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TuBaFrost 4: Access rules and incentives for a European tumour bank ☆

J.A. Lopez-Guerrero[a,*,m,n], P.H.J. Riegman[b,m,n], J.W. Oosterhuis[b,m], K.H. Lam[b,m], M.H.A. Oomen[b,m], A. Spatz[c,m], C. Ratcliffe[d,m], K. Knox[d,m], R. Mager[d,e,m], D. Kerr[d,m], F. Pezzella[e,m], B. van Damme[f,m], M. van de Vijver[g,m], H. van Boven[g,m], M.M. Morente[h,m], S. Alonso[h,m], D. Kerjaschki[i,m], J. Pammer[i,m], A. Carbone[j,m,o], A. Gloghini[j,m], I. Teodorovic[k,m], M. Isabelle[k,m], A. Passioukov[k,m], S. Lejeune[k,m], P. Therasse[k,m], E.-B. van Veen[l,m], W.N.M. Dinjens[b,m], A. Llombart-Bosch[a,m]

[a]Unit of Molecular Biology, Fundación Instituto Valenciano de Oncología, C/Profesor Beltran Baguena, 8 + 11, Valencia, Spain
[b]Erasmus MC, Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands
[c]Institut Gustave Roussy, Rue Camille Desmoulins 39, 94805 Villejuif, France
[d]National Translational Cancer Research Network, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, United Kingdom
[e]Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom
[f]U.Z-K.U-Leuven, Herestraat 49, B-3000 Leuven, Belgium
[g]Netherlands Cancer Institute, Plesmanlaan 121, NL-1066 CX Amsterdam, The Netherlands
[h]Centro Nacional de Investigaciones Oncologicas, Melchor Fernández Almagro, 3. E-28029 Madrid, Spain
[i]Alllgemeines Krankenhaus, University of Vienna, Waeringer Guertel 18-20, 1090 Vienna, Austria
[j]Centro di Riferimento Oncologico, Via Pedemontana Occidentale, 12, I-33081 Aviano (PN), Italy
[k]EORTC Data Center, Avenue E. Mounier 83, B-1200 Brussels, Belgium
[l]Medlaw Consult, Postbus 11500, 2502 AM Den Haag, The Netherlands

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ABSTRACT

When designing infrastructure for a networked virtual tumour bank (samples remain at the collector institutes and sample data are collected in a searchable central database), it is apparent that this can only function properly after developing an adequate set of rules for use and access. These rules must include sufficient incentives for the tissue sample collectors to remain active within the network and maintain sufficient sample levels in the local bank. These requirements resulted in a key TuBaFrost rule, stating that the custodianship of the samples remains under the authority of the local collector. As a consequence, the samples and the decision to issue the samples to a requestor are not transferred to a large organisation but instead remain with the collector, thus allowing autonomous negotiation between collector and requestor, potential co-authorship in publications or compensation for collection and processing costs. Furthermore, it realises a streamlined cost effective network, ensuring tissue visibility and accessibility thereby improving the availability of large amounts of samples of highly specific or rare tumour types as well as providing contact opportunities for collaboration between scientists with cutting edge

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* *Corresponding author:* Tel./fax: +34 961114337.
E-mail address: jose.a.lopez@uv.es (J.A. Lopez-Guerrero).
[m] The TuBaFrost Consortium.
[n] These authors equally contributed to this article.
[o] Present address: Instituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italy.
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technology and tissue collectors. With this general purpose in mind, the rules and responsibilities for collectors, requestors and central office were generated.

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1. Introduction

Since the 1980s, cancer research has largely shifted from using cell lines and animals to using tumour specimens. This has especially been the case for research focused on human tumours, for which there are relatively few good animal models.[1] Moreover, in recent years, there has been a rapidly growing awareness that by applying the evolving molecular technologies to clinical tissue specimens researchers can fully exploit the still growing capabilities of the genomic revolution in medicine.[2]

The concept of 'molecular signatures', in which the neoplastic tissue might be 'typed' according to the pattern of gene and protein expression, and correlated with cancer stage, prognosis and natural history,[3–5] is an important step towards individualising subsequent treatment selection, such as adjuvant chemotherapy, radiotherapy or treatment with novel anticancer agents.[6] There is currently a high level of research activity aimed at assessing a range of molecular markers which might allow definition of the poor prognostic subgroups, in need of more aggressive treatment regimens and pharmacodynamic markers enabling the selection of those individuals most likely to respond to particular cytotoxic drugs.[7]

In this framework, the quality of genomic DNA, mRNA and proteins used must be high,[8] especially when one realises that it has been estimated that over the next few years, as much as 10% of clinical laboratory tests will be based on RNA or DNA analysis.[9] Also, the human body is a unique resource, therefore it is imperative to develop consistent guidelines with specialised protocols for procurement, preservation, registration and distribution of human tissues.[10] This means that significant efforts should be dedicated towards obtaining not only high quality tissues, but also data on clinical outcomes and informing investigators that such data are available for analysis as they pursue their molecular studies on bank-derived specimens.[11] However, these efforts will only be successful when sufficient tumour bank activity is employed with associated computerised information systems acting as the translational bridge linking new molecular information to its clinical significance.[12–14]

Tissue banks and bio-repositories exist in almost every sector of the scientific and medical community. However, standards for collecting and storing tissue vary, and researchers can potentially encounter difficulties gaining access to samples from centres other than their own. In this sense, one of the main objectives of the European Human Frozen Tumour Tissue Bank network (TuBaFrost) is to stimulate cooperative efforts to collect and distribute human residual fresh frozen tumour tissues enhancing cancer research.[15] In addition, another purpose of networking tissue banks is to bring together large enough quantities of tissue samples, in order to reach critical masses to perform critical experiments. The integration of individual local bio-repositories into TuBaFrost, with internal and external users approaching the collectors for use of the collected tissue specimen, makes it necessary to set up rules for access and use of the network. Therefore, during the TuBaFrost project a strong dialogue between the participating institutes was established in order to reach a common set of rules and incentives for taking part in the tissue bank system.

In this document we describe these rules, along with the incentives necessary for the optimal use and control of a networked virtual tissue bank research purpose.

2. Custodianship over the collected tissue samples

One of the most important underlying principles within the network is that the local collector retains complete custodianship over the collected tissue. The samples are not given to a large organisation, which takes top–down decisions on participation of requests of tissue samples, but instead the tissue samples remain easy to access by the collector for use within their own organisation, yet still available to the larger network. Collectors need only to update the central database system when the tissues are 'in use' or 'exhausted'. This ensures maximal involvement by the collectors. And therefore even active and particularly valuable (on a local level) project-driven collections can be entered into the central database. Depending upon the quality of the proposed research and possible opportunities for collaboration offered by the requestor, the tissue can either be issued or kept in the collection. This allows for autonomous negotiation between the collector and the requestor regarding collaboration, co-authorship in publication or compensation in collection and processing costs. Furthermore, this approach results in a streamlined, cost effective central organisation, maximising tissue accessibility and thereby improving the availability of large amounts of samples of a highly specific or rare types as well as opportunities for collaboration between tissue collectors and scientists with cutting edge technology. We feel that this approach, in contrast to a more central (top–down) approach, will fit better in the existing European culture.

3. Participation in TuBaFrost

In principle, all European institutes that can collect tumour tissue samples can participate in the TuBaFrost tumour tissue bank network. However, to enable experiments utilising tissue specimens from several collectors within TuBaFrost it is fundamental to define minimum requirements for standard operating procedures and quality control that all collector institutes must adhere to. This enables comparison of results obtained from samples originating from different institutes and minimising possible inter-institute variability in the

results. In this regard, many European institutions already have their own procedures for collecting frozen tissue and in some cases they need only to adjust their systems to the TuBaFrost requirements. These requirements are published in the paper on standardisation and quality assurance.[16] They specify, for example, the minimum standards, the required number and qualifications of personnel, infrastructure, responsibilities.

It is essential that each collector institute identifies an individual responsible for the scientific tasks of the tumour bank and who is responsible for all functional aspects of the local tumour bank according to the standard operating procedures set up by the TuBaFrost consortium. This includes proper consent procedures, selecting and harvesting surgical specimens, processing, cryo-preservation and storing of the samples, quality controls, legal and ethical aspects, management of the documentation of each sample, evaluation of requests and finally the distribution of the samples.

4. Incentives for participating institutions

The utilisation of tumour banks in research depends as much on the quality and accessibility of the tumour samples as on the reliability and extent of the annotated information. This will enable researchers to correlate at the level of individual patient and groups of patients their experimental findings with these data.[17] To date, the most common tumour banks have been developed as the so-called 'project-driven' tumour banks, which are specialised in collecting tumours on which their research is based. In fact, the systematic collection of all available 'residual' tumour samples for research purposes has been less common and in addition, many institutions have been reluctant to invest in such efforts because specific research objectives were lacking. However, this situation is changing and it is now widely appreciated that we have much to gain from high-throughput analytical approaches using tissues which are systematically collected.[4] Integration of local tumour banks into a networked structure like TuBaFrost represents a great progress in the field of the bio-repositories. The benefits are not only for collector institutes but also for the future management of cancer patients, as it is now possible to do research, especially on tumours occurring in small numbers, which would not have been possible.

The terms of the actual tissue transfer are offered to the collectors in a standardised Tissue Transfer Agreement, which already provides a complete legal and ethical base for the transfer. However, other aspects, such as collaboration, publication co-authorship or collection and processing cost compensation, can still be negotiated. In the event that experimental data obtained using samples from the TuBaFrost Network results in a publication, the TuBaFrost Consortium has established that the following statement should be included in the acknowledgements or material and methods section of the manuscript: 'The tissue used in this publication was provided by TuBaFrost the European Human Frozen Tumour Tissue Bank'. Furthermore, if additional facilities were utilised at the collecting institute(s) (beyond the sole activity of issuing tissue) and those contributions have significantly contributed to a publication, the persons involved should be treated as co-authors of that publication.

Since the surgical resection specimens of tumours in almost all cases need to be further diagnosed by pathologists and the diagnostic process must never be compromised by the tissue banking activities, the collection of tissue will ideally be performed within or closely associated with a department of pathology in cooperation with a pathologist. It is essential to have a pathologist's support and involvement as the pathologist has the responsibility over the diagnosis and can decide which residual tissue can be taken out of the surgical resection material for storage without harming the diagnostic process. Direct relationships between collectors and requestors (as facilitated by the TuBaFrost network) will enable pathologists to be involved in the field of research of the samples they have diagnosed. In addition, they will have access to new opportunities, such as: collaborations; access to rare tumuor types and large collections; rapid feedback on histology review via the Virtual Microscopy tool; feedback on results of research; co-authorship in the case of substantial contribution; and have access to new technology.

5. The tissue request process

Before requesting for a tissue, the requestors must register with the TuBaFrost Central DataBase. Once registered, the researchers are given access to the search engine through a login-name and password that is sent to them by e-mail. Tissues of interest can be found using the search engine by input of combinations of parameters such as diagnosis, tumour type and stage. The TuBaFrost inventory number contains coded information regarding the collector institute where the sample is located and coded information for local sample identification. After that, tissues can be selected and put into a 'cryo-cart', a tool based on the same idea as most shopping carts used by Internet shops and that can be combined with several searches and selections. As previously indicated, the final decision as to the destination of the stored tissue remains with the collector institute. To enable local judgment of the research proposal for a given tissue request, specific information regarding the requestor, their institute and their research proposals is needed in order to decide whether to provide the stored tissues or not. Therefore, the TuBaFrost Consortium decided to develop an extended *tissue request form* (TRF) to obtain sufficient information regarding the requestor and the proposal with the sole aim of facilitating the collector's final decision on the destination of the stored tissue. The requestor is required to fill out this form on-line in the preparation of a tissue request. Upon submission of the request, this information together with the information on the requested tissue samples is sent by automatically generated e-mail to the local collector involved.

The TRF includes the following items:

- *Principal investigator*. Already known from registration on the web site and login procedure and will automatically be added to the request mail.
- *Requestor Institute*. Full address.
- *Number of samples necessary to perform the research proposal*. In order to avoid the requestors asking for more tissues than they need. This item will limit the amount of samples that can be added to the cryo-cart.

- *List of chosen samples*. Those samples incorporated in the cryo-cart.
- *Description of the research project and experiments to be performed*. This field is restricted to 250 words and must be in English. The requestor will have the possibility to upload a pdf version of the research project (at the same time as completing the tissue request form).
- *Approval of the Local Medical Ethics Committee or Multi-centre Research Ethics Committee, whenever necessary in accordance with regulations applicable to the requestor institute*. This item appears in the TRF as a YES or NO question.
- Number of the approval of the Local Medical Ethical Commission, MEC, or Multi-centre Research Ethics Committee, MCREC.
- Address of the Local MEC or MCREC.
- Comments of the Local MEC or MCREC, when available.
- *Is additional clinical patient data required?* With this field the requestor will inform the collectors of the need for additional data on requested samples once the experimental study has begun. As the on-line tissue data-entry method is a key part of the database, the additional information can be updated in the tissue record on the Central Database system. The TuBaFrost Consortium recommends that the requestor should be informed of the possibility of acquiring additional data before the collector gives their samples.
- *Research activities of the requestor*:
  1. Publications in the last five years (only the five most important).
  2. Most relevant publications related to the project research (only the five most important).
  3. *Summary of the scientific activities*. The knowledge of the scientific activities of other institutions might open up the possibility of future collaborations between the collectors and the requestors, including those not related with the proposal of the project.
  4. Any additional information that the requestor thinks important or relevant for the collector in making a decision.
- Expected benefits derived from the investigation.
- Is there any possibility that the project will lead to a patent application or is it part of a larger project aimed at a patent application? If YES, TuBaFrost Consortium recommends an extended tissue transfer agreement between the requestor and all collectors implicated in the research proposal, covering the expected patent.
- Financial support for the project, indicating the financing bodies: government, pharmaceutical industry, private funds, others.

When these forms are completed and submitted to the Central Database, the system will automatically generate e-mails to the TuBaFrost Central Office and the collectors involved in the request (recognised using the TuBaFrost inventory number of the samples). The e-mail generated for the collector will also include the e-mail address and the contact names for all those collecting institutions implicated in the same request. A schematic representation of the tissue request process is depicted in Fig. 1.

TuBaFrost Consortium estimates that the time for the collector's decision is 1 month, and that if more time is needed the requestor must be notified. Once the collector has taken the decision concerning the request, he will send a TuBaFrost transfer agreement to the requestor for ratification of the final agreement between the collector and the requestor. This document will commit both parties to:

Collector:

- Provide the tissue and related data as described in the request form as far as possible.
- Notify the requestor as soon as possible if providing the tissue and/or data meets obstacles, such as (but not limited to) the tissue is needed for further diagnostic procedures for the donor, the tissue has become unavailable or has become unsuited for the requested use due to unforeseen circumstances, the tissue cannot be shipped or exported due to applicable regulations.
- Provide tissue and related data which may only be used for the research as specified in the request form according to the regulatory and ethical standards applicable to the provider.

Requestor:

- Use the tissue and data only for research as specified in the request form.
- Use the tissue as allowed by the regulatory and ethical standards applicable to recipient.
- Make no attempts to find the identity of the donor or to derive other data from the tissue as follows from the research described in the request form.
- Not to sell tissue and its derivates, or to distribute it free of charge to third parties. The tissue may only be used to produce commercial medical products (including the production of cells or cell products for sale) in collaboration and with written permission of the collector and consent of the patient, subject to the regulations of the country of origin.
- Bear the costs of preparing the tissue as requested in the request form and of handling and shipping the tissue to the recipient.
- Return to the collector the remaining tissue and their derivates after performing the agreed research. The requestor agrees to assume all risks and responsibilities in connection with the receipt, handling, storage, use of the tissue and return shipment of the remaining tissue.

In addition, the tissue transfer agreement includes the following general clauses referring to the handling of tissues and co-authorship contribution:

- The requestor understands that while the collector attempts to avoid supplying tissue contaminated with highly infectious agents such as for instance hepatitis and HIV, all tissues should be handled as if potentially infectious. The requestor acknowledges that he/she is aware of and follows applicable

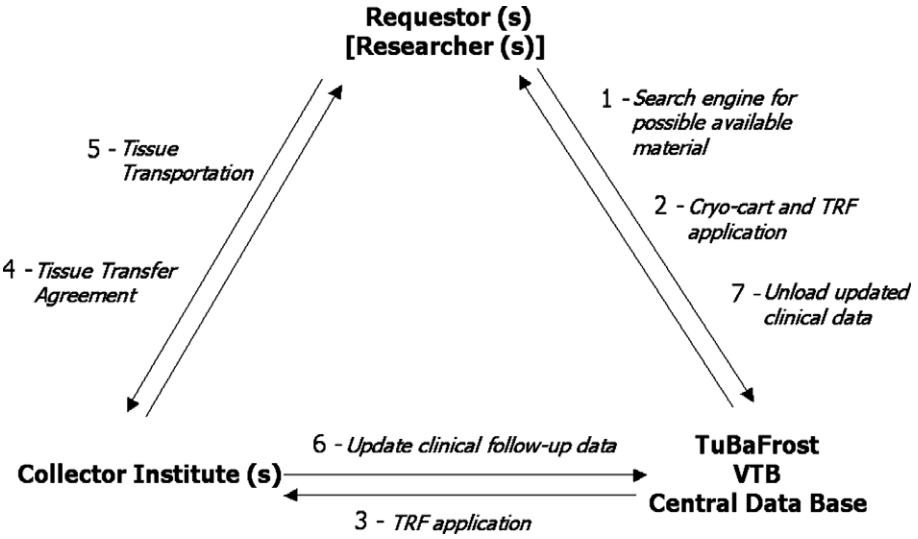

Fig. 1 – The tissue request process: VTB, virtual tumour bank; TRF, tissue request form.

regulations for handling human specimens and will instruct the staff to abide by those rules. The requestor further agrees to assume all responsibility for informing and training the personnel in the dangers and procedures for safe handling of human tissues.

- The tissue is provided as a service to the research community without warranty of merchantability or fitness for a particular purpose, including that which is described in the request form, or any other warranty, express or implied.
- Neither the collector nor the TuBaFrost consortium can be held liable for any loss, claim or demand made by the requestor, or made against the requestor by any third party due to or arising from the use of the tissue by the requestor, except to the extent permitted by law when caused by gross negligence or willful misconduct by the collector.
- The requestor hereby agrees to acknowledge the contributions of TuBaFrost in all publications resulting from the use of these tissues. Recommended wording to the acknowledgment or methods section being as follows: 'The tissue used in this publication was provided by TuBaFrost, the European Human Frozen Tumour Tissue Bank Network'. Furthermore, if additional services or facilities were utilised at the collecting institute(s) (beyond the sole activity of issuing tissue) and the results have contributed to a publication, the persons involved should be treated as co-authors of that publication.

The agreement between the collector and the requestor will be notified to the TuBaFrost Central Office, which will provide the requestor with a request reference number so that the requestor can follow the progress of the request on-line. Furthermore, TuBaFrost will also provide the collector with a series of recommendations for adequate frozen tissue transport between collector and requestor institutes through the TuBaFrost web site, with the aim of maintaining the quality of the frozen samples. In this sense, TuBaFrost recommends isothermal boxes containing dry ice in sufficient quantity to guarantee the optimal preservation of the frozen samples during the period of transport between collector and requestor institutes. In addition, it recommends using a transporter who can provide refreshment of dry ice in case a time limit has passed or a delay in transportation occurs.

Although the collector institutes are responsible for organising the sample transport to the requestor institute, the requestor will however assume the total costs of the operation. The TuBaFrost Consortium recommends that the minimum time for the transportation of samples will always be less than 72 h, in order to avoid deterioration of the sample.

6. Conclusion

In summary, the framework for access rules and incentives developed by the TuBaFrost consortium guarantees a minimum of conditions to provide simple and effective functionality for all users, whilst ensuring sufficient incentives for collectors and requestors and the guarantee that the tissue is used for the most ethically and scientifically sound research purpose.

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