Pat Price:

asking the right questions

Marc Beishon

Pat Price pioneered the use of PET imaging to investigate how cancer drugs move in the body and the effect they have. She worries that oncology has lost its way: 'translational research' has become a byword for sample collection and biology, masking the lack of experimental oncologists able to identify key questions in patient care and do the experimental clinical studies needed to answer them.

To win the battle against cancer, few would disagree that we need to develop and deploy all the most promising tools to hand. That would certainly seem to be the case with the fields of radiation oncology and molecular imaging. With radiotherapy used at some point in 50% of all cancer patients, and technologies such as PET (positron emission tomography) uncovering the secrets of how drugs work in the body at the molecular level, they should be at the forefront of funding from both clinical and research standpoints, argue their proponents.

But as Pat Price, professor of radiation oncology at the University of Manchester, England, points out, only 6% of UK cancer research funding finds its way to radiotherapy. And the huge potential offered by her specialist area, PET, to speed up targeted drug development, for example, is hardly being tapped, despite significant recent investment in funding in the UK.

That may be the result of being a pioneer – Price has been described as '15 years ahead of the time' for developing the first PET imaging of drug activity in brain tumours. As she says, "The strength of PET is quite simply the quality of the data – the answers to so many questions are in this information. For the first time we could see what was actually going on in the body – it has the potential to fill the knowledge gap between all those preclinical animal studies and basic biology, and conventional clinical drug trials."

What's more, Price feels the problems in her field exemplify this major gap in what she terms experimental medicine, or true academic clinical research. "I feel the oncology community has lost its way somewhat in asking the key questions that need answering about patient care and then going to the labs to do the research – the terms translational research and even experimental medicine have been largely hijacked for just sample collection and biology. We need to reverse this situation and address many more clinical, patient-based research questions."

While gaps in clinical research have been recognised in the UK, and various research networks and resources have been put in place, Price feels this key issue – expressed strongly by many committed research-based clinicians in other countries too – is endemic in worldwide oncology. She points to the heavy investment in cancer biology in the UK and the

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Thinking big. With husband and collaborator Terry Jones, digging the foundations of what is now one of the most advanced molecular research centres in the world

US, in particular. "We have seriously prioritised biology in the UK. What happens is that, if you have a critical mass of biologists, we tend to go on funding them. Meanwhile the National Health Service [NHS] and industry are prioritising clinical drug trials. The problem is that we don't have enough oncologists working and trained in experimental clinical research to bridge this gap – as who's left after people have gone to work in biology labs and on clinical trials? Funders do not then see much to get behind. Other branches of internal medicine, such as cardiology, neurology and psychiatry, are far more mature about prioritising clinical research."

As Price adds, "It does not need to be like this. As clinicians, we have to be much more focused on what's meaningful, as we have a mission to improve cancer treatment and care – and that's why people give money to cancer research, after all."

Price has been the Ralston Paterson professor of radiation oncology at the University of Manchester since the post – named after a UK radiotherapy pioneer – was created in the year 2000. She also holds an honourary consultant's position at Manchester's Christie Hospital, one of the largest cancer centres in Europe. As an academic clinician with a post funded by the university she enjoys the privileged – and enviable – position of being able to devote the majority of her time to building up radiation oncology and imaging research.

Her previous career path also allowed her much freedom to pursue research – but progress may have been slower in her field due to the major organisational issues around the many disciplines that converge in imaging and radiation oncology. Molecular imaging alone combines chemistry, cell/molecular biology, molecular pharmacology, physics, mathematics, bioengineering, imaging sciences – and not least, clinical medicine. And as she notes, "Expensive technologies are needed for radiotherapy, and they have their own training, expertise and clinical challenges. There is no industry or academic sector that takes ownership of the total development."

What clinical research needs, she feels, is much more visionary leadership that will overcome the structural problems in combining disciplines – and of course direct more resources into answering the right questions. But Price recognises that such direction is probably beyond the scope of any one country, certainly in the 'big science' field of molecular

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imaging, and to some extent in radiation oncology generally, and that international collaboration is crucial. That's the way other 'big science' – the search for nuclear fusion for example – is done. And interestingly it was another great international physics project – CERN in Geneva – that contributed much to the earlier development of PET.

For her own part, Price has helped put Manchester on the map as one of the few centres that specialises in research into clinical molecular imaging in cancer, by establishing the Wolfson Molecular Imaging Centre on the Christie site. Her professorship marks the first academic department in radiation oncology at the university, although there has been a long tradition of oncologists and other scientists pursuing various research in the field. As for PET, like much other 'big science', most of the last 20 years or so has been spent establishing methodologies to ensure that high-quality data can be obtained from experiments – but now the technology is fit for purpose and ready to ramp up for more clinical research.

Price is one of those oncologists who always wanted to be a doctor, although she cannot recall why and, like many, she found her way to cancer more by accident than design, after completing medical school in Cambridge. "My career was shaped more by what I didn't want to do – I knew I was not interested in surgery, for example, and I found myself back in Cambridge on rotation and by chance one of the jobs was oncology, where I met Karol Sikora [one of the UK's most outspoken oncologists]. I found from him and others that cancer had the right balance of medical skills and research interests, and it's very much a holistic, people subject – not just a plumbing job, like some other branches of medicine."

She applied for oncology training at London's Royal Marsden cancer centre, and was rapidly immersed in a broad curriculum and a top research environment, where she was able to do laboratory studies as well as clinical work. "I'm trained as a clinical oncologist, which in the UK means both radiotherapy and chemotherapy. Our syllabus requires clinical oncologists to pass an exam to show we know how to treat cancer in every way, which I think is very important. I do think, for instance, if you are just trained in chemotherapy, then radiation oncology can be a black spot, as it is quite difficult to understand in the way it's given and the side-effects. In the work I went on to do in upper-gastrointestinal [GI] tumours, interactions between the two types of therapy have been extremely useful for me to know. I do think if you are just 'single trained' you can't have the same overview."

In the UK, she adds that people who opt for medical oncology do get basic radiotherapy training now, and of course the key for most oncologists and for optimal service provision is to develop a specialty, such as upper GI, as she did. "It's also true that a broad clinical oncology course may not give you the same in-depth training in all the technical aspects of radiotherapy as some dedicated courses in other countries. But you can move on to specialise in this side if you want to."

The structure of the NHS, she adds, plays to opening up opportunities for a broad range of specialisms working in multidisciplinary teams. "The NHS is good at defining a service in which we need to fit in, so we don't get so hung up on being possessive about particular fields," she says. "Countries with private models may not be as good at service planning."

Working in the Marsden, it was assumed that you would do research and an MD degree (a medical PhD), Price adds, but when she moved to a big general hospital – the Royal Postgraduate Medical School at the Hammersmith in London, as an academic consultant oncologist – she found that cancer was competing, often unfavourably, with the other big medical disciplines. "We had to push hard for oncology, as some others in internal medicine looked down on us and this was a huge challenge, as has been establishing oncology imaging."

There was, though, a world-leading imaging centre based at the Hammersmith, the MRC (Medical

"PET could fill gaps in knowledge by looking at the biology of tumours in real time in patients"

Research Council) Cyclotron Unit, which specialised in PET, and this field soon became her primary research interest. Meanwhile, her clinical work developed with the specialism in upper GI cancers, a niche area where she was able to apply combined radiotherapy and chemotherapy expertise, together with some of the top surgeons specialising in these less common tumours.

"Surgery is the main treatment, but high-dose radiotherapy optimally delivered to reduce toxicity can cure some oesophageal cancers, and in other tumours it can improve survival and keep people well. My aim was to ensure radiotherapy was prioritised in GI – until then it had not been – and for research it offers a good balance between radiotherapy, chemotherapy and tumour biology. While cancers such as pancreas tend to attract top surgeons, they have been less popular with oncologists because of lack of survival and treatment options. Finding a niche and not competing in the more crowded fields of breast, head and neck and so on was a good way forward for me."

The focus on imaging was also prompted by a relatively quiet time in radiotherapy research in the 1990s. "It was more about the input of physics into the equipment, but that's now changed with the introduction of image-guided radiotherapy (IGRT), which offers more scope for the clinician." IGRT uses 3D and 4D imaging to deliver more precise radiation doses, and Price has recently led a network in the UK that, among key topics, is investigating how best to promote IGRT into wider clinical and research use.

IGRT is exciting both for its ability to image the tumour in real time – making it possible to control for small movements caused, for instance, by breathing – and for research avenues with tumour biology. It can also be integrated with a range of radiation and imaging types, including conventional radiotherapy, protons, CT, MRI and PET. But it is PET as an imaging tool in its own right, and its capacity to take imaging down to the more fundamental molecular level, that excites Price even more – and has done since the early 1990s.

At the MRC Cyclotron unit, much of the PET work was in other fields such as neurology. Price used her academic positions, in particular a post at London's Imperial College, to push forward with oncology applications. "PET can quantitate molecule interaction and pathways in the body, and it was clear to me that it could fill gaps in knowledge in pharmacokinetics – how a drug behaves in the body – and pharmacodynamics – the biological effects of agents – by looking at the biology of tumours in real time in patients. But many of the methodologies for PET were not being developed for oncology and I helped convince the MRC and Cancer Research Campaign [CRC – then one of the major cancer charities] to move the field on. It really was a very new area of research."

It is only now that the skills and methodologies to answer more key questions with PET are coming together, she says, but the principle has remained the same. "You tag a molecule with radioactivity, inject it, when it binds to specific biological sites it gives off ionising radiation and you detect it in time and space so you know where a molecule is and its time course at that location. By looking at kinetic curves and other data you can define what's happening – and the more I did, the more I realised that there was no other way of seeing molecular binding in man in life. It was fantastic then and still is."

She had early and spectacular success with demonstrating how one novel anticancer agent worked – temozolomide, a drug that is now used primarily to treat high-grade brain tumours. In 1991, the CRC supported Price and medical physicist Terry Jones – they later married and remain an enduring double act – together with the PET team at Hammersmith, to create a positron-emitting form of temozolomide (by labelling it with radioactive carbon-11). Temozolomide had been discovered at Aston University in the UK and was starting early trials – and the PET work led to a number of 'world-first' pharmacokinetic and pharmacodynamic studies.

Price is particularly grateful to Gordon McVie,

then head of the CRC and now at the European Institute of Oncology, for backing the research. McVie himself says the work was well ahead of the time. "No one had ever seen anything like these fabulous scans of brain tumours before – it was an extremely elegant way of demonstrating how a drug could be targeted to a cancer." The late Tom Connors – famous for developing the UK's phase I/II trial effort – and Mike Peckham, who went on to head NHS R&D, were also key figures.

As both Price and McVie note, medical oncologists were not thinking on these lines – protocols for testing drugs revolved around upping doses to test toxicity. By imaging the action of drugs, a rapid picture of effectiveness can be built up that both saves the patient from toxic doses and avoids the need for invasive collection of blood samples. A cause for celebration for all concerned with temozolomide is that this year it achieved the status of a billon-dollar blockbuster drug – it was licensed to Schering-Plough – and royalties are flowing back to Cancer Research UK (the successor to CRC).

Price showed the pictures to the US National Cancer Institute – where decision makers were duly impressed – and has been giving talks about the potential of PET for drug discovery and related topics ever since. "But we have had to spend a lot of time on methodology, learning about drug binding and its quantitation, *in vivo* kinetics, blood flow and delivery of agents, what's important in response – there has been a large amount of work. This has involved a 'team science' approach and people don't understand how difficult it is to do – you have to get each step right or you can get the wrong answer."

When the government privatised the Hammersmith imaging unit, the opportunity to carry on with the methodological work was curtailed, but funders agreed to transfer the research to Manchester, which gave Price the 'carrot' she needed to take up the professorship – the chance to build an imaging centre from scratch. Along with partner Jones and other colleagues, she's been able to put £20 million made available from a number of UK and European funding bodies to good work by setting up the Wolfson Molecular Imaging Centre. "This is a research institute built on the 'team science' ethos to develop and exploit PET for both clinical and preclinical research, with all the team players under one roof. But the focus is on experimental medicine – with patient studies at the centre of attention."

In addition it was designed to conform to new regulations, including GMP (Good Manufacturing Practice) standards that specify, for example, quality control for injectable radioisotopes into humans. "But we were able to use the regulatory structure to improve the quality of the data – a high-quality PET system in an experimental medicine environment really hadn't been done before. I feel we've moved the field on methodologically and have now produced more examples of what PET can do."

Price has written and talked extensively about the experimental potential of PET in areas such as drug

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Team working. Good management skills are especially important in this area of research – Price would like to see a Nobel prize awarded for organisation and strategy

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discovery and cancer drug resistance, and studies are now in train in Manchester. "For example, we have just been doing work with an antisense molecule – the opposite of either RNA or DNA – and we have radiolabelled it, got it into man and we can see for the first time where selective probes go. This particular study is about dose scheduling – how to give the right dose of a drug at the right time to get the maximum effect in any tumour. You can see the binding in tumours and where the drug goes in the rest of the body and by scheduling in different doses you can work out what you need to do to optimise the tumour to normal tissue ratio – the therapeutic advantage. But if you only did this conventionally, all you are asking is when you get toxicity, as you wouldn't have a clue where the drug has gone." For PET – as for all clinical research – Price cannot emphasise more the importance of asking the right questions.

The search for biomarkers for cancer drug effectiveness is critical, with so many failed phase III trials (some 70%), and the appeal of PET is not only its remarkable noninvasive imaging ability, but also that it can uncover effects using very low doses of the imaging biomarker. Adding probes to commonly used drugs at therapeutic levels can also help to find out much more quickly if and how they are working. But tagging new and common chemotherapy drugs is difficult to do, and it can take two years or more to develop the radiolabelling procedures and validate a probe in humans. Without more resources and groups, says Price, there is a danger of missing opportunities with the huge number of drugs in development. The wide range of PET probes on various agents and tracers now under study for drug resistance mechanisms, for example, shows the great potential for PET, and includes metabolism, blood flow, DNA repair, gene expression and hypoxia, as well as pharmacokinetics.

While the expertise and resources needed to conduct experimental PET molecular imaging work are formidable, many studies may only need small groups of patients. "But the problem is that PET is also squeezed out by the success of PET in diagnostic fields. Of course the PET-FDG [radiolabelled glucose] combination can generate a lot of money in diagnostics, while there is also a lot of cash for biological and preclinical studies. But we need more than just another pretty picture of an animal study on the cover of cancer research journals. We have to think how to bridge the gap."

While the UK still has relatively few PET scanners – about 15 – the key point from Price's viewpoint is what the machines are used for. In the US, where there are many scanners, she says there are few groups engaged in her field – and she of course knows most of the key players worldwide.

Other work at Manchester revolves around Price's position as an academic radiation head, where she has helped to develop existing resources such as a radiobiology lab, including a tie up with the Sanger Laboratory in Cambridge, for work on the genetic basis of radiation sensitivity. The Christie is also one of the centres in ACORRN – the Academic Clinical Oncology and Radiobiology Research Network – which Price established in 2005 to progress areas such as IGRT and sample collection for radio-

sensitivity studies in the UK. In 2003, when president of the British Oncological Association, Price was approached by the UK's National Cancer Research Institute to develop a strategy for radiation oncology research – which led to the formation of ACORRN. The network has also caught the eye of colleagues abroad. Norman Coleman, for example, a radiation oncology expert at the NCI, considers that bringing together many of the radiation oncology, biology and imaging experts in the UK has been 'visionary'. He is now an international adviser to ACORRN, which is also now bringing together some 1,300 website participants around the world.

Networking at international level, however, is still relatively weak in radiation oncology, and Price feels that pooling resources is even more critical now that the 'credit crunch' is putting yet more pressure on already overstretched budgets. She's a veteran member of both ESTRO (European Society for Therapeutic Radiology and Oncology) and the EORTC (European Organisation for Research and Treatment of Cancer, where she has chaired the functional imaging group), and she is very positive about the achievements of both. But the projects fostered by various organisations, national and regional – and there are encouraging new directions for research from ESTRO, for example, such as a tissue bank project – need to be harnessed in an 'overarching international strategy', she says, with a good start being joint meetings between ESTRO and ASTRO (the US equivalent). "I cite one of our famous physicists – Ernest Rutherford – 'When you have no money you have to think.'"

Price has not made herself too popular at times in the UK with calls for more targeted funding in her area, but she recognises limits. The NCI's Coleman describes her as "a very positive person who understands the hurdles and barriers but does not lose sight of the importance of the goals... she has tremendous passion to do the best for the patient and her plans are well considered in size, scope and phase."

She also points out that rushing in and throwing money at a technique or technology without very good evidence can be counterproductive. "What we are known for in the UK is providing the world with many down to earth studies of comparative effectiveness in the radiotherapy area." The UK Cancer Reform plan, drawn up by cancer czar Mike Richards (see also *Cancer World* 25, July–August 2008), has some solid initiatives for improving radiotherapy training and provision in hospitals, she adds.

Money may be a big issue, but Price has attracted an impressive number of grants to Manchester, and has also been in a position where she enjoys very good relationships with the drug and equipment industries. "That's because we work together at the pre-competitive level – and the drug companies in particular are happy to share information that could cut the massive costs of drug development." There are, however, ongoing issues about how facilities can be shared between the public and private sectors.

Many oncologists would give a lot for the research freedom Price enjoys but, as she says, she is accountable both for fund raising and for the quality of the research, "And I feel a big responsibility for moving forward – to some extent I'm my own regulator." She's interested in raising a higher public profile for her field – perhaps with radiation awareness days – and would also like to see more teaching on the subject in medical schools, although there has been no shortage of applicants to her group. "If we could package the advantages of radiotherapy and market it like blockbuster drugs we'd make billions," she jokes.

Price has worked professionally with partner Terry Jones for some time – "He's a big gun in PET and works as a consultant now" – and has a large family that takes most of her spare time, with two children and three step-children.

Her plans now include working more on the vital organisational theme. "I'd like to translate my experience to help the broader radiotherapy and molecular imaging communities realise their full potential to improve care for cancer patients, and for this we need more strategic thinking and empowering individuals to deliver. Sometimes I think we could do with a Nobel Prize in organisation and strategy."

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