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Pat Price discusses the potential of molecular imaging for drug development

Interview by Joanna Owens

Pat Price
Director, Wolfson Molecular Imaging Centre

Pat Price is the Ralston Paterson Professor of Radiation Oncology at Manchester University and is based at the Christie Hospital in Manchester, UK. She is also the Director of the new Wolfson Molecular Imaging Centre. She previously worked at the Medical Research Council (MRC) Cyclotron unit at Hammersmith Hospital in London, UK, running both the MRC and Cancer Research UK (CRUK) Positron Emission Tomography (PET) Oncology Programmes. Her initial training as a clinical oncologist was at the Royal Marsden Hospital in Sutton, UK, and the Institute of Cancer Research in London.

Professor Price formed, and chaired for six years, the European Organisation for Research and Treatment of Cancer (EORTC) Functional Imaging Group and is a member of the CRUK PKPD (Pharmacokinetic/Pharmacodynamic) Technology Advisory Committee. She is currently President of the British Oncological Association.

Can you tell us about your role in setting up the Wolfson Institute and explain why this institute is so important?

We had the vision to set up a stand-alone building for molecular imaging in oncology in the UK. The facility is being built in Manchester, and will be jointly funded by the Wolfson foundation, the University of Manchester, the Christie Hospital, CRUK and the Medical Research Council (MRC). Manchester was an ideal location because the research will be clinically led and we needed a big patient population. The Christie Hospital is one of the biggest cancer centres in Europe and so obviously draws a big patient base. Its proximity to Manchester University is also ideal for bringing together multidisciplinary expertise in areas such as chemistry, physical sciences and biological sciences. Manchester University, right up to vice-chancellor level, is very committed to clinical science and not that many universities are, so this was the right environment for the centre to flourish.

Why is this new research centre important for drug development?

We can now non-invasively image molecules and their interactions within the body without the need for biopsies of tumours or normal tissues. This enables us to accurately quantitate and investigate what is going on at the molecular level. Now that new classes of drugs are being developed for cancer treatment, and we learn more about the human genome, we need to investigate how these new agents work in humans. That is why this technique is really important.

What aspects of molecular imaging will be researched at the Wolfson Institute and what is its main aim?

We are going to develop molecular imaging methodology to study *in vivo* pharmacodynamics, concentrating on looking at how drugs act, whether they hit their targets and what the downstream effects of hitting those targets are on tumours and normal tissue. We will also be able to study *in vivo* pharmacokinetics (are the drugs actually getting to tumours?) and look at drug uptake and retention. This is especially important now for more targeted therapies where the plasma drug concentration does not necessarily reflect tumour drug concentration. We can study the phenotype and physiology of the tumour and, again, now that we know more about the genome and new molecules, we can work out how the body responds to these new classes of drugs. My role is the Director of this research, which will be the core activity of the CRUK programme at the institute, but others will also be carrying out some imaging research in neuroscience.

How do you see the institute advancing the field of molecular imaging and benefiting patients?

It is dedicated to and will provide clinical research studies with positron emission tomography (PET)-based molecular imaging. Thereby effecting quite complex protocols of combined tracer studies. Obviously with more knowledge we will be able to find out whether drugs are working as they are supposed to, we'll be able to optimize their activity, and select the right patients for those drugs. We really envisage it rapidly accelerating the development of new therapies, and through our increased knowledge of tumours, finding ways to improve treatment.

How will the institute interact with pharmaceutical companies and other imaging centres?

We will have the clinical research environment for molecular imaging, pharma have the molecules. We have had collaborations with biotech companies, such as Oxygene and Xenova. Biotech companies often have molecules that they want to investigate by molecular imaging to look at mechanism of action, proof of principle or early clinical and preclinical trials. We also maintain links with larger pharma companies such as GlaxoSmithKline, Novartis and Eli Lilly, where the work is usually in Phase I/II trials investigating *in vivo* pharmacokinetics and pharmacodynamics.

Are there any plans for spin-out companies from the Wolfson Imaging Centre?

Although there are certain aspects of our work, such as radiolabelling, image processing, image analysis or data analysis, that might be appropriate, that is not our number one goal. We are more interested in working with companies, partly because they have the molecules that could help us with methodology development, but also because we are interested in actually investigating how these molecules work.

What are the limitations of current cancer imaging technologies?

Most imaging is anatomical imaging, which has its role, but we need to do more at the

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functional and molecular level. Much of the technology for this has not yet been developed because it is highly complex. Above all, there are very few specific probes for *in vivo* molecular imaging. Here the challenge is not specificity per say, but the presence of non-specific binding and metabolism breakdown. For PET you need a multidisciplinary approach and the research needs to be clinically led to focus on clinical questions and develop the technology to answer them, rather than developing a technology and then seeing what questions we can answer. An extremely good relationship between imagers, drug developers and oncologists is also needed, and that can be hard to achieve.

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What recent advances in molecular imaging do you think are really promising?
Bioluminescence is used a great deal in the preclinical setting for studying gene expression and gene therapy. It is more simple than PET and thus more user-accessible, and there has been great progress in this field. Magnetic resonance spectrometry (MRS) is limited by its sensitivity and needs to be more advanced, but there are not enough groups working on it. Finally, magnetic resonance imaging (MRI) is an important technology that is very accessible, and there are now new tracers and contrast agents being developed.

Who is doing the most innovative work in this field at the moment?
The National Cancer Institute (NCI) has invested recently in molecular imaging, but there are many centres and I wouldn't really want to single one out. The main groups using PET in the USA are studying gene therapy, for example, the Sloan–Kettering Memorial Cancer Center in New York, and at the UCLA School of Medicine. We might collaborate in the future, although they are focusing on gene therapy and expression, and we are concentrating more on patient-orientated methodology development, which the UK is well-placed to do.

How will the merger of biology, molecular therapeutics and imaging advance the field of cancer research?
A great deal, but the challenge is to get the imagers and molecular biologists together with a common understanding. It is easy to have a technique and then apply it to a question, but it is more difficult to decide on the question and then develop the methodology. However, this is now being recognized; the NCI are providing funding to forge these collaborations, and the American Association for Cancer Research (AACR) organized special symposiums in 2002 to bring imagers and molecular biologists together. These associations are now actively trying to forge links, which is the secret of it. These advances are not going to succeed until we all work together.

With imaging technologies advancing greatly, what finer details of biological and chemical processes can now be imaged?
We are good at measuring vascular parameters, such as blood flow, cardiac output and volume distribution in tumours and normal tissues. We can measure thymidine kinase activity and hypoxia, although some of these techniques are only just being validated, and we can quantify thymidine uptake into tumours as well as early work on measuring apoptosis. Of all the progress that has been made in past five years, only now are we seeing these technology advances coming through in various stages of validation.

We know that genes signaling in cell growth can now be imaged but do you believe that PET scanners will help us discern the molecular errors that cause diseases?
I think we need biopsy data to tell us what errors to look for, but hopefully once we develop the methodology we can look in humans to discover how important these errors are. Obviously with tissue we have a static environment, we can see that there is an error but we have to actually look in humans and see if it that error has the predicted effect. Molecular imaging will allow us to investigate these leads in humans, rather than relying on preclinical models, which do not always work. A Holy Grail here is to be able to image signal transduction, which needs advancement, and the use of nucleic acid technology, for example, anti-sera probes as a means for such specific imaging.

How often does molecular imaging information change the way that a physician prescribes cancer treatments?
Molecular imaging is used, particularly in the USA, to look at glucose uptake in tumours for staging patients and identifying the position of the tumour. This can change treatment management, for example, by reducing the number of operations when metastatic disease is found, and so on. PET is used quite extensively in the clinical environment in the USA. In other areas, new molecular imaging techniques are only just being validated.

Do the costs of PET currently create a problem in UK National Health Service (NHS) hospitals for patient care?
It depends on what you think molecular imaging will be used for. The UK has a problem with using PET for tumour staging because it is unclear whether it is cost effective enough to introduce it under an NHS system. We aim to develop better tracers and more specific markers, then the cost effectiveness will improve because patients who would completely benefit from a treatment can be selected from those who would not. For research, the actual cost of the camera is no more expensive than many molecular biology techniques, but it is the cost of the methodology development and infrastructure to undertake comprehensive research programmes which is high. However, because developing drugs is extremely expensive it is likely that PET could save a lot of money in many areas.

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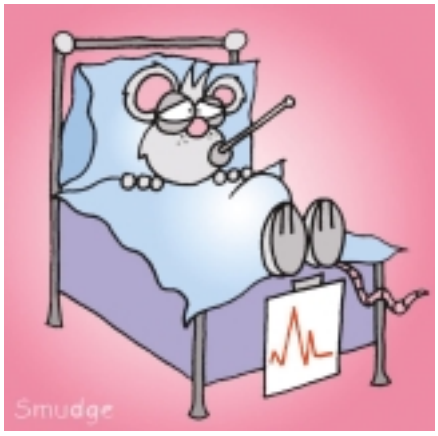
What impact do you think the early detection of disease by imaging technologies will have on mortality rates from cancer?
The methodology is not available yet to validate screening methods using molecular imaging, and I doubt it will happen. PET has got kinetic resolution but not anatomical resolution, and often the most effective screening methods, such as in breast cancer and cervical cancer, is to look at normal areas of tissue with some subtle premalignant changes. Molecular

imaging is never going to be a microscopic technique and so currently its use in screening is limited. If there was a specific marker of a premalignant state, for example, a certain genetic change that means you are predisposed to a certain cancer, then this could be imaged. Some work is under way using microarray techniques to identify targets for imaging. If we then could image high levels of this genetic change then that could work as a screening tool.

Could this research lead to personalized treatment for cancer?
Yes, there are some patients who will benefit from a treatment when others will not. Obviously we need to see new molecules coming through that are more molecularly targeted and then we can image patients to see whether those targets are expressed and stratify patients according to these criteria.

What valuable information can your research provide to the drug development process?
Molecular imaging can be used to study *in vivo* pharmacokinetics and pharmacodynamics early on in drug discovery, to aid the selection of lead compounds. We can also image physiological changes, target expression and downstream effects from target interactions. Another area of application is pre-Phase I, where molecules are injected at one-thousandth of the therapeutic starting dose. Using molecular imaging you can then actually screen compounds, looking at the upregulated genes in normal tissues, before any upscaling or entry into man. That means you can make your decisions much earlier and at far less cost – it could have huge potential.

Big pharma is now using miniature PET scanners to test new drugs on mice – known as 'the little patients' in the drug industry. How do you think this is likely to advance their drug development efforts?
Animal imaging is becoming extremely useful for looking at gene expression and so on. However, for clinical drug development I don't think it is being used optimally. Currently, insufficient effort is being put into the required methodology development. What I have seen is that, because animal PET scanners are now commercially available, effort is being put into very attractive pictures that look more



dramatic than volume changes on a graph! We should be concentrating on developing the technology that can address a specific question, close monitoring of changes associated with that question and then get these techniques into man. Knowing that a mouse shows a change in uptake of radiotracer in response to a drug is still no substitute for the same experiment in humans. We see small animal PET imaging as being an important means for developing and validating PET paradigms, protocols and analysis before their use in patients.

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Do you think the pharmaceutical industry has been too slow to incorporate molecular imaging into R&D?
Yes, and are they actually embracing it now? Some companies are setting up their own centres, but generally they are slow because they are not sharing the risk with academia. Very few centres can actually do the complex imaging, and so pharma is not really being exposed to the full potential of the technology. I think it will benefit the late-preclinical and early Phase I stage of drug development. Biotech companies have bought into imaging much more because once they know their molecule actually does hit their target, then it becomes a much more important molecule. A dedicated Molecular Imaging Centre, such as the one we are establishing in Manchester, has the remit to bridge these divisions and we look forward to the pharmaceutical industry sharing in the risks and excitement that such a focus will bring.

Will molecular imaging ever help to streamline the discovery and clinical trial process?
Yes, but only if more money is spent on good methodology development and pharma get involved more. If they leave it all up to the academic world then it might take a bit longer.

'Some [pharma] companies are setting up their own centres, but generally they are slow because they are not sharing the risk with academia.'

What has been the biggest achievement of your career, to date?
It would be linking up the images with the drug developers and clinicians, which worked well when I was at the MRC Cyclotron Unit in London with CRUK. So, if I have done something to bridge that gap, that will have moved the field on. Also, I have hopefully stimulated youngsters to think outside the box. We are generally in a field where we have to take risks and think laterally. So I am happy to be creating this sort of ethos – and more of it – to try to improve science and patient treatment.

If you could invent one technology that could improve cancer drug discovery, what would it be?
In drug development, I think that molecular imaging will make a massive impact. Molecular imaging is essentially a media for translating between basic lab-based discoveries and man.

What is your greatest career ambition?
To create a group of like-minded people around me, so that we can do some really good science.

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