewarding.