Currently health services in Europe face the seemingly insurmountable challenge of funding trastuzumab (Herceptin) within their limited budgets for women with early stage breast cancer. Martine Piccart-Gebhart (Institute Jules Bordet, Brussels, Belgium) believes we would not now be confronting this huge financial burden had a translational research component been introduced upfront to trastuzumab trials. Studies suggest that only half of HER-2 positive patients with advanced breast cancer benefit from trastuzumab, and the same probably applies to the adjuvant setting, yet all patients are being offered treatment.

"With more extensive translational research in adjuvant trials, we might have identified gene signatures associated with clear benefit or failure," said Piccart-Gebhart, speaking to the European Journal of Cancer earlier this year. "It’s a lesson in the way we design and conduct trials. We only have one opportunity!"

Fatima Cardoso, who works with Piccart-Gebhart at the Jules Bordet Institute and is scientific director of TRANSBIG, believes important lessons can be learnt from trastuzumab in the way trials are designed and conducted. "We’re fast realising that we can’t prescribe every new drug to every patient and that we need to understand exactly who will benefit. This can only be done by including translational research in all studies. Without this many scientific opportunities will be lost," says Cardoso.

Mitch Dowsett (Institute of Cancer Research, London), faced an organisational nightmare, when he returned to do a retrospective biomarker analysis of the ATAC study data—a trial which had examined the role of anastrozole versus tamoxifen as adjuvant endocrine therapy for 5880 postmenopausal women with breast cancer at 381 centres in 21 countries. In the biomarker study, presented last December at the San Antonio Breast Cancer Conference, Dowsett explored the relationship between oestrogen, progesterone and HER-2 receptor status with recurrence. Results show higher oestrogen and progesterone levels are associated with better outcomes on both tamoxifen and anastrozole, and trends for HER-2/neu negative tumours to respond better than positive tumours.

“ATAC recruited patients in the mid-90s when translational research just wasn’t included in studies,” recalls Dowsett. “To get our data we had to go back to patients for individual consent, and get permission from ethical trial committees at each centre. It was a lot of work, which I’d never go through again.”

Altogether the team managed to trace around one third of the samples, largely from UK institutions. “Issues remain about whether our data was significantly powered and whether just reviewing samples from the UK is representative,” says Dowsett. “Had we collected the material prospectively and asked the right questions upfront we’d now be much more sure about our conclusions.”

Recently there has been a paradigm shift in the culture of cancer trials—it’s no longer considered ethically acceptable to support studies that do not include a translational research component. “I firmly believe that if you are using patient material you’re morally obliged to try to achieve maximum output for your study, and that can only be achieved by including translational research” says Fred Sweep (EORTC Pathology Group and University of Nijmegen, Netherlands).

At the European Organisation for Research and Treatment of Cancer (EORTC), the Translational Research Advisory Committee, was launched recently to review all EORTC protocols to ensure that a translational component is considered. “We believe that it’s better to do one or two trials with a translational cancer component, than 10 trials without,” says Piccart-Gebhart (President EORTC).

Many pharmaceutical companies are also introducing a requirement for translational research. “Biomarkers are firmly embedded into our early development philosophy – it lets us loose the losers early,” says Andrew Hughes (Translational Science Department, AstraZeneca). “The traditional
view has been that unless you see clinical activity you don’t proceed, but we’re now much more interested in the effects on biomarkers.”

Industry was at first concerned that subdividing markets as a result of translational research would prevent companies from recouping their initial investments. “This just hasn’t been the case,” says Hughes. “Increasingly we’re finding that if you establish a targeted population who’ll benefit from a treatment, health authorities are willing to pay a premium price.”

With the advantages of scale afforded by its 500 million population, and 1.6 million new cases of cancer each year, Europe offers enormous potential to lead the world in translational cancer research. While no one doubts the enthusiasm and vision of European investigators, serious questions remain over whether Europe is organizationally up to the task.

“In Europe translational research is complicated by the existence of 25 heterogeneous member states, with no central co-ordination of cancer policy,” says Gordon McVie, (European Institute of Oncology, Milan). He adds that most countries, (bar a few notable exceptions) don’t even have a national cancer plan, let alone a national cancer research institute. Huge disparities exist between the funding of cancer research among member states. In 2002–2003, three EU countries spent more than €100 million, nine more than €10 million, and ten less than €1 million.

“Member states are mostly driven by their short term agendas of managing health care systems, which is total suicide because if they don’t have the vision to invest in research they’ll never have an impact on mortality,” says McVie.

In attempting to get TRANSBIG underway, Cardoso knows all too well the logistical problems of organising translational research across Europe. “Instead of getting on with our science we’ve had to solve many legal, ethical and financial problems on a country by country basis,” says Cardoso. “All the small issues add up and have led to huge delays in getting the first trial (MINDACT) underway.”

TRANSBIG – a research network of 39 world-class institutions in 21 countries – was launched three years ago to accelerate the incorporation of new technologies into breast cancer clinical practice. The organisation has the advantage of being linked to the existing network of groups around the world that conduct clinical breast cancer research – the Breast International Group (BIG).

The first project MINDACT (Microarray for Node-negative Disease may Avoid Chemotherapy) – a 6000 patient-trial which enrolled its first patient in February 2007 – is using new microarray technology (involving the 70-gene prognostic signature developed at the Netherlands Cancer Institute), together with traditional clinical-pathological assessments to better classify node-negative early breast cancer patients into high and low risk of relapse, and hence determine those who need adjuvant chemotherapy and those who can safely be spared treatment.

Funding MINDACT has been one of the biggest challenges facing the TRANSBIG team.

Unlike the USA, where the National Cancer Institute (NCI) provides centralized ring-fenced funding for cancer research, European cancer investigators compete with investigators from all other scientific fields for Framework money. In addition, the EU imposes further restraints, where it will only finance new organisational structures, and not the trials themselves. “In order to achieve EU funding we had to demonstrate that our initiative was completely new and create TRANSBIG out of BIG, which was completely surreal. And to get any funding for further translational research it seems we might need to create more totally new organizations. It all causes totally unnecessary levels of complexity and bureaucracy,” says Cardoso.

MINDACT was awarded €7 million from Framework 6, leaving TRANSBIG with a budgetary short fall of €28 million. Finding additional funding has proved problematic. Frameworks provide the only pan-European funding available for cancer and individual EU countries are reluctant to invest in European projects, preferring to allocate money to projects in their own countries. “In consequence, we’ve been forced to bring in commercial partners, which has brought complexity to the trial design and forces us to share the legal rights to any data generated,” says Cardoso.

Contrast this to the Trial Assigning Individualised Options for Treatment (Rx), TaylorX, a trial running in the USA that utilizes a similar diagnostic test, (measuring the expression of 21 genes in breast cancer, developed by Genomic Health Inc.), to assess the risk of recurrence, compared to traditional clinical assessment in over 10,000 women recruited from 900 sites in the USA and Canada. The trial, which started recruitment in May 2006, is entirely funded by NCI.

A pan-European survey to analyze the way cancer research is funded across Europe, published in the Public Library of Science’s (PLoS) Medicine in March 2005, shows the average public spending on cancer research was €2.56 per person in Europe, compared with €17.63 per person in the USA. Additionally, as a percentage of GDP, the USA paid four times more on cancer research than Europe.

Richard Sullivan, chair of the European Cancer Research Managers Forum, believes the latest survey, to be published shortly, reveals an evolving picture. “Since our last survey cancer research productivity has gone up in Europe. We’re now comparing more favorably with the USA where science budgets have shrunk by 10–12% as more money is directed to defense programs.”

One of the biggest logistical challenges facing MINDACT, says Cardoso, has been that the microarray techniques require frozen samples to be sent to Amsterdam from participating institutes around Europe.

Europe faces huge problems with tissue samples in each centre governed by national laws, making it almost impossible to organize research across national boundaries. “For some countries with strict laws it just hasn’t proved practical for them to participate in MINDACT,” says Cardoso.

There are many legal differences. In the Netherlands, for example, patients have to explicitly “opt out” of contributing material to tissue banks; while in Sweden they have to “opt in”. Some countries allow the shipment of slides and not tumour blocks, while others will allow RNA to be transported, but not whole tumours.

With data protection countries vary over whether they consider data which is anonymous at the level of the controller, but coded, should be considered personal or not.
Even ownership of biological material, varies between countries, with surgeons, pathologists, patients or even institutions having rights. “With tissues used for commercial gain, real issues could arise as to who should receive the royalties,” says Ian Stratford (EORTC Research Advisory Committee, University of Manchester, UK).

“There are also technical issues about ensuring the reproducibility of high quality clinical samples, and then linking them to data about long term clinical follow-up,” says Alexander Passioukov, head of the translational research unit at EORTC.

The reality of European cancer research is that many problems are being overcome by “good will and friendship”, rather than strictly obeying the letter of the law.

“We need to have the foresight to sort these issues out once and for all,” says Manfred Schmitt (Technical University of Munich, Germany). “So long as we all have different national laws, true collaborations just won’t be possible.”

TuBaFrost, one of the first projects to start addressing issues around exchanging tissue in Europe, adopted the “home-country” principle to solve problems relating to diverging national regulatory regimes. Here tissue may be used for research in the country where it is sent in “the context of the laws” of the country in which it was collected, even if the recipient country has other regulations in force.

“What’s need is the introduction of a European directive to override national laws,” says Passioukov. “If we don’t sort these issues out soon it will lead to many lost opportunities.”

A further obstacle facing translational research, says Cardoso, is lack of recognition of medical qualifications between European countries, limiting the mobility of both researchers and clinicians. Medical oncology, for example, is not recognized as a discipline by all European countries. Cardoso herself, for example, initially trained as a medical oncologist in Portugal, but had to retrain for a year in internal medicine when she moved to Belgium.

Research is restricted by shortages of MD-PhDs. Unlike the USA where physicians can undergo scientific training during their education, research is rarely part of the medical curriculum in Europe. Italy, for example, has no tradition of clinicians doing both science and medicine. “We need to take the heat off clinicians and allow them to take time to do PhDs and work a third of their time in the lab,” says McVie.

Those clinical scientists making it through face “financial penalties” for choosing research over clinical practice.

Europe has placed itself at a further disadvantage through the introduction of the EU Clinical Trials directive (EUCTD), which hinders all forms of cancer research. “The directive is interpreted differently in each member state, making it difficult to implement multi-national trials,” says Cardoso.

A survey of directors and senior staff in eight “Clinical Trials Units”, published in European Journal of Cancer, shows that the EUCTD has doubled the costs of running non-commercial UK cancer trials, and is delaying the start of trials by between 6 and 12 months.

Many believe the issues facing translational cancer research can only be resolved by achieving a stronger, more consistent voice for cancer in Europe. This, they argue, can only be achieved, through the creation of a centralised cancer organisation for Europe, run as a “one stop shop”, along the lines of NCI in the USA. “It’s vital to bring the top cancer scientists in Europe together to achieve a cross fertilisation of ideas,” says Harry Bartelink (Chairman of Radiation Therapy at The Netherlands Cancer Institute) “Only then do we stand any chance of reaching a critical mass that can compete with the USA.”

“Harnessing the different ways European people have of looking at research questions would allow blue sky thinking that helps them think out of the box,” says Stratford.

Cardoso agrees: “There’s a need for central co-ordination to eliminate duplication and prevent the wastage of resources. Coming together would allow us to complete trials in record time. We have to stop funding small projects that’ll never achieve answers. We need to appreciate that the future is to think big and collaborate.”

A number of candidate institutions, such as the EORTC, European Association for Cancer Research and Federation of European Cancer Societies (FECS), are already in existence that might provide the basis for a European institution. Others believe that Eurocan-Plus, a new initiative funded by Framework 6 to run a feasibility study looking at networking patients for large scale trials, might provide the way forward. Debate also exists over whether the resulting organisation should be a bricks and mortar institution or a virtual institution.

John Smyth, president of FECS, doubts that a physical centre would prove practical. “If you put all your best scientists in one centre, it’s detrimental to the training of new talent in other institutions,” he says.

Sullivan has a sense of déjà vu. “Two earlier attempts to create a European organisation hit the wall due to lack of money and internecine war fare,” he says. “Every country first needs to build on their own translational research capacity to create strong cohesive national networks.”

A new organisation could be used to play an active lobbying role to place translational research higher up the EU’s funding agenda. There is also an urgent need to get the message across to the public. “The people of Europe need to be made aware of the potential for microarrays and proteomics, and to understand that translational research avoids excessive chemotherapy, and reduces the wait for the outcome of clinical trials,” said Bartelink.

A lack of patient-advocacy and public participation, says Cardoso, hinders cancer politics in Europe. “In the USA Patients’ groups are active, and have the power to make politicians listen to them. In Europe, patients are much less involved, there’s just not the tradition of people rolling up their sleeves and getting on with the job themselves. Europeans are only just becoming aware of the power of patient advocacy,” says Cardoso.