John Crown:

Move aside bureaucrats and let us take a lead

➜ Marc Beishon

Good healthcare managers will always be needed, but decisions on how best to deliver high-quality care should be left to the clinicians who run the services. John Crown, who has long played a leading role in both the clinic and research, is by no means the only oncologist to make this comment. He is one of the few, however, to seek elected office in order to pursue the point more effectively.

Outspoken oncologists, willing to take on 'the powers that be', can often play a very helpful role in galvanising administrators and policy makers and pushing the priorities of clinicians higher up the agenda. There are notable such characters around Europe, but one oncologist has taken a bigger step into the realm of politics by becoming a senator in his parliament – from where he is able to directly challenge politicians and bureaucrats with the protection of parliamentary privilege.

John Crown's day job is consultant medical oncologist at St Vincent's Hospital group in Dublin, a position he took up in 1993; he also holds professorships at two Dublin universities. A breast cancer specialist, he was elected last year to Ireland's senate as one of a caucus of six academics in the upper house. His move into politics follows a long history of confronting the Irish authorities about cancer care and resources, in particular about his specialism, medical oncology, and with good reason.

"When I came back to Ireland after working in the United States, I was just one of four medical oncologists in the whole country, and we were all based in Dublin. We also had no radiation oncology in some areas. Women were routinely getting mastectomies with little adjuvant treatment outside of Dublin and those with metastatic disease were often referred to hospices, not to an oncologist. It was a catastrophic situation."

Much has improved since Crown decided to go public on these issues in the mid-1990s. Not only was he taking on the politicians, but also the 'old school' health professionals who were part of the problem. "It was only when a new minister of

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health, Michael Noonan, came into post and stated that he wouldn't send his relatives to certain hospitals if they had cancer that things really started to change," he says.

Now there are more medical oncologists, better care throughout the country, and Ireland has become a substantial contributor to cancer research, thanks to Crown and colleagues starting up high-quality translational research collaborations and entering a good percentage of patients in trials, especially in breast cancer.

As he points out, there is no reason why a country the size of Ireland should not have a first-rate oncology effort. "We are more than four and half million people, and Dublin is a cosmopolitan city of well over one and half million in its metro area [Greater Dublin]. There are only a few very rare conditions where we should send a patient abroad for treatment. But we tend to have a defeatist attitude that a country that was historically poorly developed shouldn't aspire to have a health-care system as good as the best.

"And as with many other countries, the politicians put bureaucracy before visionary leadership. It's a fundamental issue that needs to be addressed not only in Ireland but throughout Europe – the leadership role of health professionals is being undermined by the emergence of a managerial class." Crown is passionate about this issue, which he believes is crucial to improving outcomes in cancer and indeed across the health spectrum. Health professionals must be allowed to assume leadership positions as they have the vision to act as true advocates for patients, he says. Professional managers have their place in any institution – but where they set the agenda it is likely to be serving

political edicts to balance budgets and meet targets.

"That often means the welfare of patients comes second, and also – and this may be an old-fashioned view – I do not think that doctors act solely in their own self-interests. We have higher ethical considerations than other professions."

The link between overbearing bureaucracy and poor cancer outcomes can be seen in Ireland and the United Kingdom in particular, he says, pointing to slow access to treatment and drug availability (in the UK especially) as two key factors. Wearing his political hat, he would 'fix' healthcare by reforming health insurance so that the "money follows the patient" and patients are able to choose their providers more easily, and of course that healthcare leadership is passed to medics.

Healthcare cannot exist in isolation from the wider economy and societal trends, of course. Crown is also concerned about how countries such as Ireland that are under severe economic pressure can become more stable. He worries, too, that science and technology are not being prioritised as they should be. While he favours measures such as lowering corporation tax and public sector reform to make it more efficient, he is no advocate of wholesale privatisation of healthcare. "I'm a social democrat at heart with the head of a pragmatist – I believe that no one should be denied care because they can't afford it, but the health system should not be a giant bureaucracy and we need to empower patients with mixed public/private insurance such as in Germany."

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A good deal of Crown's formative years in oncology were spent at one of the world's top cancer centres, Memorial Sloan-Kettering in the US, and his first-hand knowledge of how excellence can be achieved at a not-for-profit institution with great clinical leadership has inspired his work in Ireland. It is a background he shares with most of his colleagues. Of the 33 medical oncologists now in Ireland – itself a gauge of how far the country has come in 15 years or so – 23 were trained at America's top cancer centres such as Memorial, MD Anderson, the NCI, Johns Hopkins and Dana-Farber. "When I was at Memorial I could be in an elevator with more Irish oncologists than there were in Ireland," says Crown. "That's a direct result of our immigration culture."

Crown himself was born in New York to Irish immigrants and as a boy was influenced by the attention cancer was getting in the US, and by healthcare in general, thanks to several nurses in his family. "I knew I wanted to go to medical school and it was in the back of my mind that I wanted to be a cancer specialist." With his family having returned to Ireland, he did his main medical training in Dublin and at Guy's hospital, London, and took the internal medicine path towards cancer, landing an oncology fellowship at Mount Sinai Medical Center in New York. In fact there was only one medical oncologist in Ireland then – the inspirational James Fennelly, who single-handedly brought the specialty to the country – although Crown also encountered other top specialists in London.

"In New York at Mount Sinai I was under Jim Holland – a great oncologist who was a founder of one of the first large cooperative groups, Cancer

"It was easy to get caught up in the excitement about high-dose chemotherapy for breast cancer"

"When I started to speak out against the poor cancer care we had then there were attempts to gag me"

and Leukemia Group B (CALGB). He was an inspiring and methodical clinical researcher. I wanted to work at Memorial Sloan-Kettering as well, and managed to get there later."

He spent six years at Memorial in faculty and staff positions, developing interests in bone marrow transplantation and high-dose chemotherapy, and was recruited by Larry Norton as the first contributor to a new breast group.

Crown says it was easy to get caught up in the excitement about high-dose chemotherapy for breast cancer because early use showed high remission rates, although very high toxicity. Many women, especially in the US, were treated in this way, and at great cost, and it was mandated by some American states. But of course when large randomised trials were carried out, including by Crown after he had moved to Ireland, with British oncologist Bob Leonard, the results were disappointing when compared with conventional chemotherapy.

As he noted in a comment in *The Lancet* in 2004, there is probably "no other treatment in medical history that has had such a meteoric rise or as humiliating fall from grace as high-dose chemotherapy". When one 'positive' trial was found to be fraudulent, there was added notoriety for the approach. "But it was very important to do the negative trials of course," he says.

Other work that Crown did in the US was ultimately more fruitful. "I also worked on paclitaxel (Taxol) and docetaxel (Taxotere) and found my feet as a drug developer, and I spent a year working in the lab with Janice Gabrilove, a great scientist, on approaches using G-CSF and interleukin."

With a post at such an illustrious cancer centre, it was only a rare consultant's position that tempted Crown back to Ireland and, as he now knows, he was competing with several others who went on to become eminent in other places. "But it was a real riches to rags experience," he says. "When I started to speak out against the poor cancer care we had then there were attempts to gag me. I wasn't one of the golf playing, rugby following physicians from a fancy family – the health system was very patriarchal, as it was too in the UK, where there were those who wanted medical oncology stopped in its tracks, and it was terribly sad that patients were being denied treatments that were dismissed by certain senior doctors." He adds that UK medical oncology was set back for years when the brilliant Gordon Hamilton Fairley was murdered by Irish terrorists in London. "That is a source of perpetual embarrassment for me, especially at the time of the ESMO award in his name."

With more public awareness of the issues in Ireland, pressure from advocacy groups and more support from government, additional posts were created for some of the outstanding medical oncologists in the Irish–American diaspora, and Crown says there has long been a solid tranche of excellent, mainly British-trained, cancer surgeons in place. At St Vincent's, as tends to be the case at other Irish hospitals, there is no head of cancer, and the various specialists have enjoyed a good deal of autonomy to work on their own systems of multidisciplinary care, with freedom to order the tests and scans they needed, and early access to drugs such as Herceptin (trastuzumab). "To British colleagues we have seemed more like an American set-up," he says. "But our bureaucrats are catching up with us now."

He is certainly no fan of Britain's NICE (National Institute of Health and Clinical Excellence). "It tends to make a generation of cancer patients suffer before it approves drugs – and the economic tools they use such as quality life years are blunt instruments. NICE has taken a narrow view on several drugs and been proved wrong – such as the four kidney cancer drugs we have now. Before we had nothing to offer these patients and we know the drugs can make huge improvements. You have to factor in the rarity of certain tumours and the availability of other treatments – I doubt that NICE would have approved the drugs used in the MOPP

He supports reorganising services around centres of excellence, but is scathing about the way it is being done

regime for Hodgkin's lymphoma at the time."

As he adds, the cost of funding drugs for a few thousand kidney cancer patients in an economy such the UK is not high, and spending on healthcare is no bad thing, particularly in a recession, given that some economists take the Keynesian viewpoint of stimulating growth. "But obviously we must ensure we do not spend wastefully. The Americans made a colossal mistake in cancer when they allowed oncologists to sell the drugs they were themselves prescribing."

Some government decisions have been easy to make in cancer services, such as cutting out hospitals performing too few breast cancer operations, but there is a constant battle to counter bureaucratic decisions, says Crown. A recent programme to establish centres of excellence for cancer care has met the full force of his pen. On reallocating services, though strongly in favour of the principle, he is scathing about what he sees as arbitrary decisions that ignore evidence of local expertise.

Another part of his armoury is a business masters degree (MBA) he completed in 2000, with a thesis on strategy for European medical oncology, such as proper recognition of the specialism and true multidisciplinary care, much of which has now happened. "One of the first things they teach you on an MBA is the difference between management and leadership," he says, pointing also to hugely critical comments he has made about bailouts of the Irish banks and what that money could have bought in the health service, from hospital funding, to hiring colorectal cancer specialists, extending mammography to the over 65s, cervical cancer vaccination and more. "We could have vaccinated the whole world against cervix cancer for what we spent on our bank bail out." His message was: "don't kill the health service to pay goons" – and now he is in parliament he has become an even more formidable advocate.

Other topics that have received the Crown broadside include complementary therapies ("intellectually dishonest"), local financial mismanagement, and – not least – attempts to gag physicians from speaking out (he himself made headlines when he was dropped from appearing on a television programme alongside health officials).

Like other oncologists returning to 'unfashionable' parts of Europe, it has been research that has helped give Crown this platform. Not only did he set up a clinical trials unit at St Vincent's, but in 1997 he founded, with John Armstrong, the Irish Clinical Oncology Research Group (ICORG), filling a major gap. Until then, Ireland had been the only country in western Europe without a national trials group.

He carried out a great deal of work on conventional chemotherapy while in Ireland, including trials with various international cooperative groups on paclitaxel and docetaxel. For the latter he was one of the senior investigators who presented evidence that it was superior to doxorubicin (Adriamycin) to the US regulatory body, the FDA, leading to its approval. His experience with trial designs for these and other drugs such as cisplatin and carboplatin was especially valuable when he became involved in trastuzumab and the dawn of clinical molecular medicine – but it was, as he admits, a lucky break.

"I got a call from Dennis Slamon, whom I knew only by repute, saying he'd like to bring a group of Irish Americans to Dublin, and we hosted a seminar on HER2. He also said he'd like to include Irish patients in the original pivotal trial of the drug trastuzumab." Slamon of course is the legendary oncology chief at the University of California in Los Angeles (UCLA) who spent years researching HER2 biology and pushing for drug development. "We said we would love to be part of the trial but unfortunately we then spent months arguing with our ethics committee, which said we shouldn't be experimenting on cancer patients, and we only managed to get one person on the trial and so missed out on authorship. But when the next trials

came along we were jointly leading them."

The trastuzumab trials run by Slamon and colleagues were under the BCIRG (Breast Cancer International Research Group), now part of TRIO (Translational Research in Oncology), and Crown says they were well designed, according to 'visionary' questions that Slamon wanted to test, and by a close-knit group of researchers – in contrast to some other trials that he describes as often "dismal".

One international trastuzumab phase III trial led by Slamon, in which Crown was closely involved with the design, was BCIRG-6, a complex multi-arm trial that tested various concurrent chemotherapies, and which he says was also radical in that some patients would not be receiving doxorubicin. "I crossed the Atlantic 13 times during the design phase, and there was much scepticism about it, including from the corporate hosts, who almost undermined it," he says. "There were several other trastuzumab trials taking place that just picked what was thought to be the best chemotherapy and added Herceptin. Our approach was that you couldn't be developing elegant, sophisticated molecular drugs as if they were chemotherapy – itself a by-product of the chemical weapons industry."

He adds that scepticism stemmed mostly from doubt that a consortium of investigators would follow a complex, radical protocol for a large trial, and that a more open, permissive design was necessary to carry out such studies. "I didn't doubt we could do it and neither did my colleagues. And for BCIRG-6 we got 3220 patients signed up – an extraordinarily high rate of trial compliance."

ICORG, which also covers researchers in Northern Ireland, has been a success, says Crown. It now employs 20 people and includes some 100 researchers, and has a full portfolio of patients in trials in most tumour types, and at one point 35% of all breast cancer patients were in studies. "Most pharmaceutical companies have now opened clinical trials offices in Ireland, and we've been able to provide many millions of euros worth of free drugs," he says. In keeping with American links, ICORG was also the first group outside of North America invited to join the National Surgical Adjuvant

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"The HER2 target may be 'low-hanging fruit'. The next generation of drugs may be far harder to develop"

Breast and Bowel Project (NSABP), the major US-based trials group.

Another concern about trials, says Crown, is the lack of effort going into looking for biomarkers in subgroups. "For example, I was involved in a study on sunitinib in breast cancer. It does produce response in some patients but all the randomised controlled trials were negative. The tragedy was there was no tissue collection to look for biomarkers. We are defining eligibility on old techniques and not matching the extraordinary precision of our new therapies with the right diagnostics and prognostics. It cost the drug company many millions of dollars and we may have lost an agent that could benefit some patients. We are determined that most of the trials we join from ICORG should have mandatory tissue collection and a translational component."

Too many companies think that finding biomarkers will restrict market size, he adds – but unless the benefit is clearly evident, there can be no market, such as with bevacizumab (Avastin) in breast cancer, which Crown says he is no longer using except in some existing patients.

"We need to stop thinking about existing phases in drug development and start collecting tissue on day one with every patient, and try and design each stage with meaningful molecular predetermination of eligibility, or if not we should at least collect larger tissue banks at phase II to see if a patient group benefits. We've become conditioned by small benefits. If we'd taken this approach with Herceptin we would have seen excellent benefits at phase I and II, and by the phase III adjuvant stage, instead of requiring four trials of 3000 patients each, I bet we would have had a positive result with one trial of say 400 patients, because the benefit was so big – as we had the right marker and the right molecule."

The story of HER2 biology just keeps expanding, he adds, with a growing family of new molecular treatments. "It's fascinating and there is the possibility that we may be able to cure metastatic breast cancer – I know we did cure some with high-dose chemotherapy but the numbers were not worth the toxicity involved. With trastuzumab, my colleague Giuseppe Gullo at St Vincent's presented a great abstract at ESMO showing we now have many long-term disease-free survivors." One of the most exceptional cases he's seen in Ireland, he adds, was a woman whose liver had deteriorated badly and was given trastuzumab outside of a trial because she couldn't take the chemotherapy as well. "We got permission to give Herceptin to her and within a year her liver had returned to normal and she's never relapsed. We stopped the drug three years ago. I believe we are curing 5–10% of advanced breast cancers we treat with trastuzumab and chemotherapy, and that's unprecedented."

He also mentions a potentially extraordinary finding from a North American trastuzumab adjuvant trial, where about 160 patients who were HER2-negative got on the trial – "But Herceptin seemed to work for them as well. It could be a fluke, or there may be a biological explanation concerning stem cells, or immunology, which is being researched."

Given the increasing complexity of medical oncology, it's no surprise to find that Crown is a strong critic of other specialists, such as surgeons and radiation oncologists, becoming involved with drugs. "Those gynaecologists who deliver babies and treat breast cancer with chemotherapy must be much smarter than me," he says. "Seriously, the discipline of drug therapy in internal medicine is critically important and we are likely to see subdivisions within medical oncology according to molecular subtypes."

Given that there has been no recent breast cancer drug successes on the scale of trastuzumab, Crown says it's possible that the HER2 target is "low-hanging fruit". He notes promising data though on everolimus (Afinitor) for oestrogen-positive disease, but overall "the next generation of

drugs may be much harder to develop". In any case, he reckons Ireland will be in the frontline of molecular selection in drug development in early-stage trials, and reports that there are now "brilliant" researchers in place. "I think you will see a lot from Ireland in translational research in the next few years," he says, mentioning a key enabler, Molecular Therapeutics for Cancer Ireland (MTCI), a 'strategic research cluster' funded by Science Foundation Ireland and set up in 2009.

Crown is the principal investigator for MTCI, which is researching mainly breast cancer targets, such as novel therapies for triple negative disease. MTCI and ICORG are uniting the country's cancer research effort, he says. Ireland has six medical schools – a high proportion for its population, despite having a relatively low number of doctors – and there is now much more cooperation than competition among them and with researchers at other locations.

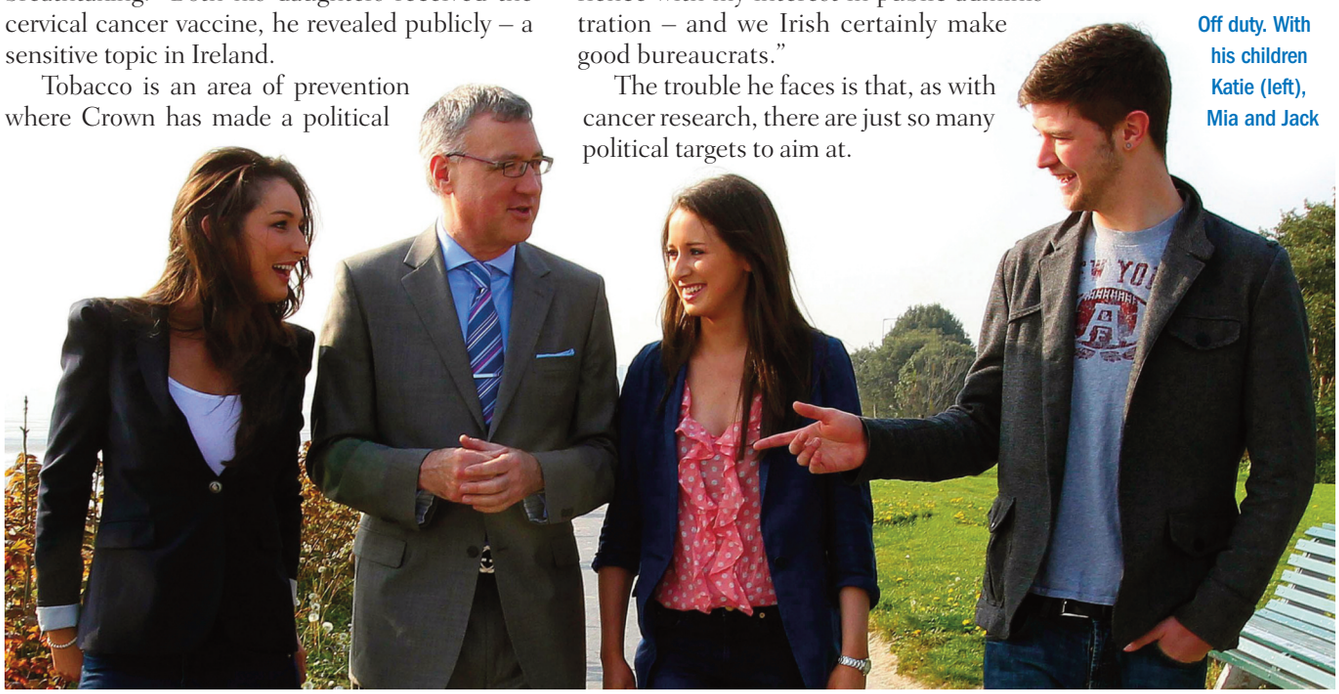
While Crown's primary interests lie in treatment, he recognises that major advances lie in prevention and early detection. "You can't overlook the benefits of ending hormone replacement therapy and factors such as obesity in breast cancer, while the advances in imaging for detection will be breathtaking." Both his daughters received the cervical cancer vaccine, he revealed publicly – a sensitive topic in Ireland.

Tobacco is an area of prevention where Crown has made a political impact, speaking out in the senate for a ban on smoking in any enclosed space where children may be, such as in cars. He described their exposure to smoke as "a form of child abuse", adding medical details of the different respiratory rate of children. "I used to be a smoker myself and I've heard all the so-called arguments about civil liberties – they are just addiction thinking. I'd like to see the European parliament giving say 10 years' notice that it will be illegal to manufacture and import tobacco products."

Europe presents a possible future avenue for Crown. On the cancer front, he is keen to promote small, fast-moving research groups, as exemplified by BCIRG/TRIO, that can harness diversity but will avoid the 'committeeism' that he feels some cooperative groups have succumbed to. He was among the founders of the campaign to stop the European clinical trials directive, and perhaps he could make a bigger contribution at policy – and political – levels by stepping away from the clinic and further into Irish and European affairs.

"I'm in the Irish senate for five years and I will continue to develop MTCI – and the big question is whether I put more time into politics. I could also aim to combine my medical research experience with my interest in public administration – and we Irish certainly make good bureaucrats."

The trouble he faces is that, as with cancer research, there are just so many political targets to aim at.



Off duty. With his children Katie (left), Mia and Jack