Julio Celis:

bridging science and politics

Marc Beishon

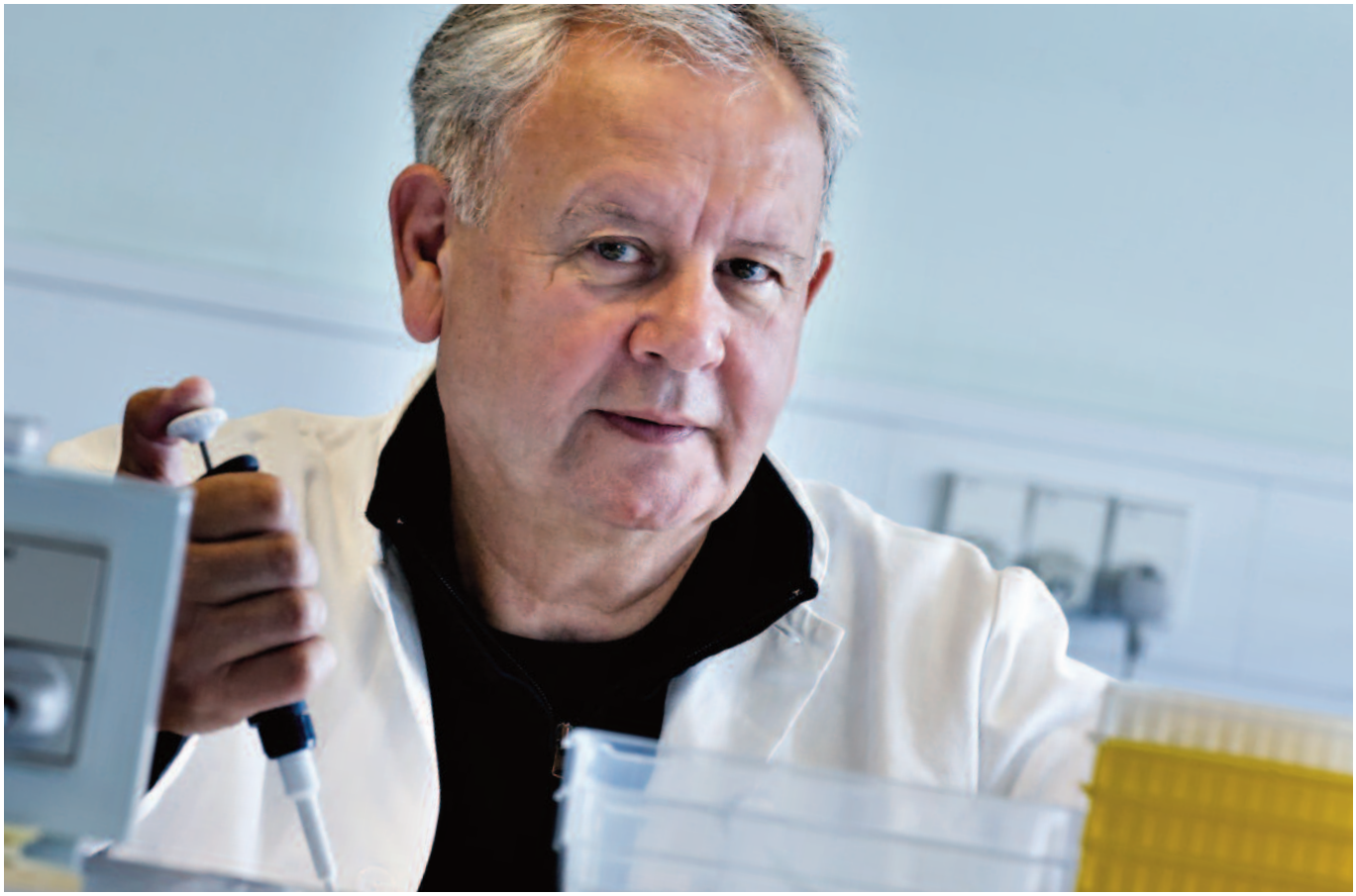
Julio Celis is a scientist to his core, and can lay claim to being one of the fathers of proteomics. But it is in helping shape the structures and vision of Europe's cancer research effort that he has arguably had the greatest impact. Better coordination and networking have shown what's possible, says Celis, the challenge now is to move from piecemeal short-term initiatives to something more sustainable.

There are two main aspects to complexity in cancer. The first is the hugely challenging biological nature of cancer, as researchers dig ever deeper into the molecular structures and pathways of tumour cells, uncovering layer upon layer of complexity as they go. The second is the world of 'oncopolitics' and the way in which healthcare and research organisations are set up to tackle cancer at national and regional levels – and there is arguably no more complex world in oncology than the European Union and its relationship with an expanding number of member states.

Understanding how best to bring these two demanding areas together is vital if resources are to be deployed to best effect, and Julio Celis has been bridging both science and politics for some time now to this end. A research biochemist of long-standing, based at the Danish Cancer Society in Copenhagen, and a veteran of many international committees, he is now taking his experience to the heart of Europe on behalf of ECCO to help drive a research policy that is formulated by scientists and clinicians in the field – and not only by administrators.

"The problem has been that the research community has not looked into the future and prepared the ground to influence decision makers about where we should be going," says Celis. "We don't tend to get involved until we are affected in a big way, such as with the clinical trials directive, and we have never really had a Europe-wide vision for cancer research. We have left it to policy makers to decide for us."

Now, if Celis and colleagues on ECCO's policy committee have their way, Europe's cancer community will be one of the leaders in the debate on how pan-European research funds can be best be allocated to pursue critical fields such as translational research, where attempts to create collaborative networks among the major comprehensive cancer centres and basic



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research centres have so far been piecemeal.

But the obstacles are formidable, as he says. Health systems are primarily the provenance of the member states, not the EU, and there is a big disconnect between the existing EU directorate for consumers and public health, DG SANCO, and the research and innovation directorate. Meanwhile, the principal research structure – the framework programmes – have been limited in scope and sustainability.

Further, about 95% of all cancer research spend is at individual country level, and the instruments through which member states might channel research funds for long-term translational research platforms do not exist. Large sums are at stake here, says Celis – the UK's National Cancer Research Institute alone spent more than €550 million on cancer research last year, nearly double the amount it spent around ten years ago.

Despite the barriers, Celis insists he knows no more exciting time in research politics in Europe. This is partly because, after many years of committee work in various pan-European agencies, the research and clinical sides of the cancer community are finally uniting with a much stronger voice. ECCO has established a policy committee to represent the views of the 60,000 strong European cancer multidisciplinary community, and the dream of a European cancer institute or centre is also still very much alive. Celis and colleagues at ECCO called recently for the creation of such a body as a logical next step to unite the continent's researchers, at least in virtual form.

Meanwhile, at the political level there has been progress in recognising the need to establish a research strategy for European science, and for cancer in particular. "Key milestones were the creation of the European Research Area [ERA] in 2000, championed by commissioner Phillipe Busquin, the creation of the European Research Council [ERC], and the initiative by Busquin in 2004 to set up a work-

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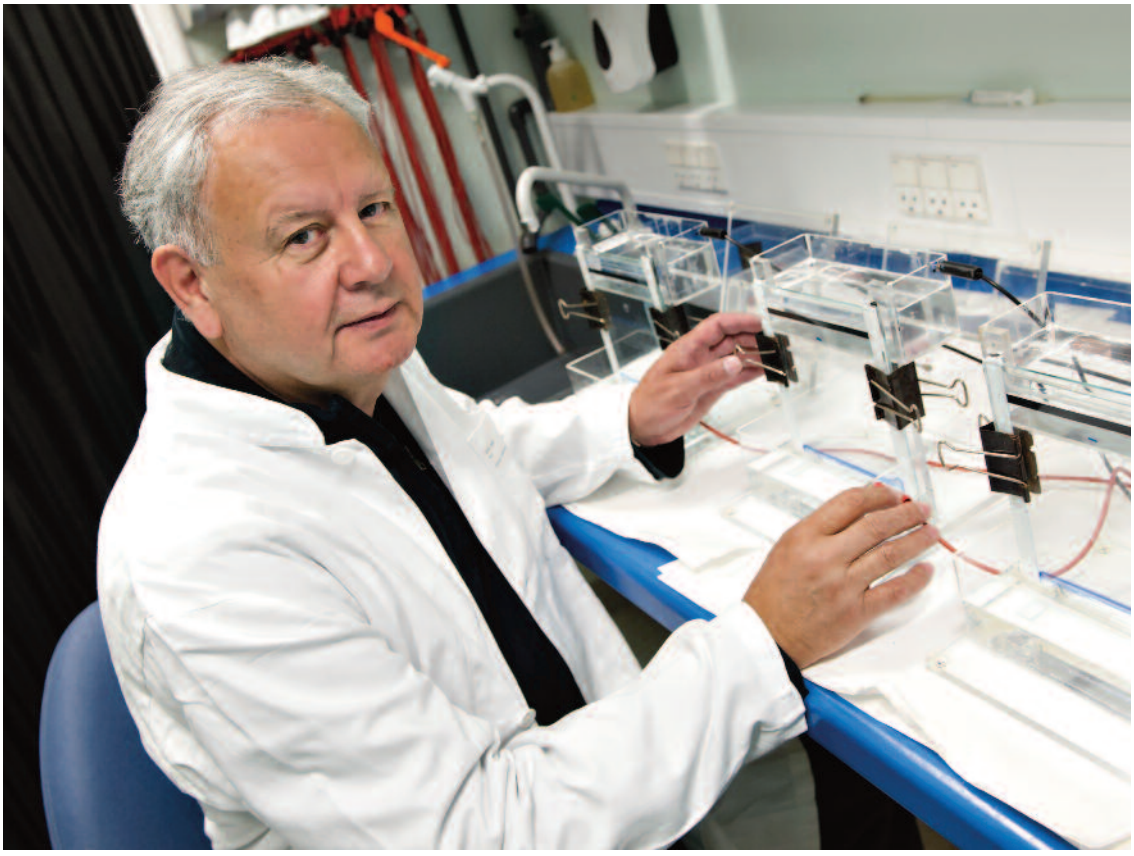
ing group to look at the fragmentation of cancer research in Europe and to identify barriers," says Celis. "I was a member of that group, which later made an application to the sixth framework programme [FP6] to set up the Eurocan+Plus project that identified where lack of coordination was particularly detrimental to the progress of scientific knowledge and the quality of care.

"One of the outcomes of the project, which was led by Peter Boyle from the International Agency for Research on Cancer, was the recommendation to establish a world-class infrastructure – a platform of European cancer centres for translational research."

There then followed the Stockholm Declaration, led by Ulrik Ringborg at the Karolinska, which is a manifesto drawn up by 18 cancer centres to achieve such a platform. "It was the first time heads of cancer centres had really sat down to look at how they could structure translational research in Europe," says Celis. "Following this, and recommendations from the ECCO oncopolicy committee and the Organisation of European Cancer Institutes (OECI), the European Commission funded under FP7 a network of excellence, led by Ringborg, to structure translational cancer research between cancer research centres in Europe, namely the Eurocan platform" (see www.eurocanplatform.eu).

The European Partnership for Action Against



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Cancer (EPAAC), with its various work packages, is another major programme that has research as part of its remit, and aims to ensure that one-third of all cancer research funding is coordinated across Europe by 2013 – a sum of some €1.5 billion. "This is not achievable of course," says Celis, but it is an indication of what the research community believes to be necessary.

Celis also expects the health component of the next framework programme to have a focus on personalised/stratified medicine. This would tie in with the EU now having an 'innovation union' strategy that stretches ahead to 2020, which focuses on major societal challenges, and may foster better cooperation among member states.

"The biggest words in Europe today are coordination and sustainability," says Celis. "We have created many networks so far, but little in the way of ensuring things continue. The vision we have at ECCO is to have a sustainable network of comprehensive cancer centres and institutes like my own to build a critical mass of expertise and resources across all the many niches we have in research to solve problems in different combinations – a sort of 'variable geometry'."

Celis, more than most, is also enmeshed in one of the most complex scientific geometries in cancer – probing the world of proteomics. Until the end of 2011, when he will make Brussels and oncopolitics his main priority, his job is scientific director of the Institute of Cancer Biology at the Danish Cancer Society in Copenhagen. The society is the largest cancer organisation in Denmark, with some 450,000 individual members. Unlike other charities such as Cancer Research UK, it directly employs its own research teams across six departments. For Celis, this position has allowed him to focus exclusively on cancer in the latter stages of his research career, and to get fully involved in oncopolitics. His pedigree as a scientist on this stage could hardly be better.

Born in Chile, he was an early convert at school to the then relatively new subject of biochemistry, enthused by a teacher who was carrying out some experiments on animals. "Chile then developed clinical biochemistry as a career option, and I was able to study subjects such as histology, physiology and pharmacology as well as the core science, which was very valuable to me later," says Celis.

He left for the US to do a PhD, and on his return to Chile was able to get a posting to the Medical Research Council laboratory of molecular biology in Cambridge in the UK, financed by the Wellcome Trust. "I can't emphasise how valuable networking was to me while I was in Chile under my mentor Jorge Allende – and these are skills I've also carried forward. Without networking, it is difficult to progress far in a career."

Certainly, that progression was stratospheric, for Celis found himself working alongside Francis Crick, one of the famous Cambridge DNA duo, and other luminaries such as Max Perutz, Fred Sanger and, in particular, Sydney Brenner, a Nobel winner for work on nematodes (ringworms). Brenner extended his stay in England as a member of the staff when the military coup in Chile made Celis reluctant to return home with his family.

There was hardly a better place for Celis to start working in the booming field of molecular biology, and it was Brenner who set him to work on proteins, which has been the core of his research ever since. "But I left Cambridge after five years to take a permanent position in Denmark at the new Department of Biostructural Chemistry, headed by Brian Clark, who was also from Cambridge – it was a critical move that helped secure my career. There is one important aspect of work in England I have taken with me, however, and that is that everyone was working in the lab, not sitting in offices playing with models – except for Crick, that is."

Being a hands-on scientist means better problem solving, especially in research that requires extensive validation such as cancer, and this has been a feature of senior English biologists, he adds. "This is not the case in every country – I see several places where it is not unusual for even younger scientists to leave the lab and direct research from their offices."

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Celis had landed in the University of Aarhus in Denmark, with his late wife Ariana, a medical technologist, where he was to spend many years on cell biology research, continuing with a productive niche in proteins, before moving to the Danish Cancer Society. Here he was able to devote himself full time to translational research from the basic science standpoint, especially on breast cancer.

"At first I took forward work I had been doing in Cambridge, with John Smith, on suppressor transfer RNAs, but found there were already many experts on this topic in Denmark. So we turned to cell biology, in particular to the cell cycle and cell transformation, drawing on work I had been doing on separating proteins using gels to study these processes using a biochemical approach. By 1981 we had discovered the PCNA protein [proliferating cell nuclear antigen] simultaneously with a group at the SCRIPPS Research Institute, a molecule that is central to cell life and death, and in 1982 we published the first extensive work on protein expression profiles of normal and transformed cells."

PCNA has been described as the 'ringmaster of the genome' and the implications of uncovering this and other proteins involved in normal and transformed cells has great importance for cancer, but as Celis says, this was just the beginning of what has turned out to be one of the most complex branches of molecular biology. There are now known to be as many as two million proteins, thanks to mechanisms such as 'splice variants' from the body's 25,000 or so genes that encode proteins, and the field of proteomics – for which Celis is rightly seen as one of the founding fathers – is even more complex than genomics.

"At the start I thought we could look at many proteins at the same time as a way of profiling changes in cells, and indeed we started to build protein databases of what we found, and later as identification techniques became available we were able to tell what the proteins were," he says.

Celis himself has long used a laboratory technique called 2D gel electrophoresis, pioneered by Patrick O'Farrell, which separates proteins according to their molecular weight and charge and allows researchers to compare proteomic profiles in different samples. It is the kind of hands-on laboratory work he is keen to promote, and he points out that, with the advent of high-throughput technologies such as mass spectrometry and protein arrays, researchers can lose sight of biological questions they should be seeking to answer and instead get wrapped up in a constant discovery mode for work on biomarkers, for example. "In cancer you need a validation mode too," he says.

In 1995, when he turned to look at clinical cancer questions using tissue samples rather than cell lines, he says he had to "convert" himself to a pathologist as well. "I realised I couldn't do anything without understanding the histology and pathology of tissue samples, which meant doing part of the work myself so I could interpret the data."

Key questions that Celis and the international proteomics community are addressing include the search for biomarkers for early detection, finding new drug targets and predicting how a tumour will respond to a therapy (see also the thematic 'oncoproteomics' issue of *Molecular Oncology* (2010; vol. 4, pp 459–566), where new approaches such as nanotechnology and imaging spectrometry are discussed).

At Aarhus, Celis worked on bladder cancer biomarkers, using antibodies to locate the proteins in diseased and normal tissue, as he recognised that an expression level on its own may not be meaningful due to the daunting heterogeneity of the tissues. This was laborious work made possible only through close cooperation with Hans Wolf, a cancer surgeon, and Torben Ørntoft, a clinical biochemist, who were committed to obtaining tumour and control tissue, and points to a much wider problem he sees in translational research.

"This type of work not only requires fresh tissue, which is very challenging to organise, but also setting up tumour, blood and urine biobanks so when we come to validate a biomarker, for example, consistent samples are at hand. But samples are often

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stored in different systems and at different times – we may have had a focus on translational research in the current European framework programme, but we have failed to create consistent infrastructure to support it – and tumour banks are one of the main resources. It's this kind of omission that means we are often paying the price of short-term solutions to long-term problems."

When Celis moved to the Danish Cancer Society he switched to translational breast cancer research with the support of pathologist Fritz Rank, taking a year to understand the history of the disease, and his institute is now a key niche player in certain aspects of this major tumour group, such as looking at biomarkers for endocrine resistance and early detection. Naturally he also runs a proteomics subgroup alongside those on breast cancer, cell cycle, apoptosis, metastasis and tumour microenvironment and genomics.

On two sides of his large office in Copenhagen he has pinned up many pictures of protein profiles in breast cancer tissues, which show where the protein is being made, in some cases from only certain cells in a tumour. "This gives you some idea of the incredible heterogeneity we are finding in tumours – there are no two sites on a tumour that look exactly alike," he says. There are images too of premalignant tissue, from which his proteomics lab is working on identifying progenitor cell types, and which could eventually result in biomarkers for early detection of cells that are more likely to progress to tumours.

The validation problem with biomarkers is well illustrated by the fact that, of the thousands of articles published on biomarkers, so far fewer than 100 of them are being used. Although he is philosophical about the enormous complexity that nature is putting in the way of the cancer community, Celis says the only way to find more answers is to build the infrastructure that will allow researchers to take the time they need to work on the most clinically relevant questions involving human tissue and fluids, as well as the much easier, but much more homogenous, cell line and animal samples that are used so extensively.

During the 1990s, Celis began to represent Denmark on European organisations in the molecular biology arena (in particular the European Molecular Biology Laboratory and European Molecular Biology Conference) and stepped up his activity in the European Molecular Biology Organization (EMBO). In 1999 he became secretary general of the Federation of European Biochemical Societies (FEBS).

It was a this point that the idea of proactively working for a coherent European strategy and structure for scientific research began to take shape.

Working with others in the biology sector, Celis and colleagues such as Fotis Kafatos and Frank Gannon created the European Life Science Forum (ELSF) to put pressure on the EU over the need for basic research and in particular to work towards the creation of the European Research Council (ERC). "We soon realised that to achieve this goal we had to also involve all the other branches of science, and we created the Initiative for Science in Europe (ISE), which I chaired after José Mariano Gago, who was science minister in Portugal, and which led to the formation of the ERC."

This was a big achievement, as member groups of ISE included existing science organisations such as Euroscience and the European Science Foundation, among others. "It took us four years, but what I have learnt is how we need to turn a diffuse idea into an object of desire – so that politicians then see the value of it. The European Commission was somewhat sceptical at the beginning, but it got to such a level that they couldn't stop it and so took it over."

Then in 2008, Lex Eggermont, then president of ECCO, invited Celis to chair ECCO's new policy committee, which aimed to pull levers at the highest levels to try to progress the pan-European cancer research vision, with initiatives such as the Oncopolicy Forum and the European Academy of Cancer Sciences, an independent entity that can provide science-based advice to policy makers.

So there are many projects, meetings and com-

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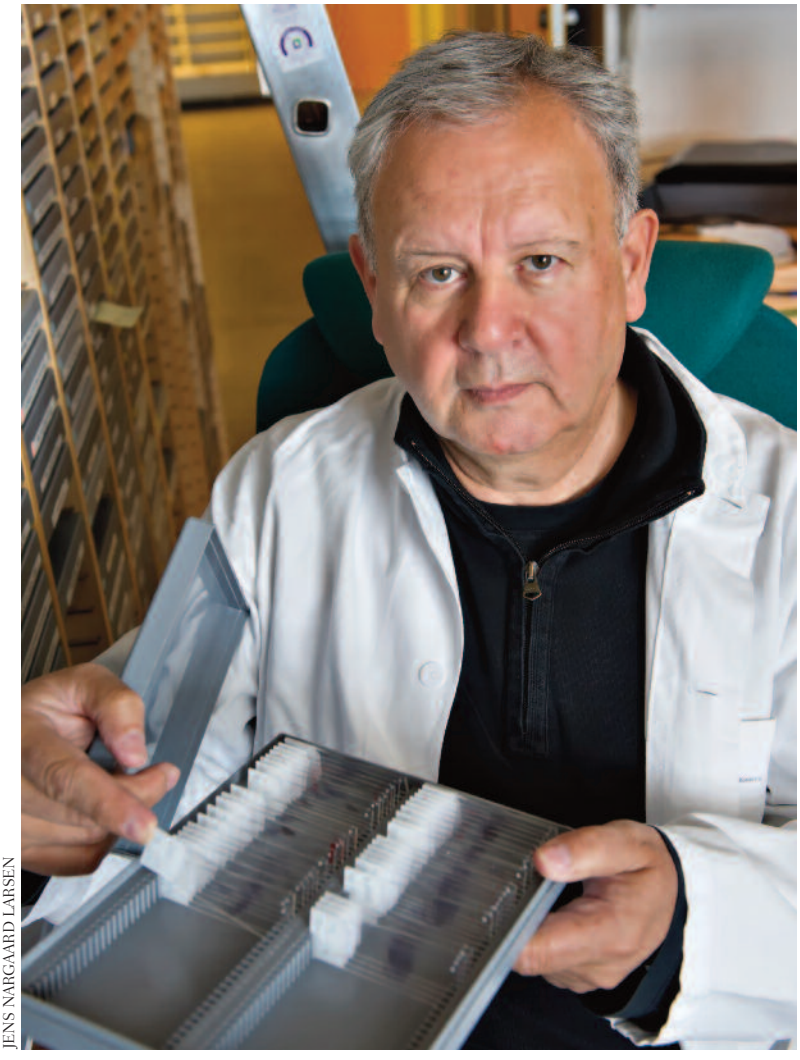
mittees now in European cancer – and to cap it all, Celis is also the current president of the European Association of Cancer Research (EACR), which gives him full ECCO board membership. What outputs does he now see coming from all this activity?

"At the science level we need to firmly establish a structure for translational research – how we standardise technology, share data, exchange patients, what type of trials we could do, and what novel projects we can take from beginning to end. If we do that it will be first time it is done on this scale anywhere. We also need to demonstrate success stories to interest policy makers.



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"Then the next step is sustainability, where we need new instruments for organising member states and the European Commission. At ECCO we have proposed for example that comprehensive cancer centres would get matched funding from the EU on a competitive basis, but overall we need new instruments for members states to cooperate on meeting their societal challenges so that we can approach that goal of increasing the coordination of research funding. One enabler would be to have national health and research ministers meet in the same way as their colleagues do for economics."

Celis says that in addition to setting up a virtual European cancer centre, ECCO would like to see a larger European Institute of Health as well as a new mechanism to support top researchers through 'dream teams', allowing industry to contribute cash and new drugs for study. He would also like to see more support for research into cancer prevention and early detection.

The ECCO policy committee has set out much of its current thinking in a response to the European Commission's green paper, 'Future EU research and innovation funding programmes: common strategic framework'. This paper sets out the aims for research and innovation funding for the next framework programme at both EU and national levels from 2014 to 2020, and by focusing on instruments 'with proven European added value' there should also be specific funding proposals by the end of this year. In a bid to connect with the public imagination, the framework 8 programme will do its bit to further European innovation and research under the name Horizon 2020.

Celis says it is imperative that basic science organises itself as well as other sectors to advise policy makers and influence funding. "Scientists

are not as visible as doctors and patient groups – we need to set out our priorities for the long term that will fit alongside the more short-term projects that tend to dominate decisions," he says.

From next year, no doubt Celis could spend virtually his entire working time in meetings and conferences as the scenario for 2020 unfolds, and with other commitments such as president of the EACR, which was a founder member of ECCO, and has 10,000 researchers in its ranks through national society membership. The EACR is naturally lending its support to the coordination effort and the expected focus on personalised medicine in the next framework programme. It will hold its biannual Congress at Barcelona next year, which Celis will be chairing.

He is concerned that the US is still attracting many of the world's top researchers, and the cancer community there enjoys a close relationship with industry. "One of the aims of the Eurocan platform is to help make Europe a more attractive place for researchers from say Asia to come and work."

Developing the next generation of European researchers is also important, and Celis is one of the organisers of a FEBS lecture course on translational cancer research, taking place in Portugal this September. "This is not just about work – it's in a nice summer school setting and is a great chance to build a personal network," he says. As if this isn't enough, he is also editor in chief of the journal, *Molecular Oncology*, which majors on issues such as the next steps in proteomics. As always, Celis will be urging that the technology race in techniques such as protein profiling is tempered with realistic biochemistry.

Ringborg, director of Stockholm's Karolinska Cancer Centre, describes Celis as "a remarkable man", in both his scientific work and his capacity for networking. "I have never met a basic researcher and cancer biologist with such a dedicated interest in the problems of the patients," he says, and comments particularly on how well Celis manages to integrate pathologists into the proteomic research he does on tumour progression and tumour subtypes, "in a way that the clinical questions steer the research strategies."

Having worked alongside Celis in some big European projects, including the Eurocan platform, Ringborg also singles out his "unusual capability to organise and convince people about both infrastructures and research strategies," and also his grasp of the need to find new types of collaboration and financial support to improve the innovative potential in cancer research.

Celis's first wife and fellow researcher Ariana sadly died 13 years ago and he has since found a companion, again a scientist, biochemist Teresa Cabezòn, who also works at the Danish Cancer Society. He has three children and six grandchildren, so family life tends to take all his free time. After he steps down from his research post in 2012 he will be spending most of his time in Brussels to concentrate on oncopolitical duties.

With his scientific achievements now largely behind him, Celis is looking for a success in getting more opportunities for researchers in the next framework programme, and more projects under the Eurocan umbrella. "And if we can get member states and the commission to agree to look for new sustainable opportunities we will be in good shape," he says. "We need to be sure we will be consulted in time when policy makers work on anything cancer related. I'd like also to see more people from outside Europe coming to do their research here."

Of course, there are some who would now say that the whole European 'project' is in peril following the economic collapse in countries such as Greece, Spain and Ireland, and there is huge strain now evident in high-level political relations. Meanwhile the European Commission is looking for a five per cent increase in the EU budget to meet 2020 goals. Whichever way this goes, for Celis there will be no let up in pushing for sustainable structures that tap into member state funding to secure a solid future for cancer research in Europe.

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