Bruce Ponder: plugging the research gaps

Marc Beishon

"Just do it" is a lesson Bruce Ponder learnt early in his research career, and it has stood him in good stead. He is now director designate of one of Europe's largest cancer research centres, where he intends to plug many of the research gaps that the cancer community has been complaining about for so long.

IN conversation with Bruce Ponder, in his fairly unassuming office in the Hutchison/MRC Research Institute on the Addenbrooke's Hospital site in Cambridge, it takes a while to appreciate just what he is presiding over. Using his background in genetics, molecular biology and clinical oncology, his mission is to build what will possibly one day be the largest scientific cancer research centre in Europe.

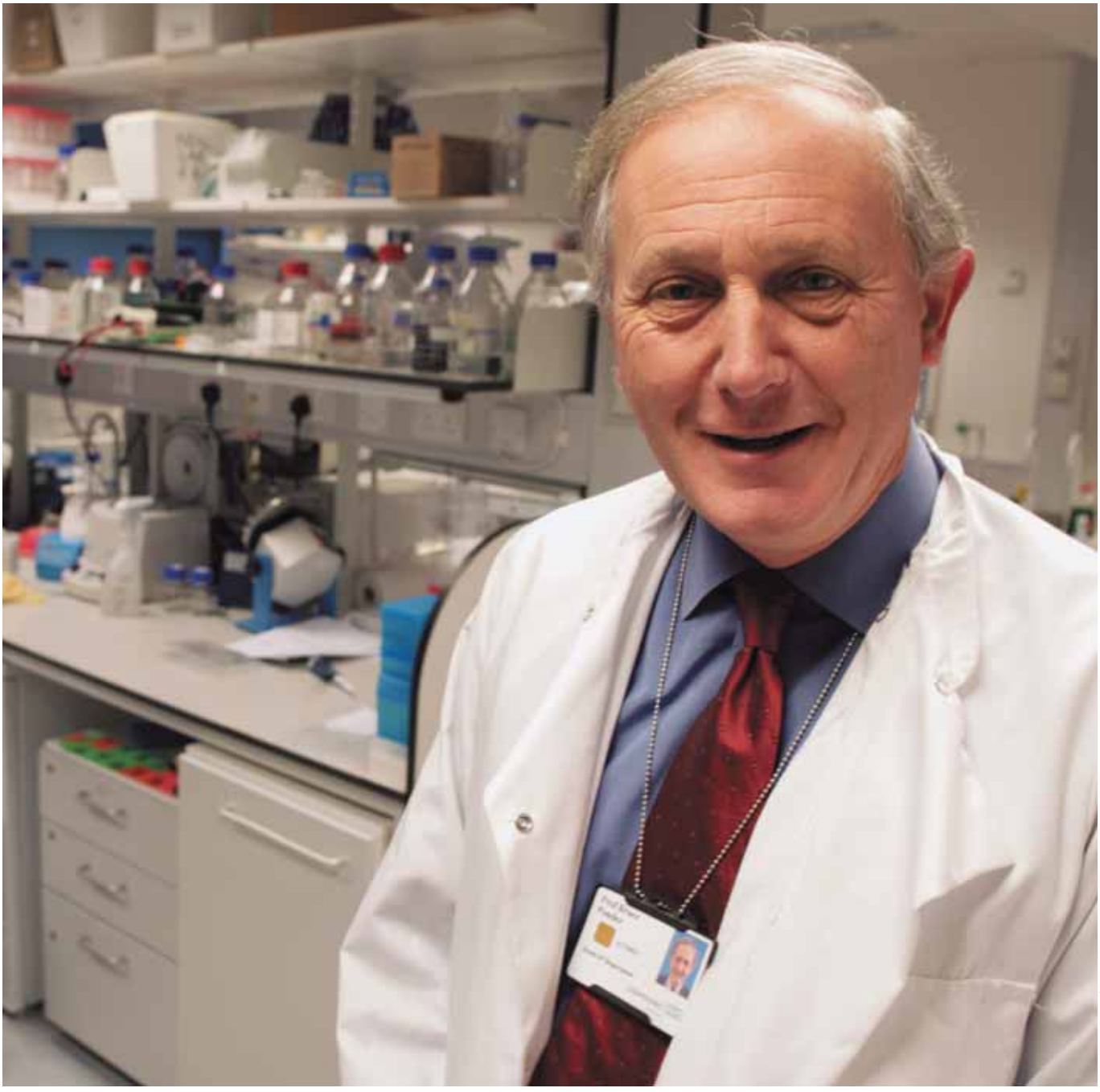
It will comprise not just a new £40 million (58.2 million euro) translational research institute staffed by 300 researchers, but will bring together existing institutes such as the Hutchison/MRC – itself a very new facility that houses cancer cell research – and academic departments and clinical facilities in a 'virtual' cross-disciplinary effort.

That new translational facility, known at present as the Cambridge University/Hutchison/Cancer Research UK Institute, is a year away from occupation, and Ponder is its director designate, as well as being Professor and Head of the University of Cambridge/Addenbrooke's Oncology Department, and co-director of other institutes. It's a potentially confusing picture, but Ponder is absolutely clear about its aim.

"What I'm keen to do is ensure that, although there will be this new institute that will be funded and evaluated like any research facility of its type, there is additional funding that supports the clinical side, and that the two are judged together. It is the interface between research and the clinical side that is really important."

It is self-evident, perhaps, that creating the best pathways for new, effective clinical practice is always the priority. But as Ponder points out, despite the UK's reputation for research excellence, funding agencies have tended to treat research institutes and clinical departments as separate entities and "not looked at the interface between them as closely as they should."

In fact, until recently the UK has suffered many of the same structural and professional problems as other countries when it comes to research opportunities, best use of resources and career pathways. As recently as 2000, Ponder gave evidence to a parliamentary committee about the state of cancer research, in which he



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pulled no punches, especially about the lack of an adequate infrastructure for applied clinical research. As a result, many of the brightest graduates are going into basic medical research – and staying there.

Some of these criticisms have started to be addressed. The formation of a National Cancer Research Institute has been a big step, while Britain's National Health Service (NHS) is looking at how its own research budget is spent to better effect, for example, by creating a national cancer research network to support clinical trials and other research.

But there is still an awful lot to do, in Ponder's view, before the UK will see a streamlined system where cancer doctors are training and working on the right subjects at the right time and in the right places to maximise that scientific-medical interface.

His own career path is a case in point, especially in his early years, as he had to continually move around to find the backing and resources to work on promising research while also progressing his medical training.

At school, he horrified his teachers by switching from English and history to science, at a time "when it wasn't respectable for an academically minded boy to do biology – it was considered a soft subject." But the seeds had been sown earlier, when a primary schoolteacher had showed him how to look at pond life under an old microscope, and he also ran a school weather station for a year.

He went to Cambridge to read medicine – although he could equally have stuck to straight science – but "it was clear that medicine was an interesting and natural way to apply your knowledge." Although he could have stayed on as an academic, Ponder chose to begin a career as clinician, moving to St Thomas' Hospital in London, and "thoroughly enjoyed six or so years of clinical practice and training," doing the usual rotations in

various hospitals, and returning to St Thomas' to finish his general training in internal medicine.

"It was then I decided I really wanted to do research and go back into science – it seemed to me that if you wanted to specialise in something like cancer you needed a strong scientific platform, otherwise you wouldn't be equipped for the future."

Casting around at St Thomas' for a research topic and supervisor, he soon found that the teaching hospital didn't have anyone really informed about lab research. He was referred to the Imperial Cancer Research Fund – "They'll give you a tough project you won't understand" – and to an array of top researchers. Director Michael Stoker duly set him up with a fellowship to do a PhD on the structure of chromatin in polyoma virus, which led to a paper in *Cell*. "I had a fantastic time – probably the happiest three years I've had," says Ponder. "I went to get training in how to do science, not anything that was applied in a particular way." Certainly, the drive to carry out research seems to have sustained him ever since.

In any case, Ponder was already interested in cancer, as it had the attraction of covering a wide spectrum – from difficult palliative care issues all the way to understanding fundamental biology. "It had everything for me – I realised I couldn't do it all, but I knew I would end up somewhere on this spectrum." On a summer school in 1975 he met John Cairns and helped him write *Cancer, Science and Society* – a book for non-specialists that is still required reading on at least one course of the same name at Johns Hopkins University.

"I wanted then to train in clinical cancer medicine, but there really was no place suitable – Barts [St Bartholomew's, London] was then the leading UK centre, but specialised in leukaemia and lymphoma – and there wasn't much epithelial oncology." The Cancer Research Campaign awarded him the first Hamilton Fairley Fellowship to train abroad for a year at Harvard medical school, but although he found the experience really useful and liked the university, he stayed only for that year, as by this point he was married with four young children. "The Americans weren't sympathetic to anyone doing anything other than working – we had very little money and my wife was rather isolated there."

Back at Barts he worked as a senior registrar in oncology and, although he was soon to move much more into research and the genetics field, he considers that his experience on the clinical side has put him in a far better position to bridge the clinical–research science gap than someone trained only as a scientist – and of course today he also heads the university/hospital clinical oncology department.

"That taught me a lesson. Don't wait for someone to tell you what to do – just go and do it"

Determined to work on a sound scientific basis as an academic, and eschewing the chance to become an oncology consultant, Ponder went back to the Cancer Research Campaign and obtained a career development grant that took him to the Institute of Cancer Research in Sutton and his own programme researching the organisation of epithelia in chimaeric mice. "I wanted to study epithelial cancer and its biology and it seemed to me that cancer wasn't just a matter of disordered or excessive growth – more a problem of the breakdown of the rules that govern the organisation of tissue." The idea was to gain insight into the clonal structure of an epithelium and how it broke down in cancer.

"We didn't have the tools then to take it further. What we needed were inducible markers linked to a gene that you can also induce, then you could perturb particular gene expression in cells that are marked and see how that affects the behaviour of the clone. And that's what

we are doing in the lab here 20 years later. It is only now we have the technology to do it."

While at the Institute of Cancer Research, Ponder also held a clinical appointment at the next door Royal Marsden, a major UK cancer hospital, presenting himself as a free resource – but found his background as a molecular biologist failed to excite. "That taught me a lesson which I keep telling young people: Don't wait for someone to tell you what to do – just go and do it. The mistake I made was thinking that anyone more senior had the time to worry about what I needed to do."

The Ponder Lab, 1989

Casting around, he joined a group of urologists – identifying the bladder as a suitable organ to contribute to his research on epithelia and their clonal organisation. "No one was doing much medical oncology in that area then."

"That's where I learnt my second lesson: to collect all the samples and work with a clinical team requires a lot more time and resource than one person doing a lab project can possibly have – people constantly underestimate the resources needed to do decent clinical research."

Then came a 'strike of fate' that often changes a career – in Ponder's case, it was on a slow day in urology. Seeing that next door the thyroid clinic was very busy, he offered to help out. He found piles of case notes on the clinic table and took two of the thickest ones there. "They were two different families with inherited thyroid cancer – and while the cancer was being looked after, it was clear no one was really looking after the families. I'd read papers about Huntingdon's and how researchers were setting out to find the genes by linkage – so I thought to do the same with cancer genes by collecting thyroid families. It took me about five years to persuade anyone I was serious, but we did it."

He was told in no uncertain terms that while his work on bladder and also prostate cancer was very interesting, cancer genetics should be kept strictly as a hobby. "They thought there was no future in it. My colleagues said, 'This is a cancer hospital – we treat cancer patients here. What you appear to be interested in is people who haven't got cancer but who might get it. That doesn't belong in a hospital – you should be in some epidemiology institute.' The model for medical oncology then was restricted pretty much to chemotherapy – my approach just didn't fit."

Fortunately, Ponder was able to take over some posts not filled in another department, and he recruited a molecular biologist and also his own wife as a research nurse to collect families, "and we linked the gene [for thyroid cancer] and so no one could really say boo then."

It was crucial, says Ponder, to be based in the hospital and also to be trusted as a cancer doctor. GPs could be confident that if referrals revealed a raised risk (there was also a biochemical screening test), then the best advice and, if necessary, treatment – which could be a thyroidectomy – could be given.

With both his gene linkage and work on mice going well, Ponder needed to expand – and it was Cambridge that gave him the opportunity. "I thought I was going to find the (thyroid) gene I had done the linkage for and understand how it worked," he says. "I was also the Chair of the International Consortium for Breast Cancer Linkage at the time, and I thought we would repeat the process for that disease too." The work with mice would then help complete the picture by manipulating the genes in tissues to find out what the effects were.

Ponder's team found the RET gene implicated in thyroid cancer in 1993. "But doing the biology for RET turned out not to be easy for me, as the gene is a receptor tyrosine kinase – a member of a large family – and there were real experts in this around the world who could do in a week

what it would take me two years to do. So I couldn't make much more of a contribution in terms of what the gene did.

"But where we could make progress was relying on my clinical and genetic epidemiology expertise. Because we knew there were different clinical forms of the syndrome, we were able to sample large patient collections and demonstrate different mutations in the gene and different forms of the syndrome. That's commonplace now but was fairly novel then and gave useful insights."

Ponder's group was then able to help draw up new guidelines for management of the families with thyroid cancer – and by the mid-1990s was pleased to report that outcomes had improved over previous guidelines.

Work on breast and ovary cancer went forward in parallel, with Ponder's team contributing to the international effort to find linkages, contributing families to Mike Stratton's work on the BRCA2 breast cancer gene and making one of the first BRCA2 'knockout mice'. That biological work is ongoing at the Hutchison/MRC institute under one of Ponder's colleagues.

As he points out, the early work on identifying often rare familial syndromes has fuelled the more recent work on cancer mechanisms. "And in the current phase we have realised that those striking families are only a small part of the total amount of inherited susceptibility. Fewer than 5% of breast cancers are attributable to single strongly predisposing genes. However, there is a distribution of risk across the population which is determined by combinations of weaker genes. We've now shown that probably half of all breast cancers occur in about 12% of people at highest risk. In fact there is probably a 40-fold difference in risk between the top 20% and bottom 20%."

Although only a model – though a robust one, according to Ponder – the idea of a wide combination of genes contributing to the distribution of susceptibility has been difficult for many. "I think I'm a fairly good lecturer, but I have to cover this three or four times," he notes. "The idea of course is well established in the literature on the genetics of flies, for example – it's just that conventional molecular biologists aren't used to it. We have identified some of the variants but not many yet – it's a massive task."

As he continues: "We would like to understand how this genetic variation causes this predisposition. It's likely to be mutations on the direct pathway of the events that turn a normal cell into cancer cell, but the genetic variants that add to risk are more likely to influence things that impinge on this pathway from outside the cancer cell, and this may be a better set of targets for prevention."

> "People constantly underestimate the resources needed to do decent clinical research"

Ponder's view is also that early work should be targeted at those at highest risk even if they comprise a minority of the disease. "If you establish the principles that your intervention is successful you can then consider generalising it more widely."

Any cancer centre head wants to carve out a distinctive profile. Ponder says that on the science side, the focus for the new institute will be more on the environment of the cancer cell in the tissue, than events in the single cell. "Most other institutes focus on cell signalling pathways, cell cycle transcription and that sort of thing – very important but we are more interested in the interaction between cancer cells and surrounding normal cells."

Meanwhile, on the clinical side, Ponder says the aim is not to be another experimental cancer therapeutics base – other UK centres are focusing on drug development and on phase III work, for example, and he's happy with that. "We will do clinical trials but based on biological research –

Visiting labs in the University of Shantou, People's Republic of China, as part of a collaborative project on the genetics of nasopharyngeal carcinoma

early stage trials of agents which impact on pathways where we think we have particular scientific expertise." Genomics and molecular imaging expertise will also be developed further.

"We think too there is mileage in finding out how to use existing drugs better – by examining molecularly well-described cancers from the local population to get insights into the determinants of response and resistance."

In the longer term, Ponder wants to hone that focus on the early stage of cancer development as the most distinctive – and most difficult – contribution. "What I'm hoping is that the new institute will provide the reagents and tools to complement the genetic epidemiology and public health work we have at the Strangeways Research Lab," (another institute where he is co-director). This all means identifying higher risk groups, running screening programmes to identify early lesions – hopefully at some point from non-invasive imaging – and developing targets for intervention and markers of response.

It also means investment in a new cancer centre at Addenbrooke's with the equipment needed for early intensive investigations.

Ponder is pleased to note that more funding in the UK is earmarked for applied research – one of the initial moves is the establishment of a National Clinical Trials Network, with Cambridge one of the first regional centres. With extra resources for nurses, the clinical trials entry has gone from 2% to 14% of new patients in four or five years. Britain also has a National Translational Cancer Research Network (NTRAC) – again Cambridge is one of the participants.

However, too many trials are determined by funds from drug companies, says Ponder, who is concerned that more intellectually useful work is not being done. "For example on local trials we've thought of ourselves, or MRC [Medical Research Council] trials, the hospitals simply don't have the money to do them." This is one gap in his parliamentary submission that he feels is not being closed yet, but he says there is "general recognition that there is a problem."

"I have, though, persuaded Cancer Research UK to invest also in the clinical department on information systems, sample collection, pathology time and so on – above what we need for NHS service – to provide an environment where clinical research can happen."

Away from Cambridge, Ponder has made many visits to other scientific research centres – including assessment visits in Europe – and feels that some lack the 'buzz' to provide a stream of top-quality researchers. "I have a lot of recruitment to do here – including 10 professorial appointments – and in all the due diligence I do I just don't find many candidates from Europe," he says. "There are individually excellent people there but I don't get the sense that overall the centres compare with the best in the US and probably not with the best here."

If top scientific researchers are hard to come by – and more need to come from the UK as well – so too are top clinical academics, with expertise in the UK being spread too widely across too

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many centres. "Many clinical academics have not had much scientific training – we are still inclined here to create new centres and professorial chairs for people who are undoubtedly good clinicians, but they do not really have the research background to sustain them." That has a knock-on effect with a lack of role models for the next generation, he feels.

Ponder would rather see a smaller number of cancer centres with some of these, often young, oncology professors dropping back to intermediate academic positions at a top quality institute, and "really getting 10 years of solid research under their belt."

He also feels oncology in the UK has been too focused on medical oncology and also radiotherapy (the latter being "academically quite weak"). "So it was quite deliberate that the first appointment I made here was a professor of cancer surgery – the delivery of cancer care and research is a combination of oncology, surgery, pathology and imaging – and we need leadership in all of those disciplines."

Again, there had been progress here, he notes, with Cancer Research UK taking on fellows in surgery and pathology as well as oncology. But there are currently relatively few professors of cancer surgery in the UK, he feels, and pathologists are particularly hard to find. He'd also like to see his own university teaching medical students more about cancer – there is only a few days on the topic, he says, and a presumption it will be covered in other organ-based sessions.

Until a recent submersion in all the administrative work of launching the new institute, Ponder was regularly seeing patients in the hospital's genetics department, sensitive always to the relationships between family members who may be present, and what they want out of the visit. As he says: "A relative may have dragooned them into it, or their family doctor may simply have thought it would interest me."

However, he feels it's not his place to be heavily involved in the ethical debate about genetic testing and the like. He has contributed to the government's Human Genetics Commission at a high level, but says that advocacy work should come from the patient side – and indeed his wife Maggie is the chair of a charity called the Genetic Interest Group, which acts for families with genetic illnesses.

"There is a danger of the tail wagging the dog – people with sincerely held views but on the whole obstructive of research," comments Ponder. "I think there is a large silent majority who wish they would go away – but that's much easier for patient representatives to say."

Ponder has the usual string of top awards with the stand-out being election to Britain's famous Royal Society. It's not been enough to tempt any of his children into medicine – although two are working as scientists. Home interests include walking, wine, golf (he's been a single handicap player for many years) and gardening – they grow vegetables and flowers and keep ducks and other animals. "It's all a bit of a shambles," (one suspects a lack of Linnaean order here).

That relaxation is understandable given what's on his plate at work – and he's got another seven years in post to build the research base that should be the rival of any centre, although of course an institute is there for the long term.

Despite the advances made in recent years, Ponder rattles off a long list of fundamental things we just don't know about cancer – how little we understand about gene expression, cell to cell and protein interactions, and cancer stem cells, for example. And why do barely one in a hundred drugs hit their targets and why do those that do work?

It's axiomatic of the field perhaps that wherever you are it feels like you've only just begun.