# How Europe is taking on the big biobank challenge

Marc Beishon

Cancer research is being held back by a shortage of high-quality, well-documented biological specimens. However, convincing hospitals to pool their specimens in a regional, national or international biobank is not always easy, adding to the logistical, technical, ethical, legal and IT obstacles of such a venture. Little by little, it seems, Europe is getting there.

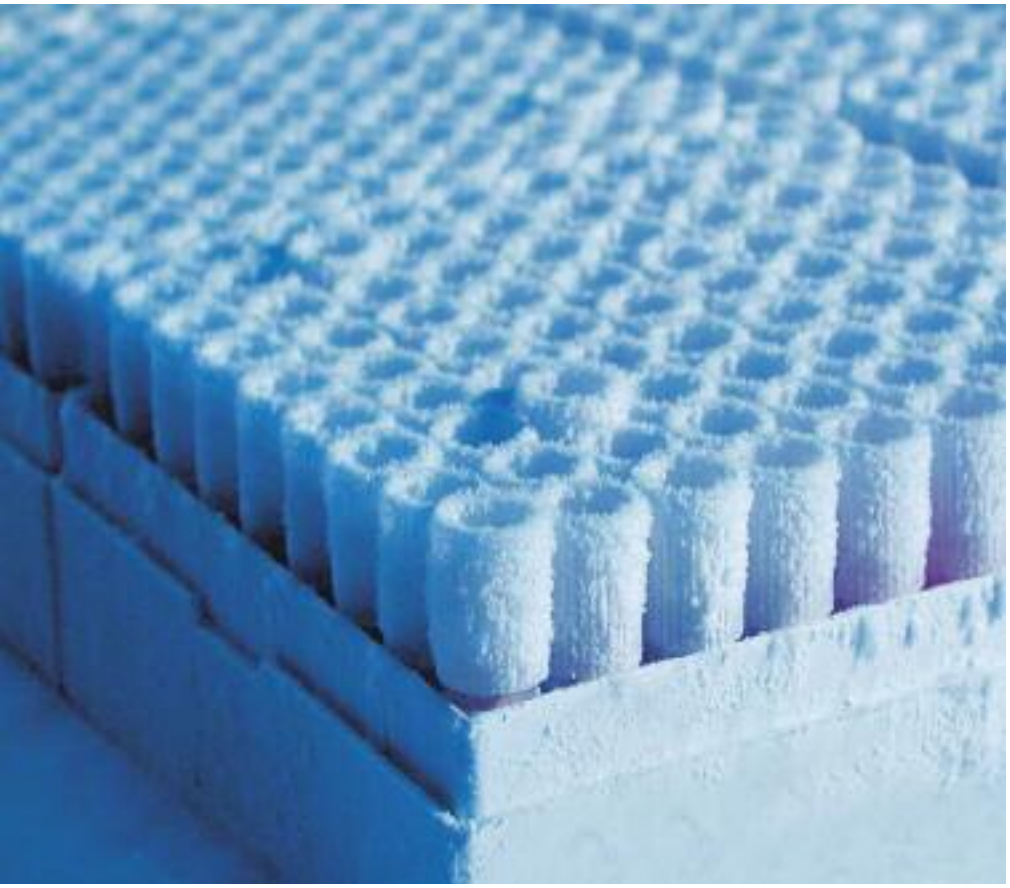
Techniques such as molecular analysis have the potential to lay bare many of the deepest secrets of cancer. But realising that potential requires access to large-scale, high-quality repositories of human biological material, linked to well-documented clinical histories. Known variously as biobanks, biospecimen repositories and tissue banks, there is now a great deal of activity in setting up the sort of standardised libraries of human samples that are necessary for keeping pace with the demands of researchers.

The terminology can be confusing – tissue banks are also used to store material used in transplants, while the term 'biobank' is now being applied to a new generation of population repositories, such as the UK BioBank, which will be taking blood and urine samples randomly from as many as 500,000 people, with a view to identifying genetic and environmental predisposition to a range of diseases, including cancer. There are also population biobanks dedicated to cancer research, but there are more disease-oriented banks in cancer, where a variety of specimens are taken during diagnosis and treatment. The term 'tumour bank' most accurately describes this type of repository, which often also collects unaffected samples for use by cancer researchers. But the various terms are used interchangeably, and 'biobank' seems to be the favoured word for any type of facility.

There is of course nothing new about collecting specimens – that goes back to the dawn of medicine – and for cancer there are probably thousands of banks around the world of various sizes and of vastly varying organisation and quality. Until recently there has been little concerted effort to lay down standards for tissue collection and storage for research purposes, or to unite collections for greater power in conducting studies. But the uses for well-organised biobanks are now compelling, and include the identification of biomarkers, identification and validation of targets in drug development, and linking disease-based resources with population biobanks and registries.

And while doors have opened with the introduction of techniques such as fluorescent hybridisation and tissue microarrays and the spectacular growth and potential in fields such as genomics and proteomics, others have been closed or are hard to shift, especially the minefield surrounding issues such as informed consent and the uses to which tissue can be put, which differ widely around Europe. Major scandals such as the retention of children's organs by hospitals in the UK without the knowledge of parents have, though, led to new regulations governing the use of human tissue in the UK and at European level, but it will be some time before rules and public views about biobanking are harmonised around Europe, if at all.

That has not stopped the launch of one of the most ambitious programmes yet in world biobanking – the Biobanking and BioMolecular Resources Research Infrastructure (BBMRI, www.biobanks.eu), one of six priorities for biological and medical research identified by the European Strategy Forum on Research Infrastructures. The BBMRI is coordinated by Kurt Zatloukal, professor of pathology at the Medical University of Graz, Austria; its



Frozen assets. A tray of specimens from the BioResource-Med tumour bank in Graz, Austria

preparatory phase is being funded by the European Union's Seventh Framework Programme.

## European infrastructure

"It is important to note that this is the first time the European Commission has considered research infrastructures for life sciences, and that this is different than other European research projects, where there is participation from some member countries but no coverage for the whole of Europe, as has to be case for research infrastructures," says Zatloukal. The aim, he says, is to include as many existing biobanks and new projects as possible, in order to achieve sufficient sample numbers and appropriate coverage of Europe's populations. At the time of the project's kick off, in February this year, there were 52 project partners and more than 150 associated organisations from 21 countries – most with biobanks, some with other biological resources and tools.

The overriding aim is to generate much larger sample sizes to power studies, and while the BBMRI will cover all diseases, cancer will be a major application. But the need for the project goes much further, adds Zatloukal. "Currently, if you perform a study within a multinational collaboration, it is very difficult to know the legal and ethical contexts across Europe pertinent to the project partners. If we help establish this knowledge and provide guidance, everyone will benefit. Furthermore, even if you identified the right biobanks and got through the regulatory hurdles, you still have the problem of combining different samples often collected by following different protocols, which may be a severe problem for your study. Our aim is also to harmonise quality standards to ensure materials can be better combined in research."

These collaboration and quality issues are echoed at country level, and any pan-European initiative will also need the support of national programmes to help participating centres to raise standards to the necessary levels. In Austria, Zatloukal says that Graz has had one of the better organised biobanks for some time (called BioResource-Med, www.bioresource-med.at). "We provide a centralised pathology service for a whole region, with good standardisation and access to patient medical data, and samples have been processed in one institute under the same conditions for more than 24 years. We have tissues of nearly 800,000 people and 3 million diseased organs. That's one of the largest in Europe – although we do not know for sure, as there is no proper inventory. Improving knowledge of existing biobanks in Europe is one of the early aims of the BBMRI."

"Until recently there has been little concerted effort to lay down standards for tissue collection and storage"

Just a few years ago most cancer biobanking activity was isolated and far less organised than in Graz. Many collections have grown up as a project of certain researchers, and stored in everything from optimal conditions with proper documentation down to filing cabinets in a dusty basement corridor. Indeed, it is not unusual for some banks to be destroyed or simply forgotten when a researcher dies or moves on. The emergence of more organised structures has been led by a number of dedicated people, pathologists in the main, but also others such as molecular biologist Peter Riegman, who in 2001 became tissue resource manager for the Erasmus Medical Centre Tissue Bank, part of the molecular diagnostics unit of the Department of Pathology, at the Erasmus Medical Centre in Rotterdam.

"There was a biobank run by a pathologist on a volunteer basis, but it was not professionally organised," says Riegman. "Here I found an environment where I could use my research expertise, in combination with my informatics skills, and found a strong advocate in Wolter Oosterhuis, the head of the Pathology Department at the Erasmus Medical Centre, whose main research interest is germ cell tumours, and who had established and explored a bank for testicular cancer. We got financial support for a formal bank for the department, but I found there was little information then about how to run one."

Since then, Riegman has built a local bank in Rotterdam and also become heavily involved in the international biobanking community, in particular leading TuBaFrost, a project set up in 2002 with EU funding, and put forward by the Erasmus Medical Centre together with the EORTC (European Organisation for Research and Treatment of Cancer) and the OECI (Organization of European Cancer Institutes). TuBaFrost provides a central European database specifically of frozen tumour tissues, with participants that have made major contributions to EORTC trials. It is now under the wing of the OECI, to be used as a basis for a cancer research platform.

At Erasmus, Riegman says he now collects about 3,000 frozen samples a year, and 2,500 are given out, with 15,000 as a steady state. Anonymised clinical data are available for some projects. He also banks the routine pathology archive of formalin fixed and embedded tissues, which has accrued about 2 million blocks over the past 10 years, and he is participating in a national programme in the Netherlands, which will involve integrating electronic patient records. Together with chairing TuBaFrost and involvement with other forums, Riegman has one of the best overviews of biobank standards and how regulation on patient confidentiality and consent differ around Europe.

## Centralised or networked?

While countries such as the Netherlands are still in the process of formalising national biobank structures, others have made substantial progress. Two models appear to be emerging for country-level cancer tumour banks in Europe – a national central repository, as in onCore UK, and a federated network with no central bank, as run by the Spanish National Cancer Centre (known as CNIO). The latter is seen by some as more challenging to run – collaboration involving remote locations often being difficult for any project. But the Spanish National Tumour Bank Network is now known in biobank circles as a great success, not least because of its director, Manuel Morente.

"As a pathologist, tissue collection, storing and custodianship have been an important part of my clinical activity for more than 20 years, and work with Spanish lymphoma study groups showed me how important well-preserved samples and associated data are for research," says Morente. "In 2000 I was invited to take a position in the new CNIO to create a collaborative network of hospital tumour banks, and I believe it is the first of its design in the world."

The CNIO networks both basic and applied researchers – "It was my first direct contact with basic science groups and I saw how difficult it is for them to obtain high-quality samples," he says. "Every Spanish hospital is invited to collaborate, and our network is open to the entire scientific community. I feel it

### QUESTIONS ONLY BIOBANKS CAN ANSWER

- Is the genetic change I have identified in cell lines expressed more in cancer than in normal tissue?
- At what stage is my gene expressed – early- or late-stage disease?
- Is my gene of interest expressed in one type of cancer or lots of types?
- Can I detect my object of study using paraffin material as well as frozen?
- Can I find a molecular or protein pattern that correlates with clinical outcomes or response to therapy?
- Can I subdivide my chosen cancer type on molecular grounds better than I can with conventional pathology?
- Can I predict from a blood sample whether someone is likely to develop cancer?
- Can I detect from a blood sample whether my patient is going to relapse?
- Is the molecular biology of a particular type of cancer related to inherited genes, the age of the patient at diagnosis or exposure to a particular agent?

*Source: Gerry Thomas, director of scientific services, Wales Cancer Bank*

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works because of the simplicity of the design and respect for the role of hospitals and pathologists."

Banks and samples remain with the hospitals, but Morente says they are now following the same procedures and quality control policy under central coordination using a computing platform developed for the purpose. "The role of our coordination office is to promote, coordinate and harmonise procedures – and to form relationships with our end users, the researchers. But the initial challenge was to obtain cooperation from pathologists and clinicians, because there was no previous expertise in biobanking in Spain."

Any Spanish cancer research team can now request samples from the National Tumour Bank Network. They send a summary of the project, outlining the funding sources, along with a completed tissue request questionnaire. "We also offer an advisory service to help researchers, mainly in non-clinical groups, to design better projects," says Morente.

Once the participation of the National Tumour Bank Network has been approved by the ethics and scientific committees at the CNIO, Morente's team then finds sufficient cases in the central database that suit the project and arranges to send them to the research team.

"We carry a mirror of each hospital's database of tissue samples – these make up our central database," he explains. "Hospitals receive details of the project, the principal investigator and the funding agency, and it is their choice whether they collaborate or not. If they do, they send the samples to the central office where they are checked for quality and anonymised again, if necessary."

The output from the network has been growing. "From 2001 to 2007, we provided support for more than 250 projects, 58 in 2007.

The Spanish National Tumour Bank Network is now supported mostly by central government funds, having proved its worth after getting off the ground through various other funding sources. It has also 'cascaded' expertise around Spain – Morente says four regional networks are now in place that share the principles of the central organisation.

Another measure of the Spanish success is the influence on other national cancer biobanks that are now springing up around Europe, and also further afield. Biobank Ireland, a recent tumour bank networking project for both the Irish Republic and Northern Ireland, is modelled on the Spanish network, and will be bringing up to 11 hospitals into the project. Morente is also involved in a tumour bank platform in Latin America.

In the UK, a model where tumour samples are stored centrally is in its early stages of development. onCore UK, says its chief executive Brian Clark, is unusual in being a standalone, neutral charity. "A traditional way to set up a national resource such as a biobank would be to make a grant to a lead university and ask it to set one up, but after the loss of trust we had in the UK over the organ retention scandal, the funders felt it was important to set up an arm's length, independent organisation – but of course our only source of samples are patients in the NHS."

onCore UK has contracted a commercial firm to store tumour samples, which are collected 'opportunistically' from a network of participating hospitals. "We are taking blood samples, which are processed into constituents such as white cells and serum, and pieces of cancer and also unaffected tissue where possible. We are only taking new materials – I am

Co-ordinator in chief. Pathologist Manuel Morente spearheaded the National Tumour Bank Network in Spain. It uses a centralised IT system and harmonised procedures, but specimens are stored at the hospitals where they were harvested

keen to stress that we are not taking over or replacing existing UK biobanks, but supplementing them. This is not a competitive environment as there just are not enough high-quality samples available for research. It is also a long-term project – there are no quick wins in biobanking. It is a slow and arduous process."

onCore UK is a member of the NCRI (National Cancer Research Institute) Confederation of Cancer Biobanks, a networking organisation in Britain, which aims to share expertise, harmonise standards and assist access, with a pool of samples (it recently announced a portal for searching for samples held by members). Another member is the Wales Cancer Bank, launched in 2004, which is in the Spanish camp as a networked model. Indeed Gerry Thomas, director of scientific services at the Wales Cancer Bank, contends that a centralised approach could cause resentment. "You only have to look around to see that the models that work take the virtual approach, but they do have to be served by a central IT system," he says.

## Promoting participation

Participation in either a networked or centralised model can be difficult to promote. At a European level, Zatloukal comments, "My view is that even more critical than trying to bring together biobanks working on varying standards is addressing the question of why researchers should make their collections available in a European context. There is a strong sense of local ownership by individuals and organisations. We have to say very clearly what the benefits of sharing are and perhaps put forward incentives such as being a preferred partner for future studies or for certain funding."

Riegman also reports problems with TuBaFrost, which he says "is not functioning as well as I would want. People say they are interested, but not many samples are being put forward." He is pleased that the OECI's accreditation initiative for cancer centres plans to use, as a quality benchmark, the requirement that every centre should have a biobank that is involved in international exchange [see also Grand Round, p14].

Clark argues that the success of a biobank is "not the number of samples but the number of outgoing samples and projects supported,"which he believes centralised models are better able to support. He feels that the BBMRI project, though laudable, will be very hard to operate effectively, and considers that onCore UK's independent status and participation in cooperative groups will avoid the problem of lack of 'buy in' from the research community. "I did not want to repeat the lack of cooperation that some decentralised projects have had. I see onCore UK as like our blood transfusion service – a separate organisation that relies on collection in many places and with central storage. It is a trusted partner – but that did not happen overnight."

onCore UK, adds Clark, also has the advantage that the NHS is good at collecting routine patient data, and electronic subsets will be available for integrating with tumour samples. "A limitation of some tumour banks is that associated patient data is just a snapshot, and their ability to collect longitudinal data is very restricted," he says.

There are many other biobanking projects either directly related to or associated with cancer. Smaller groups working on rare cancers have a particular interest in international biobank projects. Riegman mentions EuroBoNet, a cooperative group working on bone tumours, which he has been working with, helping to assemble a virtual bank of tumour specimens and cell lines. Europe's leukaemia research groups are also heading in the direction of pan-European biobanking [see Spotlight, p 42].

Though all this is still at a fairly early stage, Europe is ahead of the US on large-scale cancer biobanking, especially with networked projects, and is likely to remain in the lead for some time. The National Biospecimen Network mooted by the National Cancer Institute in the US is still in a conceptual phase, although a pilot for prostate cancer has been launched and there is activity on

MARIA DIAS

**Information retrieval. Biorepository technician Gemma Bullock removes samples from one of the freezers at onCore UK's centralised storage facility, in Hertfordshire**

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fronts such as best practices for biospecimens and a specimen locator (see http://biospecimens.cancer.gov).

The slow progress in the US has led to advocacy organisations stepping in with their own initiatives. The Multiple Myeloma Research Foundation (MMRF), led by the dynamic advocate Kathy Giusti, launched its own tumour bank in 2005. Having first set up a research consortium among leading cancer centres, such as the Dana-Farber Cancer Institute, the MMRF set about obtaining a significant volume of high-quality bone-marrow biopsies and peripheral blood samples, and says it has created the only resource of its kind in the US.

"It integrates patient tissue samples with corresponding genomic and clinical data, enabling researchers to identify and validate optimal molecular targets for myeloma and drugs active against these targets, as well as conduct correlative studies to determine patients' responses to current and emerging therapies," reports the MMRF.

One recent use of the bank includes a genome mapping programme that reported finding genetic similarities among certain types of multiple myeloma, following analysis of nearly 100 tissue samples. These data were released last December at the same time as the launch of the Multiple Myeloma Genomics Portal, said to be a world first.

Other US groups taking a similar approach include the Lance Armstrong Foundation, which is funding a germ cell tumour bank in Los Angeles for national access, the Inflammatory Breast Cancer Research Foundation, and Mary Ellen's Tissue Bank (also for breast cancer).

## Ethical issues

In Europe, the German breast cancer patient group Mamazone has done something similar, with the founding of the Patients Tumorbank of Hope (PATH). But European advocacy organisations are also addressing key ethical questions governing information, consultation and consent. Getting these right will be key to minimising unnecessary red tape while maximising patient participation.

Europa Donna, the European Breast Cancer Coalition, is canvassing members and becoming involved in national reviews on the use of samples, such as in the UK when the country's Human Tissue Act was consulted on. But this is unusual – a survey of members by Europa Donna revealed that in several countries there is still a system of presumed consent, and many countries do not yet have legislation specifically covering tissue banks. Europa Donna's UK group also ran a campaign to help explain tissue banking issues.

Bettina Borisch of the Institute of Social and Preventive Medicine, University of Geneva, says the public has fears about being "disposed by an authority outside one's own will", and says the very word 'bank' can confer images of property and profit. She stresses, however, that bottlenecks in clinical

## The private banking sector

The commercial sector, of course, also has a strong interest in biobanking. Some firms collect specimens purely for resale to researchers; others are setting up repositories for their own research. There have been many new entrants in the first camp, mainly in the US, but according to Clark of onCore UK, their number is falling. "I believe that is because a biobank is more like a civic amenity – it is difficult to make a commercial model work," he says, adding that onCore UK offers its services to pharmaceutical companies.

AstraZeneca is an example of the second camp. Chris Womack, principal clinical histopathologist in cancer discovery, is very active in biobank circles. "We are looking for biomarkers that will show us proof of mechanism, and we use tissue arrays and immunohistochemical techniques," he says. "A lot of the information is already out there, but we need to build internal confidence in the published data, as well as investigating new targets and markers."

The company works closely with hospitals in preference to buying samples in from commercial suppliers, which Womack says can be variable in quality (and there are still plenty of suppliers – he lists 24 in a presentation). "Quality can suffer if samples have been left too long before being fixed in formalin, or if the formalin penetrates poorly. And hospitals have expertise in pathology and immunohistochemistry we can tap into."

research are worrying groups such as Europa Donna, and they are keen to support well-conducted studies with a high degree of transparency, such as the MINDACT breast cancer trial, which requires analysis of fresh or frozen tissue.

Another important aspect of biobanks is computing and bioinformatics. Biobank projects in Sweden are among the world leaders in the use of technology – for example in 2004 the Karolinska Institute partnered with IBM to build database structures to integrate research projects around the country, and automation such as robotic DNA extraction systems and sample dispensing systems are in place. Sweden also has a large national programme of population biobanks and registries, including the world's largest twins collection, and several long-standing tumour banks.

IBM itself has a strong interest in biobanking – it has developed a biobank information management system designed to integrate research data originating from many sources, and has been running worldwide biobanking summits. It is also one of the sponsors of BioBank Central, a US website (see www.biobankcentral.org), and has started a World Community Grid to provide computing power for analysing the output from tissue microarrays, as manual analysis is another major bottleneck.

Overcoming these bottlenecks will be essential to speeding up progress in cancer research. But an equally important challenge, according to onCore UK's Clark, will be getting the basic research community to shift from non-human alternatives to more relevant human tissues. "They often think they can work faster with other models," he says. Riegman agrees that the red tape for using human tissues is an obstacle. "People can simply give up rather than go through all the paperwork needed for permission to work on samples." TuBaFrost, he says, was originally designed to also support trials, but the narrow permission laid down by the European Clinical Trials Directive has changed its focus to become a more open access model for research on residual tissue left over after diagnosis. National and international lawyers are playing a key role in biobanking. "For TuBaFrost," adds Riegman, "the advice is laid down in a Code of Conduct for residual tissue, that the laws of the country of origin determine what you can do with tissue in another country. Accepting this principal for all human samples as a rule would cut down red tape enormously and also respect the laws from the country of origin and therewith the general democratic opinion of the donors of the country of origin. But people know which countries are 'difficult' and avoid them."

At this stage of the evolution of cancer biobanks, networking among professionals is vital. Morente notes that the most important organisation is the International Society of Biological and Environmental Repositories (ISBER), while a less formal group is the Marble Arch International Working Group, which is a group of international experts in biobanking management, currently with about 20 representatives worldwide.

There is also a growing discipline in the management and science of biobanking, which involves design principles, data protection, quality, long-term storage, identifying new fixatives for tissue, and the many other issues that determine what molecular biology research is possible. Agencies in France have been working on a national standard for biobanks based on existing ISO specifications, which the Marble Arch group is supporting as a possible model for an international standard. As Clark comments, "At present there is no obvious national or international standard against which research biobanks can implement their quality management system." The emphasis now, he says, is rightly on professionalising what has been a haphazard and low-priority area, and also securing long-term funding, dedicated staff and a strategic rather than a project-based purpose.

### LOOKING FOR THE BIG PICTURE

A project that is linking both population and tumour biobanks with cancer registries is Cancer Control using Population-based Registries and Biobanks (CCPRB), an EU Sixth Framework Programme, and one of the largest initiatives of its type. Coordinated by Joakim Dillner, professor of virology and molecular epidemiology at Lund University, Sweden, it has linked large biobank projects with up to 30 years of follow-up and more than 60,000 prospectively occurring cancer cases, with cancer registries that have more than 40 years of population-based registration. There are 18 partners in the project from nine European countries.

Research highlights include a linkage of the Swedish cancer registry and multigeneration registry for assessment of familial risks for many cancers; a number of large-scale association studies within the participating biobanks for familial or sporadic breast cancer and colon cancer; and a linkage of maternity cohort biobanks with cancer registries, which has identified a large study base (more than 1,000 cases and 2 million controls) for intrauterine exposures and risk of childhood leukaemia.

Apart from medical research, the project has helped establish quality standards for linking biobanks and health data registries, and also the first formal graduate school in biobank-based epidemiology, as part of the European Programme in Public Health and Epidemiology. This is organised by the Public Health School at Tampere University in Finland.