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TuBaFrost 1: Uniting local Frozen Tumour Banks into a European Network: an overview ☆

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ABSTRACT

TuBaFrost is the consortium responsible for the creation of a virtual European human frozen tumour tissue bank: a collection of high quality frozen residual, accurately classified tumour tissue samples, which are stored in European cancer centres and universities. This virtual tissue bank, searchable on the internet, has rules for access and use, and a code of conduct to comply with the various legal and ethical regulations in European countries. The easy accessibility and the European scale of the bank will result in the availability of a large number of samples even of rarer tumour types. Standardisation of collection, storage and quality control throughout the network is achieved minimising inter-institutional variability. A website providing access to upload, search and request samples is a key tool of the tissue bank. The search engine makes use of virtual microscopy. An overview of the

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development of the European virtual frozen tissue bank infrastructure is described in this paper. The various key aspects are described in more detail in a series of articles to appear in this Journal.

1. Introduction

The almost complete unraveling of the human genome and transcriptome and the technical advances in high throughput techniques for analysing DNA, RNA and protein have the potential to make a major impact on prevention, diagnosis, prognosis and treatment of many human diseases. One of the major challenges is to identify specific molecular markers or combinations of molecular markers, often referred to as 'molecular signatures', from this wealth of molecular data. These molecular signatures can give information on, diagnosis, prognosis or treatment of a specific disease with high accuracy. To fully exploit this genomic revolution to combat human disease, it is vital to have access to large quantities of human tissue samples, ideally both diseased and normal tissues from patients and normal tissues from healthy control individuals.[1–3] The relevant diagnostic, prognostic and predictive markers can be retrieved by studying large quantities of tissues from comparable cases with regard to diagnosis, treatment and clinical outcome. This implies that the collected tissue as such is of limited value, but that the combination of the collected tissue with patient and clinical data is of immense importance.[1]

Many diagnostic and therapeutic procedures include the removal of (parts of) the diseased and surrounding normal tissue. This tissue is almost always used for diagnostic pathology. However, the removed specimen is rarely entirely exhausted during the diagnostic process. The remaining tissue, or residual tissue, not used for diagnostics, is an extremely valuable resource for both basic and translational research. For more than a century, the standard procedure in handling the removed tissue specimen for diagnostic pathology is fixation of the tissue in formalin, followed in the overwhelming majority of the cases by embedding of selected small parts of the tissue in paraffin, after which histological examination is performed. This histological classification, including the immunohistochemical characterisation of tissue is at this moment the corner stone of diagnostic pathology. However, medical treatment is becoming more and more individualised, as a result of the generation of the so called molecular signatures based on the patterns of DNA aberrations in variations and gene or protein expression in diseased and normal tissues. For these sophisticated techniques, formalin fixation and paraffin embedding of tissue is often detrimental. For both these new diagnostic procedures and for many research applications there is a need for unfixed tissue.[1–5] Ideally, tissue parts are sampled and frozen in liquid nitrogen or cooled isopentane immediately after removal from the patient to ensure optimal preservation of nucleic acids and proteins. [1,2,5] Partly forced by the new molecular profiling techniques, systematic sampling and banking of fresh tissue is becoming more and more commonplace. In addition, many 'project-driven' frozen tissue banks already exist, established by individual investigators with a particular research interest, mostly organ or disease specific. A third distinct category of tissue banks are in the so-called population banks. [1,6–8]

To date, a description of the practical considerations of uniting European pathology based frozen tissue banks in an international network within a temporarily financed time frame has not been given in great detail. Over the past three years of project development, the TuBaFrost consortium has gained much knowledge and experience, which will be shared through a series of articles in the European Journal of Cancer. [9–13]

In this paper we describe the development of such a European virtual tissue bank based on the experiences of the TuBaFrost project, resulting in the development of many scientifically effective and useful tools.

2. Rationale of the TuBaFrost project

To fully exploit the potential of molecular signature techniques for diagnosis and treatment of patients it is necessary to have access to large quantities of adequately frozen tumours and normal tissue, combined with sufficient clinical data including follow-up. Such resources allow clinical and translational studies with sufficient statistical power to yield strong correlations between molecular signatures and patient outcome.

At the single institute level it is virtually impossible to collect sufficient numbers of comparable samples in a short period of time. A possible approach is to unite frozen tissue and associated clinical data by uniting frozen tissue banks on a supra-institutional and even on a supra-national scale. To this end the TuBaFrost consortium was established, financed by the European Commission within the 5th framework of the division 'Quality of life and living resources'. The creation of a platform for 'virtual' tissue banking where tissue samples remain stored at the collector's institute, and the clinical and sample inventory data are stored in a central database (as well as locally), requires considering specific methodological aspects. To enable comparison of results produced in experiments using tissue samples obtained from many different institutes, it is instrumental to standardise operating procedures for collection, storage and quality control. It is also important to identify those specific measures, which are pivotal for maintaining high quality standards and the best available systems to implement these. Another aspect is the requirement of rules for access and use of the tissues, which have direct impact on the chances of a productive collaboration between the collectors and requestors. Incentives for collectors must be defined to ensure that the collectors continue adding new tissues.

A top down approach with the implementation of a review board, which oversees the issuing of samples to requestors, may potentially deter collectors as they have no part to play in the decision-making process and may feel that their samples could be wasted in projects which they consider useless. Such top down decisions can cause problems between local collectors and the virtual platform. In addition, it can limit future collaboration between the collectors and requestors. Consideration of these facts led the TuBaFrost Consortium to conclude that the collector must retain custodianship over the tissue collected and stored at the local institute and that lines of communication are established between all the collectors involved in a request in order that a consensus between collectors might be more easily reached. In addition, samples will stay available for local use as collectors were used to before taking part in TuBaFrost. The only extra task needed when issuing a sample locally is updating the central database on availability.

The final 'virtual' issue is the central database application. The collectors must have access to an environment where they can upload samples and update the availability or 'status' of the sample in accordance with requests. External users and potential requestors, on the other hand, must have easy access to the contents of this database in the form of a web-based search engine with the appropriate forms to request a selection of tissues. Once submitted, the request is distributed automatically by e-mail to all involved collectors and the central office. Samples can be selected from the database according to specific search parameters. The search can be facilitated by histology images of the samples to minimise selection errors. The virtual images are of sufficient quality to enable the requestor to review the pathological classification.

To develop a tissue bank network across Europe increases the challenge substantially. Language differences and variations in coding systems make uploading of local data to a central database difficult, as all terms used in the clinical data are in the local language and must be translated into English.

Variations among national laws on the secondary use of residual tissue result in significant differences between consent procedures, e.g. informed consent, opt-out systems, no consent procedures at all. Consent is a broad concept that can range from an umbrella consent that residual tissue can be used for future research to specific informed consent for each protocol, as required for clinical trials. Such specific consent will be difficult to obtain when the tissue has been stored for longer periods of time. Recent publications show an 'avalanche' of international instruments on this issue,[8] However, recent national legislation has often chosen for alternatives instead of the options described in those instruments.[9] TuBaFrost had the task to find a way out of the resulting dilemmas in order to enable exchange of residual tissue.

For any platform working according to a strictly limited funding timeline a critical balance between cost and effectiveness needs to be found in every decision. Involvement of costly personnel should be avoided as much as possible. Therefore, automated procedures have to be built into the central database application, to reduce the operating costs of the virtual bank.

3. The creation of TuBaFrost

It is clear that many issues need to be considered and difficulties overcome to create a European Virtual Tumour Tissue Bank. The options were first discussed within various groups within the European Organisation of Research and Treatment of Cancer (EORTC) and the Organisation of European Cancer Institutes (OECI). Institutes were selected based on their accrual rate of patients in trials as a measure of their ambition to join Europe-wide initiatives. In addition, to form the basis of this complex infrastructure the selected institutes must be evenly spread throughout Europe and the number of institutes must be limited to ensure that the meetings, discussions and most importantly decision-making procedures stay manageable. In particular, pathology departments of these institutes were approached to join this initiative, due to their potential as future tissue collectors. The most obvious host for the central database was considered to be the EORTC datacentre, because of its central role in cancer research in Europe and its ambition to promote translational research in side studies to clinical trials. For the European legal and ethical work package, a non-commercial law firm became part of the consortium. This firm had already played a pivotal role in setting up a National Code for Proper Secondary Use of Human Tissue in the Netherlands, which contains an opt-out system for coded, anonimised residual tissue. Together with representatives of patient organisations it was found that this system provides an appropriate balance between research needs, patient rights and privacy protection.[14]

The resources required to develop the virtual tissue bank were provided by the European Commission under infrastructures in Framework Five. To overcome the difficulties outlined in the previous paragraph, it was instrumental to define clear goals and to break down the overall workload into manageable packages. The aims were formulated in the mission statement: Create an innovating virtual European human frozen tumour tissue bank for the whole scientific community composed of high quality frozen tumour tissue sample collections with a corresponding accurate diagnosis stored in major European cancer centres and universities, searchable through an uncomplicated query system on the Internet provided with rules for access and use of the tissues complete with a European code of conduct to comply with the various legal and ethical regulations in the different European countries.

The resulting platform not only improves the tissue sample visibility and accessibility for cancer research, but in addition, facilitates the rapid accrual of large amounts of tumour tissue samples of a defined subtype, including the uncommon cancer types. Furthermore, this initiative is expected to boost collaboration between different European institutes, specifically between scientists (with access to cutting edge technology) and the actively tissue collecting groups, often clinicians.

The breakdown of the overall workload and assignment of the leadership of the resulting tasks led to the organisation shown in Table 1. All institutes and involved organisations were actively involved in the evaluation and development of the work packages described in Table 1, thus resulting in a successful project proposal, which led to the formation of the TuBaFrost consortium.

Table 1 – Constitution of the TuBaFrost Consortium

Tasks	Leading Institute	WP nr[a]
Project management	Erasmus MC Rotterdam	1
Market orientation, state of the art storage system	Institut Gustave-Roussy	2
Standard operating procedures	NTRAC, University of Oxford	3
Internet access and web design	University Hospital Leuven	8
Implementation and evaluation	Netherlands Cancer Institute	B
Quality control	Centro Nacional Investigaciones Oncologicas	3
Implementation and evaluation	Allgemeines Krankenhaus Wien	B
Rules for access and use	Valencia Institute of Oncology	6
Implementation and evaluation	Centro di Riferimento Oncologico	B
Central database	EORTC datacentre	4
Virtual microscope	EORTC datacentre	5
European laws and ethics	Med law consult	7

a WP nr stands for: work package number as given in the project. B stands for a participant not leading a work package, but is, like every other participant, actively involved in the participation, development and evaluation of all work packages.

3.1. *Standardisation of collection and storage protocols and associated quality control*

Tissue bank excellence is based on validated procedures for the collection, handling, freezing, storage and shipping of human samples of clinical origin. TuBaFrost standard operating procedures (SOPs) and quality control policy are instrumental in ensuring uniform tissue quality across decentralised networks such as TuBaFrost. A consultation process preceded the drafting of the policies and procedures: best practices in each participating centre and a number of key tissue bank initiatives worldwide were reviewed. Following discussion and evaluation of the findings during the TuBaFrost Consortium meetings these procedures were implemented at all participating institutes. Implementation difficulties were reported back and discussed for improvement. All aspects of the collection and storage were judged on the effect on the final quality of the sample, e.g. snap freezing method; lag time between tissue excision and freezing; inventory system; labeling methods; storage repository alarm systems; and procedures to check the quality of the samples.

To ensure that TuBaFrost SOPs reflect current best practices and most appropriate storage methods, several systems were examined for their suitability within a tissue bank network. A sophisticated collection and storage system using cryo-straws was trailed. The standardisation, quality assurance and trailed system are described in the associated article in the TuBaFrost series.[10]

3.2. *Central database application and Internet access*

One of the articles is focused on the design of the central database for the virtual European tumour tissue bank,[11] clearly describing the considerations and tools needed in a database application of a virtual tissue bank and also the differing requirements of each user group. Operational costs have been minimised by installing specific tools, e.g. a cryocart facility for selecting tissues whilst using the built-in search engine; automatically generated e-mails; electronic forms to be completed during the tissue request process. The dataflow within the network, depicted in Fig. 1, reflects events and work flow in associated work packages. The communication is automatically set-up between collector, requestor and central office and the application offers facilities to upload and manage the dataset for requestors, collectors and central office.

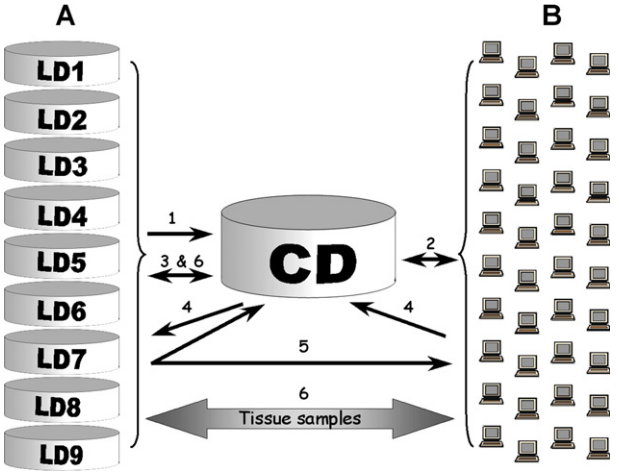

Fig. 1 – Dataflow in the virtual tissue bank platform: (A) local databases of collectors LD1–LD9 and (B) registered users or requestors. Dataflow: 1. enter sample by collector in the central base; 2. search and selection of samples by registered user; 3. sample status update on availability; 4. request of samples by automatically generated e-mail; 5. decision of collector; and 6. sample status upon sample exchange.

TuBaFrost is a virtual network and hence pivotal to its operation is the development of the TuBaFrost website which must be tailored to the needs of each user group. Requestors and collectors require instructions on how to access and use the central database. The general public can access information regarding the aims of the project, the way information and residual tissue are treated, and the precautions taken to protect patient privacy. The web site is very important, as it is the 'front-office' of the virtual tumour bank to all external users and will indirectly act as a reference for the abilities of the consortium on the IT level.

3.3. *Virtual microscope for the support of sample selection*

New opportunities in histological review are enabled by the implementation of a virtual microscopy system. The virtual microscope scans whole tissue slides at high resolution and the information is stored on the hard disc of a computer (Image server) with large storage capacity. This server is accessed through the database via the Internet (using a standard Internet browser) and quickly produces simple images of the requested location and magnification from the large stored image file. The images are then sent over the network to the user elsewhere. This process reduces errors in tissue selection thus reducing unnecessary retrieval, shipping and the associated potential degradation of valuable samples. The virtual microscope can therefore be used to diagnose difficult cases where normal digital histological images do not suffice[12]. In these cases expert pathologists in several countries can simultaneously review the image.

3.4. *Legal and ethical issues*

A Code of Conduct enabling sample exchange within Europe is essential when planning research using tissues obtained in European countries with different national legislations and ethical views. Therefore, a review was carried out on international instruments and on the relevant laws and regulations in the participating European countries. The case was made for either harmonisation of all regulations or the establishment of a common co-ordinating system for exchange of tissue within Europe. The choice was made for the latter: essentially the legislation of the country where residual tissue was collected for research determines whether it may be used in another country with different rules. This principle of 'home country control' was supplemented with custodianship of tissue. It respects the legal and ethical regulations in the country where the tissue was collected, regardless of where is it eventually used with the minimal requirement of an opt-out system as consent procedure: if tissue may be legitimately used for certain research in the country where it was collected and under whose jurisdiction the patient falls, it may also be used for such research in the country where it is sent to in the context of a scientific program, even if that other country has more strict regulations enforced for residual tissue research collected from patients under their jurisdiction.

Together with the development of a Tissue or Material Transfer Agreement it plays a pivotal role in the virtual tumour bank becoming operational. The issue of privacy protection had to be addressed as well, which again is influenced by variations in European law. Many design issues, e.g. the web site, access to the database, coding or labeling of the sample, etc. could have major implications for the conditions on how to work with and exchange tissue samples between the different European countries by law. The specifics of this subject are discussed in more detail and presented in a dedicated article in the TuBaFrost series.[9]

3.5. *Access rules and incentives for collectors*

When designing the infrastructure for a networked virtual tumour bank it is apparent that the bank can only function properly when underpinned by an adequate set of rules for access and use. The final article in the TuBaFrost series[13] focuses upon communication between the requestor, collector and the TuBaFrost central office — this is key to the successful operation of the tissue bank. In addition, the rules, responsibilities and rights for each type of user have been defined specifically for the unique open infrastructure of the virtual tissue bank. Rules for use and access, and defined incentives for collectors and requestors ensure smooth operation of the bank and contribute to its longevity. The rules are beneficial to all users, they ensure moderation of access to, and use of, valuable tissue collections and as the requestor can communicate directly with the collector this opens up opportunities for collaboration.

4. Future perspectives

The development of the European Human Frozen Tissue Tumour Bank has been funded by a European Commission project grant and as the funding period ends there are already a number of institutes collecting high quality tissues for the network. In the coming years it is important to enlarge the platform of collectors and disseminate information about this resource to potential users. Therefore, it is crucial to operate under the umbrella of a large influential European cancer organisation that plays a pivotal role in cooperation between and standardisation for cancer institutes in Europe. The European Organization of Cancer Institutes (OECI) was asked and decided to totally adopt and integrate the TuBaFrost infrastructure to make future use of this sophisticated infrastructure that has already been established with strong support from this organisation. This relationship is synergistic as the OECI members can easily access large amounts of high quality tissue specimens giving them more critical mass for future use and in joint project proposals. Furthermore, the OECI has a program to establish comprehensive cancer centers where care, prevention, research, development and education are integrated and multidisciplinarity is optimized, to improve quality of care and innovation. Tissue banking in a network is one of the aspects of a comprehensive cancer institute. In the future networked biorepositories can be expanded to other types of tumour bio-repositories in the form of xenografts, low passage cell lines and body fluids e.g. blood, serum, buffycoats, urine, bone marrow, cerebrospinal fluid etc. can be organised and shared in this unique way.

The inclusion of information from cancer registries can be beneficial for both parties. Information describing the patient's history can be added to a sample thereby increasing its scientific value for translational research, whereas the epidemiological findings can be directly tested, challenged or supported on a molecular level, gaining new molecular insights or even markers on the basic epidemiological findings.

New developments in research techniques require TuBaFrost to remain dynamic and flexible in its approach to tissue banking. The quality standards required for the application of the new techniques might cause a shift in the minimum standards for collecting, freezing and storing tissue samples.

The opportunity to use residual tissue in translational cancer research is of inestimable value and therefore indispens-

able in the field of cancer research.[1–5] Accessibility to residual tissues for medical research purposes in the past has clearly shown to result in many benefits for the treatment of patients today. Policy makers must remain aware that shifts towards stricter legislation on the use of residual tissues might lead to a situation where exchange of residual tissue samples or where data become impossible or too expensive to secure the future use of the valuable repositories. Therefore, it is of utmost importance that legal and ethical issues, such as consent procedures, represent the views of the majority of the patients. Since studies have clearly shown that only about 1% of patients refuse to donate their residual tissue for research even if commercial interests are put forward[15], the case for an opt-out system should be considered. This would fully serve the rights of the patient who does not wish their tissue to be put to secondary use and would not inconvenience the consenting majority.

The scientific value of a tissue sample is not only determined by the high quality of the methods used for collecting, freezing and storing, but also by the amount of accompanying clinical data. An increasing demand for detailed clinical data will be inevitable since molecular research techniques and bioinformatics applications are continuously developing. Correlations could emerge and bring new insights into the disease process and treatment possibilities. In conclusion, it can be stated that continuous investment in the development of tools or methods to enable the extraction of the desired information from residual diagnostic tissue, without compromising the privacy of the patient, is of great importance.

Conflict of interest statement

None declared.

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