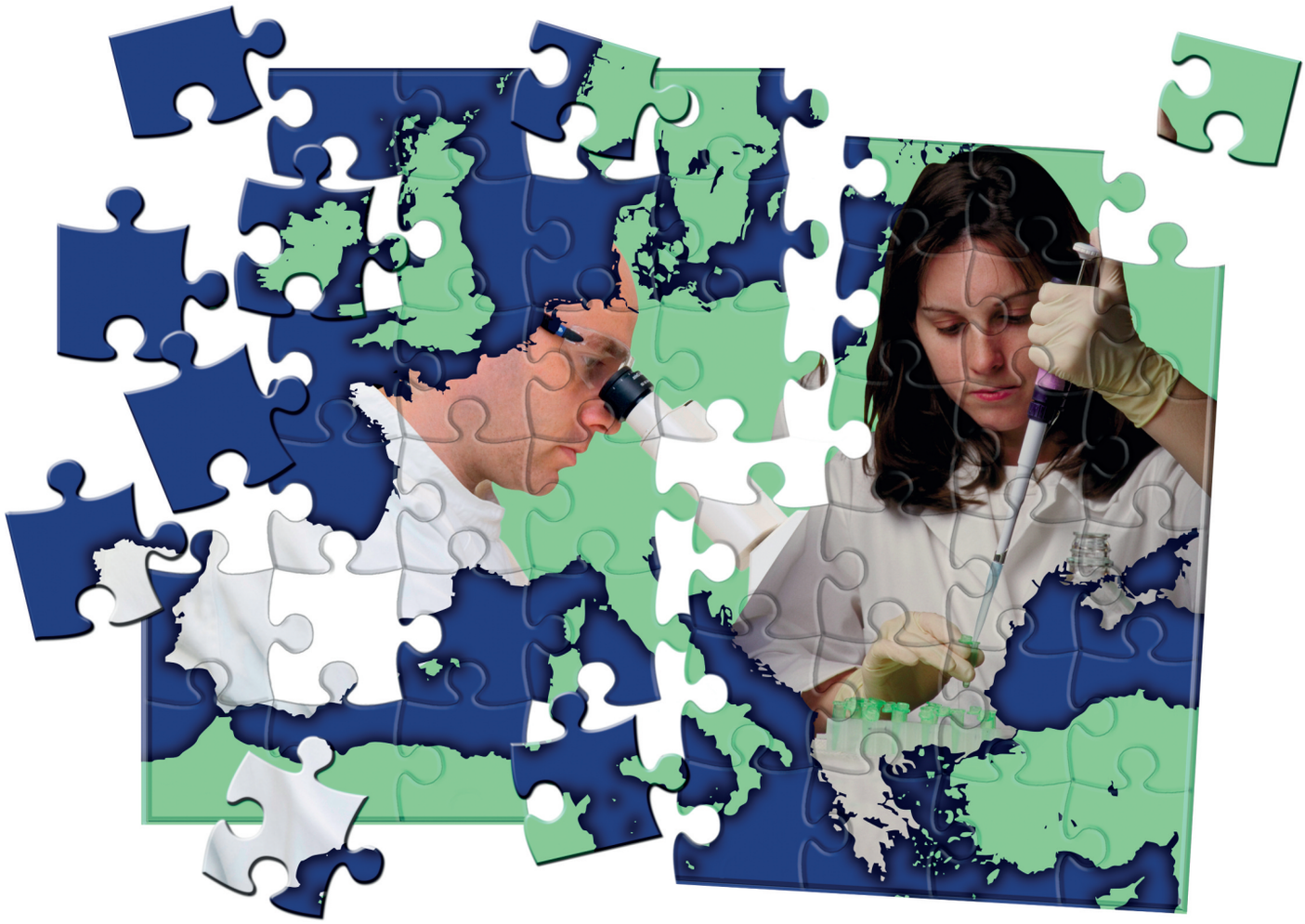
Translating good science into new treatments

Hannah Brown

Europe has money, human resources and a basic-science base that produces world-leading cancer research. Why, then, aren't these assets being translated into clinical advances?



With a list of research interests that includes several types of vaccine against the carcinogenic human papillomavirus, and a group that has produced candidate products waiting for clinical testing, Lutz Gissmann, a professor in the Division of Genome Modifications and Carcinogenesis at the German Cancer Research Centre in Heidelberg, was expecting to have no trouble translating his basic research findings into clinical developments.

But despite a firm emphasis on such translational research from his institution's management, Glissman has found organising phase I clinical tests of promising vaccine candidates far from easy. His frustration is palpable. "There is a lot of high-quality basic research in Europe, but we are missing the bridge to bring good ideas from the research lab to the clinic," he explains. "We need to run phase I clinical trials because, unless we do, we can't proceed into phase II – and big pharma will not be interested."

So if he has institutional support and good ideas, what is holding up Glissman's research? "Funding, funding, funding," he answers. "Not enough funding, and that which does come is at the wrong position." Glissman says the European Commission, the executive branch of the EU, is partly to blame for this unfortunate situation. Its excessively complicated grant application process is laden with burdensome regulations, generating a lot of hard work for scientists seeking financial support, and frequently rewarding their efforts with failure. "It's good money but it is tough to get," he says. But the main problem behind the financing gap for translational studies, claims Glissman, is that while in the US, small to medium-sized biotechnology companies take on promising product candidates at an early stage, in Europe they are reluctant to do so.

On the surface, at least, entrenched attitudes to financial risk on either side of the Atlantic seem to underlie this impasse. According to Tomas Jonsson, who works in the Enterprise Directorate of the European Commission on issues to do with biotechnology firms, companies in Europe are risk averse because it is more difficult to raise capital here, so they are less likely to invest in very early-stage products. But this, he says, is not the full story.

An October 2007 meeting at the European Medicines Agency, where pharmaceutical and biotechnology companies were invited to share their opinions on barriers to product development, drew out deeper concerns with the European research process. Rather than cultural differences being the obstacle to investment, there seems to be a more fundamental problem with cross-border research: fragmentation at almost every level of the process among EU Member States.

A heterogeneous mix of 27 nations with different research standards, equipment, infrastructure and policies, Europe is by no means a natural candidate for harmonised research efforts. And although by encouraging cross-national collaborations, the €50bn budget for science that is channelled through the central European Framework Programme (FP) has forced scientists to look outside their national borders for research partners to receive a share of EU funding, the bureaucratic and practical barriers to such work mean it rarely achieves what the Commission and the scientists had hoped.

This situation is not only professionally unsatisfying for scientists, but cancer outcomes are also lagging behind as a result. Jonsson explains: "Europe has academic excellence in pharmaceuticals and biotechnology, but there are problems trying to commercialise these. We don't necessarily need more research or the capacity to invent new biopharmaceutical drugs, but we do need to make it a bit smoother to get to the point where products can go through clinical trials and be commercialised. This requires improvements in finance, the patent system, and in collaboration between academics."

Sadly, an extension of the fragmentation problem within the EU's governing structure itself means these issues are extremely challenging to solve. Translational research cuts across the disciplines of healthcare provision and biomedical research – responsibilities that are inconveniently distributed between national governments and central European power. Politicians juggling the complex issues of national sovereignty and effective supranational government are careful not to impose too much top-down regulation on Member States wary of giving away their national flexibility in healthcare. But where science is concerned, unless there is a way to make a more coherent and less patchy research framework across the continent, it will be extremely difficult to address the fact that few, if any, cancer centres are sufficiently large to deliver multidisciplinary care and to undertake the kinds of trials that are now necessary to advance cancer research.

There is another driving factor behind the recent awareness of the need to better coordinate research across the continent: the departure of the pharmaceutical industry to more profitable and less bureaucratic shores. "Pharmaceutical companies are

Fragmentation at every level of the research process is holding back the development of new products

"We need to link centres of excellence in basic science and clinical areas to harmonise infrastructure"

moving from Europe to the USA," explains Ulrik Ringborg, a professor in oncology and pathology at the Karolinska Institute in Sweden and head of the Organisation of European Cancer Research Institutes, who is advocating for a formalised network of cancer research centres in Europe as a way to increase what he terms "critical research mass" (see also Cover Story, p4). "When we ask them why they are moving, they say they want better collaboration with academia in Europe," he adds. "Specifically, they want long-term collaborations on translational research, drug development, and personalised medicine."

So, if Europe is to continue to make significant contributions to the advancement of cancer care – and attract the necessary funding from industry – politicians and scientists alike are now realising that something has to be done to coordinate cancer research more effectively. What is more, according to Ringborg, since current trends predict that more and more clinical trials will focus on increasingly selected patient groups, requiring large multinational collaborations and the coordinated funding to support them, there is an urgent need for some common ground rules on standards for data collection, tissue storage, and sampling. But what form this coordination should take is far from clear. The problem is, while all stakeholders are at last in agreement over the scale of the problem fragmentation poses, there has not yet been a successful effort to implement solutions. Though not for want of trying.

Defining the problem

Efforts to tackle the fragmentation issue in cancer research first found a high-level champion in 2001 when European Enterprise Commissioner Philippe Busquin brought together European cancer research managers and top cancer researchers in a meeting aimed at bridging the research performance gap between the US and the EU. As a result of these discussions, the European Cancer Research Managers Forum was set up to create "a European vision regarding cancer care and research." It is currently headed by Richard Sullivan, a professor at the London School of Economics, and formerly Director of Clinical Programmes at Cancer Research UK.

Part of the organisation's work has been a series of ongoing studies focusing on defining a set of criteria for what constitutes a 'comprehensive cancer research centre' – a research institution of sufficient size and diversity to deliver multidisciplinary care to a large patient population and bring together basic scientists and clinicians in the quest to advance new treatments through clinical testing. According to Sullivan, while there are several such centres dotted across the EU, the lack of classification criteria means other centres are not necessarily aspiring to the accolade, so innovation is somewhat stalled. Creating a labelling system, he reasons, would generate a methodology to improve the centres in Europe.

Underlying the proposed accreditation system is the rationale that the main function of comprehensive cancer centres is innovation. Ringborg is also an advocate of the power of recognising the unique situation of these institutions: "In order to be innovative you need cancer care of very high quality along with integration with research," he says. An accreditation system developed by the Organisation of European Cancer Institutes, which he heads, is now in the final phase of testing. "We will soon have methodology available for analysing and benchmarking the centres," he says. The hope is that the act of benchmarking centres as higher quality will create harmonisation and stimulate collaboration.

But this plan is fraught with difficulties. There is a lot of disagreement over what constitutes a cancer centre. "We have a kind of mix and match approach," says Sullivan of the current system of classifications. And he cautions that a comprehensive cancer centre 'club' is only a useful concept if it solves some of the other problems in cancer research – specifically funding. "It has got to have a raison d'être," he says, "otherwise it is a waste of time. If it is about lobbying for money from the Commission and getting money into trans-European research projects, then fine, but otherwise not. You don't want researchers focusing on accreditation, you want them to do the research."

There is further doubt – including from Glissman – over whether such a classification system will actually add anything to the numerous well-run and large centres performing this function already. However, according to Ringborg, such administrative discussions are an important precursor to solving another of Europe's key fragmentation-related issues: lack of critical mass. He has been strongly advocating for a formalised comprehensive cancer centre network for several years, because he believes it is a necessary step to reflect the changing climate in cancer research. "If you go 10 years back in time, many people in cancer centres thought that their institution was good enough,

big enough, and that they could do research well enough. But that has changed," he says.

"We now need to link centres of excellence in basic science and clinical areas in order to harmonise infrastructure: biobanks, patient data registers, and so on. People agree very well that we should collect biological materials in the same way that we should have technical platforms producing results that can be compared between different centres, that we should have patient data registers that can also be compared and that we should be able to harmonise outcomes. But the problem is mainly economic. We are talking about infrastructure in 15 different areas," he says.

Convincing the commission

The reasoning behind Ringborg's argument seems to have hit the mainstream in Europe's cancer research community. Since 2005, the International Agency for Research on Cancer has been pursuing an initiative called Eurocan+Plus aimed at better coordinating cancer research and care in Europe by thrashing out some of these issues. Recognising that cancer research in the EU is fragmented and frequently duplicative, the project was set up in 2005 to identify specific barriers to collaboration and ways to overcome them. After two years of intense consultations, the final report of the EC-funded study identified six areas in which cancer research was being held up and chief among these is the issue of fragmented infrastructure, funding and priorities.

While the results of Eurocan+Plus have yet to be made public, many of those who were involved in the initiative have seized on the findings and are already pushing the agenda forward with the hope of winning the financial and political support of European Commissioners for rapid change.

In November last year, just as Eurocan+Plus' findings were starting to filter through to researchers and managers in the EU, 19 of the most influential cancer centres came together to debate the next steps. The result of their deliberations was a document entitled the Stockholm Declaration, coordinated by Ringborg along with Julio Celis, director of the Institute of Cancer Biology at the Danish Cancer Society, calling for immediate action to create a network of basic and clinical research centres to start the process towards greater cooperation and harmonisation across the EU. One of the key tenets of the Declaration is that, because the infrastructure already exists, visible improvements should be possible within a few years.

Perhaps the most important outcome from these community-wide discussions about cancer research, says Ringborg, is that for the first time, all stakeholders in European cancer research seem to have a common position on the challenge of improving research outcomes. And this unprecedented unity should help push the Commission into supporting the sentiments of the Stockholm Declaration and Eurocan+Plus. He cautions, however, that solving the fragmentation problem still presents a bit of a catch 22 situation. It is a necessary step to ensure funding from industry, but a large injection of cash is needed first to glue these networks together. "What will be costly is the next step," he says – actually bringing about change. He believes the final sum could amount to €15–20 million per year over a number of years. "We are talking big money," he says. Time will tell whether this need for substantial investment is, as with many pan-European dreams, too great a barrier to overcome.

THE STOCKHOLM DECLARATION

Signed by 15 leading organisations from 10 European countries, the Stockholm Declaration sets out a shared vision and commitment to tackle the fragmentation of Europe's cancer research efforts in order to "accelerate the translation of basic discoveries into clinical applications" and "improve diagnosis and care of cancer patients".

The signatories commit themselves to work towards "a collaborative platform comprising leading CCCs and basic/preclinical research centres in Europe" as the only possible way to reach a critical mass and sustainability necessary to innovate and deliver in all areas of cancer research.

While membership of the collaborative platform will be limited to centres fulfilling certain criteria, the Declaration signals a commitment to help bring in new insitutions by disseminating knowledge and strategies that would help them fulfill the membership criteria.

The Stockholm Declaration was signed by:

Belgium: Institut Jules Bordet (Dominique de Valeriola), **Denmark**: Institute of Cancer Biology, Danish Cancer Society (Julio Celis), **France**: Institut Gustave-Roussy (Thomas Tursz), Institut Curie (Sergio Roman-Roman), **Germany**: German Cancer Research Center, (Otmar D. Wiestler), **Italy**: Alliance Against Cancer (Angelo Paradiso), European Institute of Oncology (Gordon McVie), Fondazione IRCCS Istituto Nazionale dei Tumori (Marco Pierotti), **Netherlands**: Erasmus University Medical Centre (Alexander Eggermont), the Netherlands Cancer Institute (Anton Berns), **Norway**: the Norwegian Radium Hospital Comprehensive Cancer Centre (Anne-Lise Börresen-Dale), **Spain**: CNIO (Mariano Barbacid), **Sweden**: the Karolinska Institute (Ulrik Ringborg), **UK**: CRUK Cambridge Research Institute (Bruce Ponder), Christie Hospital Manchester/Manchester Cancer Research Centre (Chris Harrison), University of Oxford (David Kerr)

Source: The full text of the Stockholm Declaration was published in Molecular Oncology (2008), doi:10.1016/j.molonc.2008.03.004