Biobanks in Europe

Seeking for Tissue, Funding and Regulations

Photo: www.andor.com

Biobanks come in many shapes and sizes. *Lab Times* talked with representatives of two specialised European biobank networks and a pan-European biobanking infrastructure about the current concerns in the field.

Researchers who, for instance, investigate rare diseases are particularly dependent on sharing of material and data, because these are so difficult to come by. Luckily, there are biobanks, which stockpile precious biological samples for research and medical purposes. In rare disease research, EuroBioBank, a biobank network established in 2001 by patients and scientists, is the first port of call. The network's membership currently comprises 21 biobanks from nine European countries, Israel and Canada.

"Biobanks are embedded in complex networks of research collaborations that span regions and countries. The legal and regulatory frameworks that apply to biobanking are still fragmented, with variation of practice across the different areas of medical research," observed Marina Mora, a founding member of EuroBioBank, who has been coordinating the scientific activities of the network since 2012.

Mora is a lab head at the Besta Neurological Institute in Milan, Italy, and a specialist in neuromuscular diseases. "By seeking professional guidance and applying professional values and culture, EuroBioBank has been able to progress and to contribute to the development of regulations. Through our network, we have also established a basis for international co-operation in rare disease biobanking," she explained.

Clear rules for sample exchange

The organisation supports research activities by providing human DNA, cell and tissue samples as a service to the scientific community. It offers training courses, provides Standard Operating Procedures for sample collection, processing and storage, and addresses ethical and legal issues. About 130,000 samples can be requested via an online catalogue from the respective biobanks. "Sample distribution is governed by the conditions set out in the EuroBioBank charter and standardised material transfer agreements," Mora confirmed. However, despite the efforts of EuroBioBank and similar initiatives, differing privacy laws and regulations between countries as well as the varying standards among biobanks continue to hamper the international exchange of samples. A further issue in biobanking is the management of incidental findings, e.g. how and under what conditions the donors and their families should be informed.

Collaborations with the pharmaceutical industry are under tight control. The EuroBioBank General Assembly has to give approval for every sample request from private 'for-profit' organisations. So far, samples have been given to the following companies: Prosena, Santhera Pharmaceuticals, Summit and Pfizer. EuroBioBank was also involved in the planning of the pan-European research infrastructure BBMRI-ERIC and recently became a partner of RD connect, an FP7 EU programme aimed at linking rare disease biobanks, registries and bioinformatics data.

Since the pharmaceutical industry has little interest in funding small rare disease biobanks that contain and exchange limited numbers of samples, one of the main challenges in rare disease biobanking is how to secure long-term funding. "Our EC funding ended in 2006. Now, the EuroBioBank network pays only for joint services such as the website, the catalogue updating and annual meetings," Mora explained. "The associated biobanks have to cover their own costs either with institutional funding or with specific grants, such as Telethon grants in Italy," she added.

An impact factor for bioresources

Another hot topic, the biobanking community is currently debating, is how to ac-

credit and evaluate biobanks and how to acknowledge and reward the scientists and institutions involved in their establishment and maintenance. Biobankers do not only provide access to samples. Sharing bioresources also requires the development of a clear access policy, quality control, documentation and regular updating of the bioresource. So far, it is difficult to assess the contribution of any specific bioresource to published research, because it is either ignored or acknowledged in a non-standardised way.

The international Bioresource Research Impact Factor (BRIF) initiative has introduced the concept of a quantitative parameter to describe the use of bioresources, similar to the well-known journal Impact Factor. Each bioresource is assigned a unique and persistent digital identifier, which makes it possible to document the quantitative use of a bioresource via indexing tools, its impact on research, as well as the scientific and management efforts of the scientists and institutions involved. The journal editors' subgroup of the BRIF initiative suggests that each bioresource used to perform a study and mentioned in the 'methods section' should be cited in the 'references section' in a standardised way (*BMC Medicine,* 13:33).

Guidance for tissue biobanking

The European Association of Tissue Banks (EATB) is a European organisation for tissue bank professionals, scientists and clinicians working in the fields of cell and tissue donation, processing and transplantation. It was inaugurated in 1991 in Berlin at the first European Conference on Tissue Banking by 280 participants from 18 European countries. EATB members are primarily public tissue banks and their staff. Recently, but with some limitations, EATB has also been open to employees of private organisations. The associated banks process and store samples, such as eye corneas and scleras, bone to fill cavities after surgical treatment of trauma or cancer, heart valves to reconstruct the heart outflow tracts, vascular allografts to restore the blood circulation, skin to cover burn wounds, and tendons and cartilage to restore mobility.

EATB is working with regulators to promote safety and efficacy in tissue banking. It was involved in European Commission Public Health projects related to tissue banking, such as the 'European Quality System for Tissue Banking (EQSTB)' and 'European Good Tissue Practices (Euro-GTPs)' and participates in the activities of the Council of Europe. The organisation nominated representatives to join the working group drafting the 'Guide to the Quality and Safety of Tissues and Cells for Human Application'. Moreover, it is collaborating with Barcelona University in the organisation of training courses for professionals dealing with the whole range of tissue biobanking activities.

Hot debates at conferences

EATB holds its annual congresses with 10 to 15 invited speakers, to provide a forum for scientific, ethical and clinical activities relating to tissue banking. "Starting this year, we have introduced so-called 'breakfast sessions' which are open to all registered congress participants," said Artur Kaminski, the President of EATB. At this year's conference in Split, Croatia, the morning sessions gave special attention to the topics of biovigilance, the cryopreservation of tissues and cells, clean room management and donor selection.

"In collaboration with the World Union of Tissue Banking Associations (WUTBA), we have organised the pre-congress symposium on 'Ethics in tissue banking', which were held on October 1st in Split. We believe that this symposium adds impact to debates regarding the risk of commercialisation of tissue banking," said Kaminski, a specialist in tissue banking and cranio-maxillo-facial surgery. "In some countries, tissues and cells are subject to VAT. The majority of our community considers this an unacceptable commercialisation of biobanking. Tissue and cell donation is voluntary and unpaid, recognised as a gift and therefore, grafts prepared from human tissues and cells should not be treated as products or goods," he added.

In high demand

This is particularly important because clinical demand is exceeding the availability of tissue and cell grafts. "We are constantly trying to raise the public's awareness of the importance of tissue and cell donations," the EATB representative said. "A solution to this problem might be extension of the donor acceptance criteria based on current scientific knowledge, provided there is no increased risk for recipients," remarked Kaminski, who is the Head of the Tissue Bank at the Medical University of Warsaw and Director of the National Centre of Tissue and Cell Banking in Poland.

Pan-European and global guidelines

In addition, managers of tissue banks face the demanding responsibility of implementing the 'Single European Code' over the next three years. This is a harmonised coding system for human cells and tissues. Kaminski also advocates a unified system to determine the efficacy of treatments with cell and tissue grafts, besides international standards for tissue procurement, testing and processing.

An important development for the tissue banking community was the implementation of Regulation (EC) No 1394/2007 on advanced therapy medicinal products. As a result, many tissue and cell banking activities became classified as somatic therapy, tissue engineering or gene therapy and were therefore regulated by pharmaceutical law. "Some tissue and cell banks became 'pharmaceutical factories' manufacturing medicinal products and not tissue or cell grafts. This created a lot of confusion and misunderstanding. Many concerns are still unresolved. There are still uncertainties re-

Photo: Marina Mora

"The legal and regulatory frameworks that apply to biobanking are still fragmented," observed Marina Mora, Scientific Coordinator of EuroBioBank.

lated to borderline products that could be classified either as tissue and cell grafts or medicinal products," Kaminski observed. The tissue banking community is waiting for further regulation regarding borderline products to ensure standardisation across all European countries.

European infrastructure in preparation

We can assume that billions of biological samples are stored in biobanks across Europe, together with information on the study subjects. To set up a pan-European biobank, Member States joined forces with the aim of facilitating access to and exchange of such samples and data among biobanks, and the academic and private sector in Europe. This 'Biobanking and BioMolecular resources Research Infrastructure' or BBMRI-ERIC builds on the legal framework 'European Research Infrastructure Consortium (ERIC)' and is supported by Member State contributions.

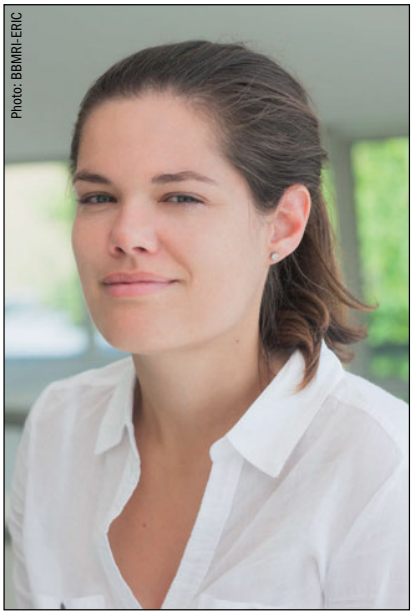

Photo: BBMRI-ERIC

"Access to samples will be primarily based on merit review of submitted proposals," says Michaela Mayrhofer, Senior Project Manager at BBMRI-ERIC.

The organisation's goal is to promote high-quality biomolecular and medical research. It does so via National Nodes in the participating countries (e.g. Malta, Estonia, Finland, Greece, France and Italy), via Common Services concerning ethical, legal and social standards and via IT infrastructures to facilitate data exchange across Europe. "In spring 2015, BBMRI-ERIC welcomed the United Kingdom as its 18th Member. The organisation is expected to be fully operational by the end of 2016," said Michaela Mayrhofer, Senior Project Manager at BBMRI-ERIC's headquarters in Graz, Austria. The research infrastructure brings together clinical, ethical and legal experts, the biotech and pharmaceutical industry as well as patient advocacy groups. They aim to achieve standards and to establish guidelines that balance individual values, such as the protection of privacy or informed consent, with shared values of facilitated access to progress in health care and disease pre-

The Complex Legal Side of Biobanking

The general foundation in Europe for the regulation of medical research including biobanking practice is the **Oviedo Convention** dating from 1997. It establishes general principles concerning the protection of human rights and dignity with regard to biological and medical applications, e.g. consent procedures, principles affecting tissue and organ donation, privacy and the right to information. Specific issues are addressed by additional protocols, such as the **Protocols on Cloning** (1998), on **Transplantation** (2002), on **Biomedical Research** (2005), and on **Genetic Testing for Health Purposes** (2008).

"**Recommendation 'Rec(2006)4**' by the Committee of Ministers of the Council of Europe deals with research on biological materials of human origin," EuroBioBank's Scientific Officer Marina Mora told us. The document gives advice on how collections of biological materials in general and population biobanks in particular should be managed. Moreover, it suggests rules for the use of human biological materials in research. It also states that biological materials should not give rise to financial gain. "The recommendation is supposed to be re-examined not more than five years after its adoption but no re-examinations are available, so far," Mora observed.

Biomedical research carried out by using personal data is regulated in very general terms by the **Data Protection Directive** (95/46/EC). A new EU General Data Protection Regulation is currently being negotiated. The **Clinical Trials Directive** (2001/20/EC) contains the major principles of medical research practice. These principles have also been applied to biobanking and, despite the lack of a specific legal instrument, they provide the main basis for the protection of research participants.

In contrast to biobanks for diagnosis and research, biobanks which store samples intended for transplantation are subject to rigorous regulations and strict technical requirements. "Several EU Directives regulate tissue and cell banking activities for transplantation in Member States," commented biobank expert Artur Kaminski. The **Tissue and Cells Directive** (2004/23/EC) lays down standards of quality and safety for human tissues and cells intended for human applications. It applies to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

Two further Directives from 2006 set out more detailed technical requirements. **Directive 2006/17/EC** covers the donation, procurement and testing of human tissues and cells, whereas **Directive 2006/86/EC** focusses on the coding, processing, preservation, storage and distribution of human tissues and cells, as well as on traceability requirements and the reporting of serious adverse reactions and events.

"In 2015, two additional directives influencing the tissue and cell banking community have been adopted," Kaminski reported. **Directive (EU) 2015/565** amending Directive 2006/86/EC sets standards for the 'Single European Code', a harmonised coding system for human cells and tissues, which facilitates their traceability. The directive refers to technical requirements. **Directive (EU) 2015/566** implementing Directive 2004/23/EC aims to ensure the quality and safety of human tissues and cells imported from non-European countries." These Directives, which have to be transposed into national law, set minimal standards. Member States may choose to introduce more stringent measures," Kaminski told us.

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vention. BBMRI-ERIC recognises the different national legislative frameworks that, together with common European legislations and directives, provide the legal basis for carrying out collaborative research involving biobanks. "We also respect the differing social and cultural attitudes in the Member States," Mayrhofer stated.

Access to samples after evaluation

The non-commercial organisation is involved in numerous projects, among these 'BBMRI-LPC', which aims to facilitate scientists' access to large prospective study sets on human health and disease and 'BioMedBridges', which supports shared data integration in the biological, medical, translational and clinical domains. Ultimately, BBMRI-ERIC is expected to provide a one-stop access to the collections of the European biobanking community, expertise and services.

The network, which is one of the largest research infrastructures for health research in Europe, plans to provide free access to the documents, Standard Operating Procedures and best practices, which it has developed. It intends to offer open access to results and data published in co-ordination with its partners, as well as fair access to samples and related clinical data. "Access to samples will be primarily based on merit review of submitted proposals by the relevant biobank scientific and ethical committee. The evaluation will take into account the scientific quality of the proposal as well as legal and ethical considerations," Mayrhofer explained.

Photo: Michał Teperek/Medical University of Warsaw

Artur Kaminski, president of the European Association of Tissue Banks (EATB), thinks that "grafts prepared from human tissues and cells should not be treated as products or goods".

Closer together

BBMRI-ERIC recently launched its Directory with over 500 biobanks and collections (*http://bbmri-eric.eu/bbmri-eric-directory-1.0*). The tool enables users to explore the infrastructure of BBMRI-ERIC and to communicate with the biobanks. Users can identify the relevant biobank samples and data and negotiate access with the sample and data custodians. Combined with already existing networking efforts, BBMRI-ERIC will bring the biobanking community closer together.

Bettina Dupont