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Report of Expert Group on Pathology

Foreword

Pathology is the cornerstone of tissue biobanking. The most basic minimal standard for any biobanking operation is to identify and define the nature and origin of the tissues to be kept in the biobank. This requires specialized pathology expertise. Futhermore, pathologists also make decisions on what should be biobanked, making sure that the timing of all operations are consistent with both the requirements of clinical diagnosis and the optimal preservation of biological products. The rapid development of biobanking as an essential process in translational research and personal medicine places strong demands on the work of the pathologist.

This document has been developed as the report of a Pathology Expert Group Meeting that took place in Munich in Dec 2008 within the framework of Work Package 3 of BBMRI. The experts have considered all aspects of the involvement of the pathologist in the biobanking process. They also discussed the impact of biobanking on pathology practice. The recommendations developed in the document are aimed at providing guidance for pathologists as well as for institutions hosting biobanks on how to better integrate and support pathological activities within the framework of biobanks that fulfill international standards.

Scope and definition

1. The focus of the working group is the banking for research of human tissues in clinical context. This activity is hereby defined as "tissue banking". It includes, but is not limited to, the banking of residual specimens obtained in the course of clinical procedures as well as of "post-mortem material."

2. Tissue banking is a chain of operations that includes informing patients and obtaining the proper consent (depending on local requirements), data acquisition, tissue procurement, annotation, preservation, storage, cataloguing, managing of access, processing and distribution. Pathology expertise is required at several steps. Tissue banking also requires expertise in cryobiology, quality management, legal/ethical aspects, project management, PR, administration and networking.

3. "Pathology archives" represent a special type of tissue repository, that may support tissue banking, provided that they fulfill required standards with respect to (1) documentation of variations; (2) cataloguing; (3) rules of access; (4) fulfillment of legal requirements for use as research resource. The primary role of these archives is to document diagnosis and to support later/metachronous diagnostic analyses but they should be developed in a way that allows them to fulfill roles in research as well.

Recommendations

R1: The working group recommends to develop a published reference framework for "organizing and managing a tissue bank" into clinical practice, defining standards that distinguish "archive" from 'tissue bank".

R2: In the accreditation process of a pathology laboratory, the quality and compliance to standard of the tissue archive/tissue banks must be taken into consideration.

Tissue banking: critical role in articulating translational research and personalized medicine

1. Tissue banking in a clinical context is essential for the procurement of high quality samples for translational research aimed at biomarker discovery and validation as well as identification of new targets for therapy. It is therefore a strategic activity for research and innovation in biomedicine.

2. Tissue banking is critical for implementing and applying biomarkers in clinical practice. It lays the foundations for the discovery of new targets for therapy and for drug discovery. It sets conditions and procedures allowing patients to benefit from new developments in biomarkers as well as personalized medicine and is therefore beneficial for future diagnosis and treatment and for public health. In this vision, each patient contributes to the care that will be provided to the future patients.

3. Translational research on biomarkers encompasses three overlapping phases: discovery, validation and implementation. Each phase has different requirements in terms of tissue banking (Figure 1).

4. Discovery phase is aimed at identifying biomarkers and molecular targets for therapy, establishing their prevalence and formulating hypotheses on their biological and medical significance in ex-vivo analyses. This requires access to well annotated and pathologically reviewed case-series, either based on specimens collected and processed in the course of clinical diagnostic activities or in specific tissue collection protocols.

5. Validation phase is aimed at demonstrating the effect and significance of a potential biomarker. This requires applying ex-vivo analyses within study designs with adequate epidemiological and statistical power. Such designs may be comparable to those of clinical trials except that they do not imply in vivo analyses. These studies may be constructed using retrospective or prospective collections.

6. Implementation phase is aimed at translating biomarkers into clinical practice in affordable, cost-effective conditions and at integrating new biomarkers into diagnostic practice. This requires applying biomarkers to large series of specimens collected using standard operating clinical protocols.

Recommendations

R3: Contributing to medical progress through participation into tissue banking should be offered to the largest possible number of patients.

R4: Tissue banking should take into consideration the need for collecting appropriate reference samples. Whenever possible and appropriate, the reference sample may consist of corresponding tissue not affected by the disease process.

R5: Clinical practice should evolve to take into account the most effective way to exploit new molecular validated biomarkers and therapeutic targets. This requires technical innovation on evidence-based protocols for tissue

procurement, preservation and processing. Innovation should also aim at better using archived collections.

R6: Given that specimens collected in clinical practice are critical for research, rules of patient information and consent should be compatible with the broad use of such specimens in conditions fulfilling strict criteria of protection of persons and data. The working group recommends that further work is developed to increase awareness on these issues and to develop ethical and legal procedures at national and European level.

Role of the pathologist

1. The pathologist has an essential role in tissue banking. His medical and scientific expertise is required at two distinct phases in the process of tissue banking: (1) in making diagnostic decisions, providing specific annotations and overseeing specimen procurement and preservation, and (2) in reviewing specimens and providing information prior to specimen processing and distribution to research laboratories.

2. Through his role in tissue banking, the pathologist is a key actor of the continuity between research and medical care.

3. The pathologist adds value and expertise to the definition of the banked tissue and is a critical scientific contributor to research carried out from the specimen.

4. The pathologist validates the appropriateness of the banked tissue specimen and its use for a particular research purpose, excluding conflicts with diagnostic purposes.

5. The pathologist has a key role as custodian of the banked specimens. Tissue collections are best developed in the context of a pathology department or pathology service.

Recommendations

R7: No tissue banking for research should take place without proper pathology documentation. All specimens used within research programs must have been reviewed and assessed by a pathologist.

R8: The standard for tissue banking is a tissue sample and not derived products or isolated molecules.

R9: The pathologist should have an active participation in decisions of access to banked specimens.

R10: Efforts should be made to better communicate the role of pathology in tissue banking.

Role of institutions

1. Tissue banking is not the exclusive responsibility of pathology departments. It should be run in the context of Institutions (mainly hospitals or universities) who are responsible for providing the whole chain of expertise and the organizational frame required for tissue banking.

2. Institutions are responsible for the maintenance, sustainability, and accessibility of tissue banks, adequate level of training of the staff and the protection of patient rights. Full cost calculation is an essential step in guaranteeing the sustainability of the tissue bank.

Recommendations

R11: Institutions should commit adequate resources and staff dedicated to acquisition, processing and proper distribution of both data and specimens and assisting the pathologist in all tasks that do not require a qualification in pathology. The basic requirements are (1) daily and technical management, (2) data and specimen collection management and (3) expertise in biobanking ethics and law, and (4) networking biobanks. Biobank staff, depending on the size of the pathology department at least, should include a tissue bank manager and a technician in addition to the pathologist. The institution should commit adequate resources for pathologists to be involved, next to their clinical task, in tissue banking activities.

R12: Technical and pathology expertise should be provided by the pathology department; the added scientific value should be recognized.

R13: Institutional commitment and appropriateness of the level of resources dedicated to tissue banks should be considered as critical elements in process of tissue bank accreditation, which could be part of a general hospital or pathology accreditation.

R14. The institution should be responsible for setting and publicizing the rules of access to tissue banks.

R15: The rights of the patients should be taken into account in the procedures and rules for access and use of the tissue bank.

R16: In granting access to tissue banked specimens, a general principle of "minimal sample amount of tissue necessary for the project" is recommended.

R17: Every procurement of banked tissue for research should be formalized through a Material Transfer Agreement (the scope and content of this MTA is a matter for further elaboration at European level).

R18: Funding agencies should be aware of the requirements of tissue banking before granting funds for a research project. Projects using banked specimens should specifically (1) provide assurance of the participation and support of the tissue banks; (2) consider the costs of specimen procurement and processing in relation with their specific research application.

R19: A European framework for the professionalization of tissue banking should be developed, e.g. through a teaching program at master level.

Tissue banking in clinical trials

1. Clinical trials offer a wide range of designs with added value for the discovery, validation and implementation of potential new biomarkers

2. Using biomarkers is critical for the interpretation of many therapeutic trials in particular for defining the characteristics of responders vs. non-responders.

3. In future medical care, biomarkers will become mandatory for allocating patients to appropriate therapeutic protocols.

Recommendations

R20: As a rule, tissue banking should be considered as an option in every clinical trial.

R21: The need for biomarker application and the possibility of using trials for biomarker validation should be taken into account in the statistical and logistical design of the trial.

R22: Pathologists should be involved in trial design.

R23: There should be a comprehensive registry in the tissue bank (ideally coupled to an institute clinical trial registry system) of the tissue samples collected in the context of clinical trials.

Improving standards for tissue banking within clinical practice

1. There are technical differences in current standards for tissue processing in pathology practice and in tissue banking.

2. Many protocols used in tissue banking, e.g. for duration of fixation, optimal time to preservation and duration of storage, are mainly based on experience rather than evidence.

3. There is need for more adequate markers of quality for the tissue banking process for the qualification of banked tissue specimens for specific research applications.

4. Discovery, validation and implementation of biomarkers and therapeutic targets in the clinics require very large series of specimens with inter-laboratory comparison. Such studies need strong networking between dedicated platforms using harmonized, comparable protocols.

R24: Innovation in tissue banking should focus on reducing gaps between standards for clinical practice and for research, and on the development of biomarkers for the quality control of tissue banking procedures

R25: The development of evidence-based protocols supported by published data should be a priority. Journal editors should be made aware of this priority and should solicit contributions to support this effort. Scientific journals should develop proper expert reviewing for the correct collection, handling and processing of human tissues forming the basis of published data

R26: It is recommended that current European initiatives and programs that develop technical platforms for large-scale specimen analysis are duly reviewed, assessed, and “harvested” for developing models for future network development.

Incentives for increasing the participation of pathologists

1. Tissue banking is an important mechanism by which pathologist participate to generating and increasing knowledge in biomedicine.

2. In many instances, the involvement of the pathologist adds scientific value to the banked specimens beyond the requirements of routine diagnosis. This added value corresponds to an intellectual property.

3. Tissue banking activities entails considerable costs and demands on pathology staff time.

R27: Efforts should be made to increase the awareness of the pathology community that (1) participating into research through tissue banking is part of their professional duties; (2) tissue banking is an instrument for managing the evolution of pathology work towards integration of biomarker analysis in clinical practice.

R28: Pathologists should be involved as scientists in developing the design of studies using banked specimens and in interpreting their results.

R29: The scientific involvement of pathologists should be acknowledged in publication authorship. This involvement may consist of specific diagnostic procedures and annotations at the time of specimen acquisition and/or pathology review before specimen processing for specific research purposes.

R30: Contributing to tissue banking should not compete with the performance of clinical pathology duties; therefore, sufficient time and resources should be committed by institutions to the performance of tissue banking activities.

R31: In developing research on banked specimens, researchers should take into account the costs of tissue banking operation and should include these costs in grant applications.

A strategic vision for tissue banking in Europe

1. In the next 10 years, the use of cellular and molecular biomarkers will become a standard part of pathology practice. Tissue banking is the key mechanism for pathologist to get involved into translating newly discovered biomarkers into clinical practice.

2. In the next few years, tissue banks will have a key role to play in the process of biomarker and drug target discovery through the procurement of annotated specimens to innovative research programs.

3. Given its strong linkage with clinical activities, tissue banking is best performed at the local level, and its sustainability requires investment into infrastructure at the local and/or regional and national levels, to avoid duplication of effort and achieve critical mass necessary to address major research programs, whether academic or industrial. Therefore, tissue banks must be organized in operational networks.

4. Networking should have fully documented standard operating procedures, share tissue bank catalogues, and open rules for access. They should also be able to run research projects based on collections developed in several tissue banks. Such projects may be retrospective (using previously banked specimens) or prospective. Running the same, hypothesis-driven collection protocol through a large network of tissue banks that adhere to the same standards will allow assembling large, cases series addressing a wide range of clinical conditions. In developing such protocols, the diversity of European populations and ecological contexts is an asset for the design of sophisticated case-case comparison studies.

5. Implementation of biomarkers will require large networks interconnecting tissue banks, analysis and distribution platforms and several other data resources such as databases of clinical information and population based disease registries.

6. To achieve this vision, it is essential to perform innovative research on improving all aspects of specimen processing, including the development of quality controls applicable to retrospective collections. This requires a dedicated effort from funding agencies and from the scientific and medical publication community.

7. Training of highly qualified tissue banking professionals will increase the standards of tissue banking as well as the recognition of tissue banking as an integral part of biomedicine. This will also facilitate the development and dissemination of a corpus of harmonized, evidence-based tissue banking procedures.