

Ulrik Ringborg: tackling the fragmentation of Europe's cancer efforts

→ Marc Beishon

Ulrik Ringborg remembers a time before pressure on cancer services led Sweden to abandon a model that combined clinical and research responsibilities. He believes comprehensive cancer centres, similar to those in the US, are key to restoring that link, and could provide the backbone to unify efforts to improve cancer care in Europe.

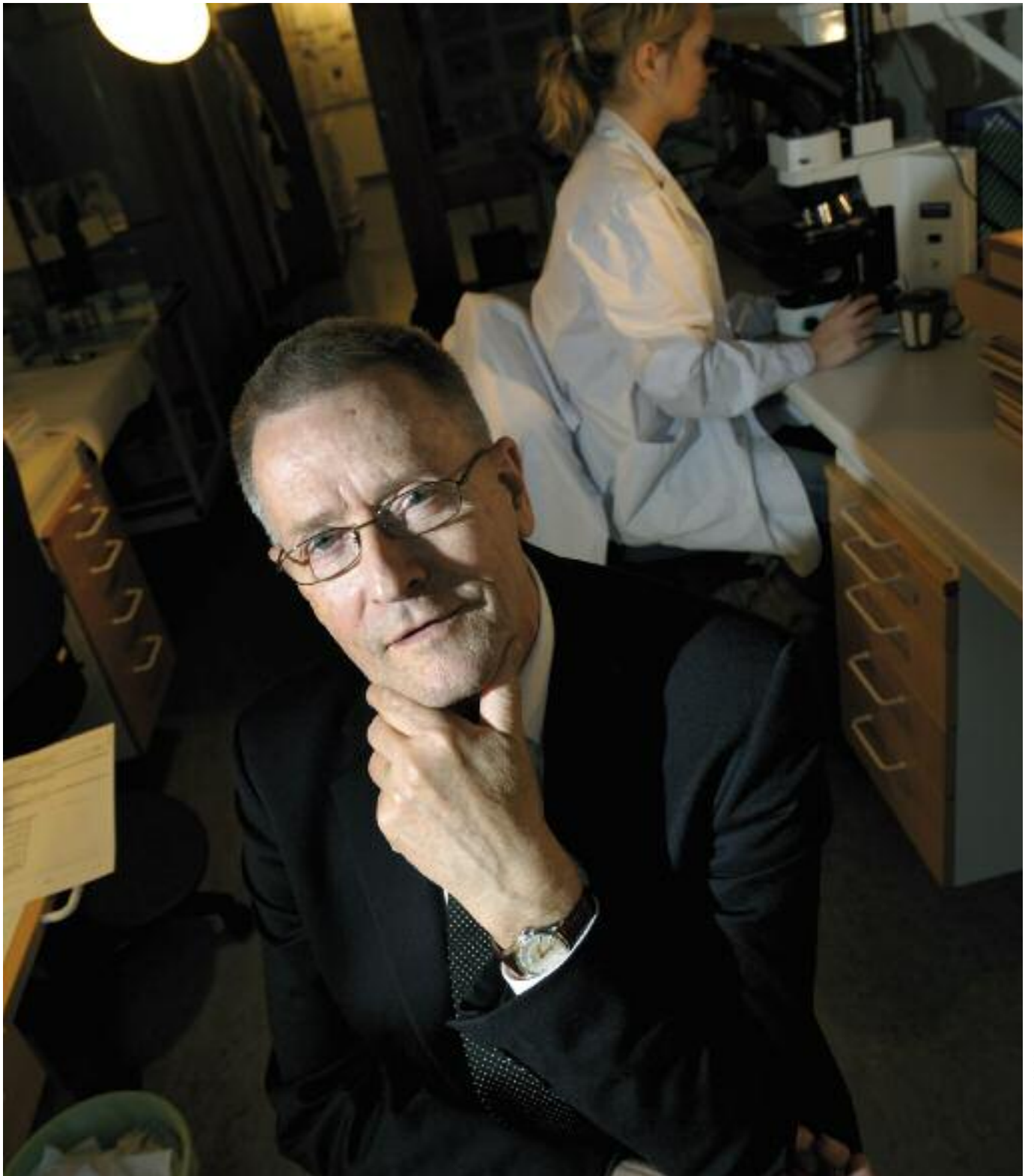
The challenge of overcoming fragmentation in the European cancer effort has been a major preoccupation among key players for some time. According to Ulrik Ringborg, professor of oncology and director of the Cancer Centre Karolinska, in Stockholm, building and strengthening comprehensive cancer centres (CCCs) – where care and prevention is integrated with research and education – will be crucial to any solution, both at a national and Europe-wide level. As president of the Organization of European Cancer Institutes (OECI), he is determined to play his part, and the Karolinska gives him a very strong base from which to work.

“Cancer is very strong here. We are the only one outside of the US to make a list of the top 15 most effective cancer centres – ranking number 12 in a recent bibliometric analysis,” says Ringborg. “Karolinska overall is a big organisation with some 18,000 employees, and up to a quarter of the resources and as many as 120 research groups are devoted to cancer. But we still have a great deal of fragmentation among the various clinics, which

means we are not carrying out true multidisciplinary working for all patients. And are all those research groups collaborating in an optimal way? Of course not. The challenge for us – and for all university hospitals around Europe – is how to delineate a comprehensive cancer centre that includes advanced treatment and research.”

Such CCCs cannot exist in isolation, he adds. Few hospitals or dedicated cancer institutes, if any, have the scale of the major American centres, and more effective translational research will not happen around Europe without collaboration both among research groups and among centres. “We need to have a common view of what translational research is,” says Ringborg. “It is not just about bridging basic and clinical research, but also about structured implementation into routine care. The whole process goes from basic to outcome research – but there is an enormous gap in introducing new approaches into healthcare systems and evaluating them. We have especially to bridge the implementation gap as well as the basic–preclinical divide.”

Pointing to success in rare cancers, such as



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some leukaemias, where cross-border collaboration is more or less forced on researchers and clinicians [see also Spotlight, p42], Ringborg mentions new pan-European organisational initiatives he believes will greatly increase such working. Last November, heads of many of Europe’s top cancer centres and institutes met in Sweden and came up with the ‘Stockholm Declaration’ – a mission statement for creating a collaboration platform among the most active centres and basic/preclinical research organisations [see also Grand Round, p17].

Meanwhile, the OECI is currently piloting accreditation criteria for CCCs, not least to help expand the number in Europe – the current membership of around 60 needs to almost double, says Ringborg.

Other initiatives he flags up include the Network of Core Institutions (NOCI), a research-oriented group of elite centres under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC); the TuBaFrost biobanking project led by the OECI; and the Eurocan+Plus project, funded by the European

Commission (EC) to look at how the European cancer effort could be improved (Ringborg was a leader of one of the work packages).

It is, he says, an encouraging picture, and these are by no means the only promising avenues – links with the EC’s Innovative Medicines Initiative and Initiative for Science in Europe are also ongoing. “We cannot put all our eggs in one basket – but we do have one message,” he says.

That message emphasises the CCC as the building block for Europe, and Ringborg says his primary mission – and one that he spends at least half of his time on now – is developing true comprehensiveness at the Karolinska.

Ringborg was not earmarked for medicine at all – he was a talented pianist and seemed destined for an arts career, but felt he was being pushed too hard in this direction. “I was also interested in psychology and how the mind works, and went into medicine with an aim of doing brain research.” After initial training in Gothenburg, he moved to the Karolinska Institute in the late 1960s, where he was able to combine research in cell biology (and landed a PhD on RNA synthesis on the salivary gland cells of midges), with the completion of his internal medical training.

He benefited from having a superb mentor – Jan Waldenström, one of Sweden’s most famous medical scientists (who gave his name to a rare type of non-Hodgkin’s lymphoma, Waldenström’s macroglobulinaemia). Thus inspired, Ringborg chose to combine his basic and clinical skills in oncology, and he went on to obtain a combined Swedish qualification in medical oncology and radiotherapy.

It was an age where, at the Karolinska at least, clinicians were actively encouraged to build research careers. “The then director, Jerzy Einhorn, understood that to build oncology it is very important to involve preclinical research, and he recruited people with academic backgrounds and provided us with small labs. It was possible then to carry out clinical duties in the morning and research later on – but

ORGANIZATION OF EUROPEAN CANCER INSTITUTES

The Organization of European Cancer Institutes held its first general assembly in 1980 – some way behind its US equivalent, the Association of American Cancer Institutes, which was founded in 1959 and currently comprises 91 of the country’s main academic and freestanding cancer research centres. With around 60 members, the OECI still has long way to go on the membership front, as Ringborg acknowledges. Its current primary initiative – cancer centre accreditation – should attract more interest, he says.

In addition to an accreditation team, the OECI has working groups for improving clinical guidelines, education, new technology development and pathobiology, where the main initiative is the TuBaFrost tissue bank project. TRANSFOG, a project working on the systematic identification of novel cancer genes, is also run by the OECI. Its next scientific conference and general assembly is scheduled for 20–24 May in Genoa. For further information see www.oeci-eeig.org

of course that's changed thanks to increased clinical demands and the huge increase in complexity in cancer research."

Cancer clinics also had dual clinical/academic responsibilities, which were later split up in the face of political pressure to deliver hospital services. Ringborg was among the last to enjoy such dual working, then common in Swedish university hospitals. Rebuilding the links – but in a way that accommodates modern working – is a key part of his work now at the Karolinska.

Ringborg's own work took him into several special interests, including head and neck cancers and sarcomas, but his main interest is in melanoma. He co-founded the Swedish Melanoma Study Group as far back as 1977, and this has provided a model for the type of multidisciplinary working that he feels is essential for delivering that weaker part of many cancer centres' activities: implementing innovation in day-to-day practice.

Having a multidisciplinary melanoma group in place at the Karolinska made it far easier and much faster to introduce new findings into clinical practice, says Ringborg (and Sweden has carried out important clinical melanoma trials on its own part). "I remember when studies came in showing that it was not necessary to carry out lymph node dissection in head and neck melanomas. We were able to agree that in just six months or so we would change our care programme and end all such procedures in the Stockholm area, as we were able to measure outcomes and show we were not affecting the prognosis negatively."

Another example was implementing a much smaller surgical margin around thin tumours – 1 cm instead of 5 cm – and also decreasing surgical margins on tumours of intermediate thickness. "When we'd looked at the data we could see we could change practices almost immediately," he says. "But without the right infrastructure to implement them and evaluate outcomes, it could be years before change happens, as indeed happens in many places."

A prevention programme of note was started in 1987 to identify people with a genetic predisposition for melanoma, now carried out in most parts of Sweden using a standard protocol for collecting data, held centrally at the Karolinska. Sweden also has a national melanoma care programme and registry as a result of work by the Swedish Melanoma Study Group. "With this kind of structure available to cancer centres you can have a dynamic healthcare system – but otherwise you are lost," says Ringborg. He singles out Scotland and Australia as other countries with strong groups in melanoma developing good patient registers, but says these are lacking in other countries, notably the US.

In 1992, as the health sector was starting to be hit by financial restraints, Ringborg reluctantly stepped up into management, filling the posts vacated by Jerzy Einhorn of director of the cancer centre and head of oncology at the hospital. "Sweden had been in a privileged position, but budget cuts were starting to bite then. It was my colleagues who persuaded me to apply, as I'd decided not to initially," he says.

He took up his new managerial responsibilities within a system of cancer care that had been reorganised in 1974 around oncology centres based at university hospitals – building dedicated cancer centres had been deemed too expensive. Each hospital had the mission of integrating cancer care in its region, and common care programmes were drawn up, regional registries established and screening developed.

It had proved to be a good model for evidence-based care, but the structure has been left wanting, says Ringborg, due to financial cut-backs and increasing complexity in oncology, which 'traditional organ-oriented clinical specialties' are ill-equipped to deal with. The growing numbers of chronically ill, and more elderly patients, are putting the system under further strain, he adds, with the result that the quality of service is patchy. "Inequalities exist, above all, in the management of patients with recurrent disease."

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It has been dubbed ‘Karolinska Inc’ on account of its commercial approach to working with industry

The lack of a national cancer plan makes it harder to address such inequalities, though plans are afoot to develop a national cancer strategy. The country does not yet have the type of networking initiatives seen in France, Italy and the UK for cancer centres and translational research, but of course it is not the only European country with such a fragmented system. It all adds to Ringborg’s determination to see the Karolinska playing its part as a comprehensive cancer centre at both national and international levels.

Yet Sweden certainly does not languish near the bottom of European cancer league tables – quite the reverse. “If you look at the Eurocare data, we have some of the best figures, such as for breast cancer, as we have a good screening programme and success in treating primary disease. But all this good work can be undone if we don’t have the right approach for the future.”

And since government funding was curtailed, the Karolinska Institute generally has been very successful at raising funds for biomedical research – indeed it has been dubbed ‘Karolinska Inc’ on account of its commercial approach to working with industry and taking advantage of a Swedish rule that allows scientists to own their own discoveries. An ‘innovation system’ was started in 1996, and the institute is to be found among the leaders in most rankings of medical universities for research.

For cancer, Ringborg has a significant set of achievements to look back on over the 15-plus years since he took over from Einhorn – especially in research. “Without doubt the best is building the Cancer Centre Karolinska research labs next door to the Radiumhemmet [the first cancer treatment clinic in Sweden, sited on the main Karolinska campus]. I helped raise a lot of money for this building and we are celebrating its 10th anniversary this year. It is very important to have researchers close to the clinic, and it has attracted groups who have moved from elsewhere in the Karolinska campus and from other institutes.” The CCK, as it is

known, is an independent foundation, and its labs are at the disposal of staff at both the Karolinska Institute and the hospital.

Strong research groups include those working on tumour immunology, the P53 protein, tumour infrastructure and biomics. Almost half of the Swedish Cancer Society’s funding already goes to the Karolinska, and Ringborg says little more national money can be expected – so the European Commission is another important source, and there are several international research groups coordinated by his teams.

Other highlights are the establishment of a clinical trials centre, and a rehabilitation centre for cancer patients – Ringborg reckons this is one of the few in Europe, and covers both psychosocial and physical therapy (he mentions the Montebello Centre in Oslo as another example).

Ringborg’s ideal of a CCC received a boost four years ago, when a combined Karolinska University Hospital was formed by merging Stockholm’s two university hospitals – Huddinge hospital in the south of the city and the Karolinska in the north. The many groups involved in cancer are now being streamlined across the sites, organised in preclinical and basic research and in wider networks based on disease type. So far 12 networks – on tumours such as skin, lung, breast, and head and neck – have been set up, each aiming to bring together clinical research, nursing, basic research and epidemiology. The hospitals had for some time been under the control of Stockholm county council, and not the state – and it is the local politicians and the Karolinska Institute, says Ringborg, who put their weight behind not just the hospital merger but also a wider strategy to overcome the divide between the clinical and academic worlds, called the Stockholm Academic Health Care System, which has cancer as one of its core health ‘profiles’.

Comprehensive means the four ‘cornerstones’ of prevention, care, research and education – working in such a way as to create ‘innovation’ – a word



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Towards a comprehensive cancer centre. Karolinska's Radiumhemmet is the oldest cancer clinic in Sweden. Ten years ago, Ringborg oversaw the establishment of the Cancer Centre Karolinska research labs right next door

used a lot by Ringborg. "A CCC is the only place where you can have both high-quality care delivered by multidisciplinary teams and an integrated research process, from basic science to innovative outcomes for patients," he says. "But you do need a critical mass in terms of size."

It might seem that, in Stockholm, Ringborg has all the resources needed to establish a true CCC. But, as he points out, large though the Karolinska campus may be, it is relatively small compared with the giant CCCs in the US, such as MD Anderson in Houston – indeed, there are relatively few very large centres in any part of Europe, he notes. "We now have more than 200 different cancer diagnoses – the subgroups of patients is rapidly increasing and we need more patients and technical platforms such as large

tissue banks to carry out advanced research."

While recognising that the US does have problems in collaborative working, partly owing to the dictates of intellectual property policy, Ringborg considers that the US National Cancer Institute has made great strides in defining the qualities of a CCC, and the sheer size of most of the centres means they are more self-sufficient in terms of infrastructure and competence. "The only way for European centres to attain the same level of comprehensiveness is to collaborate," he says – and to participate in accreditation to help ensure that common standards are practised.

The OECI's accreditation initiative is modelled on that of a registration methodology for CCCs in the US, says Ringborg and, suitably adapted, it is currently being piloted in a few European centres

Twelve networks, based on disease type, bring together clinical and basic research, nursing and epidemiology



A culture of collaboration. In 2005 Ringborg and Thomas Tursz, director of the Institut Gustave-Roussy in France, signed up to a programme for cooperation. Ringborg is now intent on widening such collaboration to encompass all of Europe's leading cancer centres

before a launch this November [see also Grand Round, p 16]. It is certainly a searching tool – comprising some 300 questions – and the aim is that all OECI members will be assessed for accreditation. “It is a methodology by the profession for the profession – to check yourself and also benchmark against other centres, and so build a structure for pan-European quality assurance,” he says.

The test of comprehensiveness involves assembling the kind of multidisciplinary teams that the Karolinska has had success with, such as for melanoma. Ringborg recognises, however, that it can be difficult to unite functions that are often fragmented – particularly as the majority of centres have been carved out of university hospitals. Apart from the dominance of organ-based surgery, he refers to imaging and pathology, where cancer is only one part of their remit. “But you can only define comprehensiveness in terms of teams that provide all the functions that patients need, preferably in one place,” he says. Local geography – reaching all cancer patients within the centre’s region – is another

challenge, and Ringborg reports that just 30% of people go to a major centre at present, taking France as an example.

He points out, however, that dedicated cancer centres, such as the European Institute of Oncology in Milan, and Jules Bordet in Brussels, do not hold all the advantages. “Increasingly, chronically ill people with cancer also suffer from other conditions that require other specialists to be available.” Some dedicated centres may also lack close ties with academic researchers, he notes. Fragmentation is also exacerbated by private healthcare – Ringborg mentions Germany as a country where much medicine exists outside of the influence of public cancer centres.

The OECI is clearly the ‘glue’ that is working to bring together the top cancer centres, alongside the European cancer societies and research groups. And Ringborg, with others who drew up the Stockholm Declaration, has the ambition to fully realise the research side in a collaborative translational research platform that will unite the most active CCCs and also basic/preclinical research groups. “There would have been objections to this level of collaboration 10 years ago, but not now, given the challenges we face,” he says.

Much debate has gone on about the divided and duplicated nature of European cancer research, and there is some talk about establishing a central European cancer institute. Ringborg and his colleagues believe that a virtual, collaborative model is the only workable solution to unite what most are agreed are particular European strengths in basic and preclinical research, at leading centres such as Heidelberg, Cambridge and Amsterdam.

The aim ties in with last year’s European Union green paper, *The European Research Area: New*

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“The hard part is persuading politicians we can succeed, and for that we must speak with one voice”

Perspectives, which contends that translational research is not as effective as elsewhere for all types of science. “But we have special potential to develop projects that are difficult to do elsewhere, such as pan-European biobanking, which could especially help address rare tumour types and develop more personalised medicine,” he says. “We need to focus on what Europe can be good at. And the question for translational research is not that it isn’t being done, but how to optimise it.”

That is where the multi-pronged attack from the OEI, the Stockholm Declaration, EORTC/NOCI and the various EC initiatives come in, and Ringborg is clearly a consummate networker, with knowledge of, or presence in, nearly all the key projects. There is less money for cancer in the EU’s Seventh Framework Programme, he says, but he is optimistic about the impact of Eurocan+Plus. “I have the impression the Commission is interested in a European cancer platform, and that the negative views some have had about specific funding for cancer will change.”

Not surprisingly, Ringborg is also a firm supporter of the widest type of European cancer society, and finds it difficult to understand why the European Society for Medical Oncology (ESMO) chose to opt out of the new European Cancer Organisation (ECCO), on which he was a board member. As Håkan Mellstedt, the immediate past president of ESMO, is based at the Karolinska, there has been no shortage of discussions on the issue, he says.

Ringborg’s key mentors go back to Jan Waldenström and Jerzy Einhorn, both no longer with us. But he is close to a number of his fellow cancer centre directors, in particular Thomas Tursz, head of Institut Gustave Roussy in Paris, and no doubt shares with him his chief frustration – local funding difficulties. He considers the controversy created by the Karolinska Institute report on the relationship between cancer drug access and outcomes in different countries to be a ‘small one’. “I have no problem with the criticism of the methodology by Michel

Coleman [see *Cancer World* Sept–Oct 2006], but there are differences in the uptake of drugs and some indication that the hypothesis of different survival rates is true. We cannot say more than this for now.”

Apart from his organisational work, Ringborg continues with some input to melanoma research, and a little teaching, and he chairs a Swedish national advisory board on UV radiation protection. He has also co-written a recent textbook on skin cancer and a commentary on the ‘forgotten’ problems of non-fatal forms, such as squamous and basal cell carcinomas, which have significant management and cost issues. Cancer centres, he adds, ought to play a greater role in prevention work in society.

Ringborg has five children, all grown up now, and sounds pleased that one is preparing for a medical career. His great pastime, not surprisingly, is music – he still plays piano to high standard and listens to a lot of music. One outstanding performance he mentions was given at the last Nobel Prize ceremony by Chinese pianist Lang Lang. Ringborg is a member of the Nobel Assembly, courtesy of his position at the Karolinska, and he votes on the award for the prize for medicine and physiology, and takes part in news conferences on awards that relate to cancer, such as the 2001 prize to Leland Hartwell, Timothy Hunt and Sir Paul Nurse for work on cell division. That must be one of the most privileged ‘extras’ for any job in medicine.

It must be especially poignant to meet the world’s greatest medical scientists – many responsible for fundamental breakthroughs – and then to gauge just how far the discoveries have really made it into clinical practice. Attaining the goal of comprehensiveness will, Ringborg says, show funders a direct correlation with faster and better outcomes.

“Too many cancer professionals see the difficult part of the job in obtaining more resources – more beds, nurses, equipment and so on. These are actually the easy bits to do. The hard part is persuading the politicians we can succeed with cancer and for that the profession has to speak with one voice.”