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TuBaFrost 5: Multifunctional central database application for a European tumor bank ☆

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ABSTRACT

Developing a tissue bank database has become more than just logically arranging data in tables combined with a search engine. Current demand for high quality samples and data, and the ever-changing legal and ethical regulations mean that the application must reflect TuBaFrost rules and protocols for the collection, exchange and use of tissue. To ensure continuation and extension of the TuBaFrost European tissue bank, the custodianship of the samples, and hence the decision over whether to issue samples to requestors, remains with the local collecting centre. The database application described in this article has been developed to facilitate this open structure virtual tissue bank model serving a large group. It encompasses many key tasks, without the requirement for personnel, hence minimising operational costs.

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The Internet-accessible database application enables search, selection and request submission for requestors, whereas collectors can upload and edit their collection. Communication between requestor and involved collectors is started with automatically generated e-mails.

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1. Introduction

The purpose of the TuBaFrost project is to develop a virtual European human frozen tumour tissue bank for the whole scientific community composed of high-quality frozen tumour tissue sample collections.¹ The 'virtual' term in the context of this project means that although the tissue material is stored locally in the laboratories of the cancer centres and universities, an online network system has been developed that links all the local tumour banks together.²

Collecting tissue samples for research immediately prompts the need for sound administration of the collected and conserved samples, enabling the availability of corresponding clinical data and tracking of the samples. The instrument of choice for these tasks nowadays is of course a database application, which can expedite the aforementioned tasks. Another crucial task for a tissue bank database is the addition of the relevant clinical data,³ because it is well known that besides the quality and the contents of the sample, it is the clinical data accompanying the sample that determines the scientific value to a large extent.⁴ The central database application is even more important when it stands at the base of an open structure virtual tissue bank serving a large group of people from various countries in the European Union. This article describes the central database application developed for the European Human Frozen Tissue Bank (TuBaFrost) illustrating many unique aspects that need to be considered when developing a virtual tumour bank in Europe.

2. TuBaFrost project and its central database management system

At the centre of the online TuBaFrost network stands the central database management system to which the institutes' tissue bank administrators or 'collectors' can add or upload tissue sample records that they have collected. These tissue sample records consist of coded-linked patient data, tissue sample data and representative histological and virtual slide images.

Tools built in the system allow the TuBaFrost Central Office to coordinate and monitor the tissue requests efficiently, as well as support communication and cooperation between the collectors and requestors in accordance with the access rules developed in the scope of the project. The purpose of the central database management system can therefore be stated as to provide a:

- solid infrastructure for tissue information collection, along with a means for collecting institutes to add their frozen tissue collections to the network;

- gateway for the scientific community to find and request tissue samples for their research projects and
- management tool for the TuBaFrost Central Office to coordinate these requests and provide assistance when required.

The structure and function of the central database management system has been developed through discussion and cooperation between members of the TuBaFrost Consortium who have all played a crucial role in establishing the TuBaFrost Network. Therefore, the central database application is not only a tool for data storage and retrieval, but is also an instrument to implement the business rules as set by playing a crucial role in complying all users to agreements made within the TuBaFrost consortium. These include rules for registration, access, privacy and use of the patient clinical and tissue data.

These rules for access and use of the central database management system and the associated frozen tissue samples are based on an European Code of Conduct, which has been developed by the consortium, in order to comply with the various legal and ethical regulations surrounding research on residual tissue material within and between European countries as described in the related articles^{5,6} of the TuBaFrost series.

A business plan was made with regard to the operational costs to support the maintenance and efficient functioning of the system for both now and in the future.⁶

3. Dataflow

In order for these tissue sample records to be added to the central database, two types of online input systems have been developed: one to upload single cases and another for batch uploads.

The central database system within the network allows the scientific community, as registered 'requestors', access to these frozen tissue samples for their research projects. This is enabled through an online search engine where the requestor can set certain parameters (e.g. morphology and topography) of interest to their research project and the system will search through the entire database for relevant tissue material. The requestors are then able to make tissue requests directly through the system to the collectors who hold the tissue material. In this way, the system acts as a tool to enable the scientists to acquire the tissue material they require for their research projects.

As mentioned above, the information being entered into the TuBaFrost network by the collecting institutes consists of coded-linked patient data, from which the key is only known through local tissue bank safeguard procedures, tissue

sample data and representative histological and virtual slide images.

As tissue material is collected after surgery or biopsy, the local tissue bank administrator will collect and store the tissue material according to TuBaFrost Standard Operating Procedures.⁸ Tissue sample information will be entered into a local database for inventory control according to local practice. The access to the database application can be directly obtained at the home page of the web site. The access rights under which the user has been registered determine which functions are available. The system has hierarchic backbone for the functions, as determined by access rights that may be used. The minimal functionality is offered to a requestor, followed by the head requestor, the collector and the head collector. The role of an administrator is the highest in the access rights hierarchy.

4. Registration and access to the central database by collectors

In order to upload tissue records and information to the TuBaFrost network, the collectors must first register via the central database and identify named data-entry personnel (i.e. tissue bank administrators) responsible for entering or uploading these tissue records. The Central Database Administrator will activate their registration and notify that person, by e-mail, of their username and password in order to gain access to the central database. This e-mail communication ensures that incorrect addresses are immediately recognised at the point of registration. That person, when being the first registration from that institute, is designated head collector of that institute, and will receive all subsequent requests of that institute to become collector for activation, verified by a check of the affiliation of the entered e-mail address. The head collector function can be transferred by the head collector to another collector within that institute.

5. Data input into the TuBaFrost network by Collecting Institutes

5.1. Dataset items

Within the participating institutes and hospitals collecting and storing tissue samples, the amount of information associated with the patient and the tissue is potentially vast. Therefore, in order to assess the data items that should be entered and stored in the TuBaFrost network and what information should be available to researchers, a dataset of the minimal requested information necessary for input into the central database was discussed and developed amongst the TuBaFrost Consortium. Table 1 shows a list of the dataset items that can be entered.

5.2. Tissue and patient information data entry into the central database

The diversity of the computerised inventory systems and IT security rules in use throughout the participating institutions of the TuBaFrost Consortium necessitated careful consider-

Table 1 – Central Database: tissue sample data-set items

<i>Patient case data</i>
Local patient case code
Histopathological diagnosis 1,2,3 (morphology)
stage (and tumour-node-metastasis (TNM))
Grade
Age at time of biopsy/sampling (years)
Gender/sex
Clinical trial involvement
Medical history/treatment/complications/toxicity/concomitant disease/secondary
Tumours/laboratory data
<i>Tissue sample data</i>
Local inventory Tissue Code
Site of tumour (topography)
Tissue condition (tumour/non-tumour/interface)
Time (in h and min) elapsed after biopsy was performed and tissue sample was frozen
Availability of tissue sample (available/in use/terminated)

ation of the data entry options available. Initially, an Internet based automatic update system was investigated but proved unfeasible both financially and technically. In addition, the local languages used for patient data description proved to form a second bottleneck for direct automatic updates.

Instead, two online data-entry methods were developed, the 'Single record form entry' and the 'Batch record upload'. Following either method the local tissue bank administrator can upload tissue records into the central database system for incorporation into the TuBaFrost network. Data items for the single record form entry method are divided into two categories within the form: Patient Case Data and Tissue Sample Data. The local tissue bank administrator is required to complete and submit the form for each tissue sample. The batch record upload method was developed to make the process more efficient by enabling simultaneous upload of multiple tissue records through export of information from the local database directly to the central database. This record upload process proved to be difficult because of the different types of databases (both in-house developed and commercial) used within the network. Therefore, it was necessary to use a universal export file type and all databases appeared compatible with a tab-delimited text file format (*.txt). Therefore by using a predefined export template (column order matching data items from Table 1), collectors can export their tissue records as a tab-delimited text file and upload this text file into the central database. The individual tissue records containing the patient case data and tissue sample data are then incorporated into the TuBaFrost network. During that process the records are checked on errors. The erroneous records are kept in a separate table and shown to the user with the errors highlighted. These records can be edited and subsequently uploaded again from this screen. This process does not need to be finished, but can be interrupted by a log out. When logging in next time the erroneous records are still there and can be edited.

Both methods of data entry, batch and single upload, were implemented in the final system.

5.3. Updating tissue and patient information in the central database

As the tissue samples are transferred and used by the scientists, the TuBaFrost network requires updating facilities. Since the tissue samples are stored locally in the institutes, it is the responsibility of the institutes to keep this central database up-to-date about the status of the tissue records.

Therefore, whenever the tissue samples are transferred to other locations (i.e. for use in research projects) the collector institutes must update the status of the tissue record (i.e. available, in-use or terminated) within the central database. This can be done by accessing the tissue record online and changing the required data item, i.e. availability of the tissue sample.

5.4. Images within the central database

As well as patient and tissue data being entered in the central database, representative images and virtual slide images can be uploaded and viewed online.

5.4.1. Representative images

Representative images produced by pathologists (usually by image grabbing from a digital camera attached to a microscope) during pathology review can be uploaded into the central database system and aid in the selection process when viewed by other pathology experts for second opinion or can be used for quality assurance purposes.

5.4.2. Virtual slide images

Virtual slide images are produced by virtual microscope systems, which can digitise the entire glass microscope slides at high resolution to produce a digital image with diagnostic quality. Online image processing software tools allow the user to view, manipulate, position and specify the magnification of the image on screen as if using a regular microscope to view the original glass slide.

One of the data items to be entered for patient cases and tissue samples within the TuBaFrost central database is the histopathological diagnosis that was determined by the pathologist reviewing the patient case. This diagnosis (or morphology) is required to allow the researchers to select the most suitable tissue samples for their research projects. Representative digital images produced during histopathology review and virtual slide images produced by the virtual microscope will greatly support the diagnostic information within the central database.⁷ Virtual slide images, produced by the virtual microscope system (in this case the NanoZoomer from Hamamatsu Photonics and Medical Solutions Plc), can be displayed and used within the central database system that is linked to the tissue samples and patient cases.

6. Database structure

Within the central database the data items need to be grouped, ordered and linked. Therefore, tables are developed to store and link information in an organised way. The most important tables with their links are shown in Fig. 1.

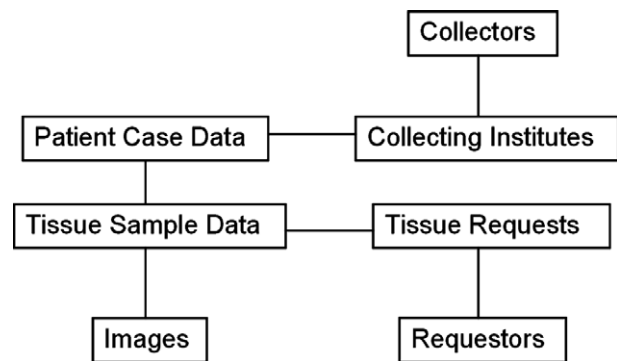


Fig. 1 – TuBaFrost Central Database structure.

7. Data output and usage by scientific community

7.1. Online searches

As mentioned in the introduction, the primary reason for the creation of the TuBaFrost network is to make frozen tumour tissue material more readily available to scientists for their research projects. Therefore, in order for the researchers to gain access to this network, online search facilities were developed to allow them to interrogate the entire central database.

In accordance with the European Code of Conduct for research on residual tissue developed for the TuBaFrost project,⁵ all tissue samples and patient case data are already anonymised at the local institute, so providing privacy protection. The tissue samples are allocated under a unique 'TuBaFrost Tissue Code' to enable tissue identification during the request process and transport – this code contains no patient identifiers.

In order for the central database to store the list and details of tissue requests, details about the requestor and other parameters, the requestor must first register as a requestor. This is accomplished by completing a simple form (full name and address of the requestor, phone number and e-mail address) that is submitted to the central database administrator or head requestor of that institute for allocation of a username and password, which are then e-mailed to the requestor.

Using this username and password the requestor can then log into the search engine. The user is confronted with a page as shown in Fig. 2 in which the user selects and enters search parameters (e.g. site of tumour (topography), diagnosis (morphology)) and the system displays tissue records matching the search criteria.

7.2. Cryo-cart (also often referred to as Basket or tissue shopping cart)

To allow requestors to keep a list of the tissue samples they wish to request for their research project, the shopping cart has been applied, see Fig. 3. When a tissue record from the search results is displayed, there is an option to add the item to the cryo-cart by using the selection procedure. This shopping cart can be viewed at any time during the search and request process and samples can be added or deleted.

Welcome to the Tubafrost Central Database

Users | ICD03 Topography | ICD03 Histology | Tissue requests | Your profile | Log off

Your tissues | Search tissues | Your orders | Your basket

Monday, 7 November 2005 - 16:55:52
Logged in: Dr. Peter Riegman (Erasmus Medical Center) - Head Collector

Search tissues

Please enter your search criteria

Local tissue code (without institute prefix)	
Local patient code	
Stage	
Grade (and TNM)	
Age at time of biopsy	eg: 65, >40, <50, 50-65
Sex	<input type="text"/>
Involved in clinical trial?	<input type="text"/>
Institute	<input type="text"/> <ul style="list-style-type: none"> CNO CRO Aviano Dutch Cancer Institute EC ESORTC Erasmus Medical Center Institut Gustav Roussy MedLavConsult Hold down 'Ctrl' to select multiple institutes
Collector	<input type="text"/> <ul style="list-style-type: none"> Prof. Carbone Antonio Dr. Dinjens WJM Dr. Eggeff E Dr. Geleff S Dr. Gloghini A Mr Gos Erik Mr Gos Erik Dr. greati ermes Hold down 'Ctrl' to select multiple collectors
Topography	<input type="text"/>
Histopathological diagnosis	<input type="text"/>
Condition	<input type="text"/>
Availability	<input type="text"/>
Search method	<input checked="" type="radio"/> Search on all selected criteria <input type="radio"/> Search on any of the selected criteria

Search Reset

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Fig. 2 – Search engine for the TuBaFrost Central Database.

Welcome to the Tubafrost Central Database

Institutes | Users | ICD03 Topography | ICD03 Histology | Tissue requests | Log off | Change admin

Your profile | Your tissues | Search tissues | Your orders | Your basket

Wednesday, 18 January 2006 - 17:18:18
Logged in: Mr Erik Gos (Spiritus) - Admin

Your basket

Tissue code	Topography	Diagnosis	Condition	Institute	Collector	
MIR_Tissue003	Q41.0	GALLBLADDER AND EXTRAHEPATIC BILE DUCTS (C238-C241,C248-C249)	non-tumor	University Hospital Leuven	Prof Van Damme Boudewijn (bo.vandamme@uz.kuleuven.ac.be)	delete

Order

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View tissue

Medical History/Treatment/Complications/ Toxicity/Concomitant disease/ Secondary Tumors/Laboratory data

Comments

Institute

Collector

Patient entered

Patient last updated

Tissue data

Tissue code	MIR_Tissue003
Topography	RECTUM (C209)
Diagnosis 1	
Diagnosis 2	
Diagnosis 3	
Condition	tumor
Time between biopsy and freezing (h:mm)	01:12
Availability	available
Comments	
Times issued	0
Patient Code	Patient003
Institute	University Hospital Leuven
Collector	Prof Boudewijn Van Damme (bo.vandamme@uz.kuleuven.ac.be)
Tissue entered	18/09/2005 11:10:11
Tissue last updated	18/09/2005 11:11:11

» Back to overview

» Add to basket

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Fig. 3 – Adding tissue items to the cryo-cart.

7.3. Tissue requests

- (i) When the requestor has selected all the tissue items that they wish to request, selecting 'Order' within the cryo-cart will bring up an online 'Tissue Request Form'.
- (ii) *Tissue request form* – As detailed within the associated access and rules article⁶ –, the tissue request form contains fields to collect information regarding the requestor and their research proposal.⁶ These fields include description of the research project and the experiments to be performed, local medical ethics committee approval, list of additional sample or patient data requests, research activities of requestor and details of financial support for the research project. This form will be submitted automatically by e-mail, along with the requestor details and list of tissue samples, to the TuBaFrost Central Office and to the associated collectors. A TuBaFrost Tissue Request number will be allocated and sent by e-mail to the requestor along with a list of the requested samples. The tissue samples available in the TuBaFrost network are stored within the collecting institutes, where the institutes retain the custodianship and responsibility over the sample.
- (iii) *Collector's decision* – Each collector involved in the tissue request will receive by e-mail a link to a list of tissue items requested from their institute as well as other involved institutes and a copy of the tissue request form completed by the requestor. The collectors will use the information contained in this e-mail (and available online via the central database) to decide whether to participate and make their tissue samples available to the research project. They will notify the requestor (as well as the other collectors involved in the tissue request) of their decision within one month via e-mail.

If the collector decides to release the tissue samples to the requestor, they must use the material transfer agreement template and adhere to TuBaFrost recommendations for sample transport and quality control. The obligation to use the material transfer is embedded within the TuBaFrost Code of Conduct, which establishes a contract for transferal and use of the tissue samples. This is in accordance with European legal and ethical regulations and TuBaFrost consortium agreements on access rules and incentives.^{5,6}

The TuBaFrost Central Office can be contacted to help solve any problems that might have occurred or simply to provide support during this process.

In the event that the requestor requires additional patient information data it can be assembled, coded or anonymised and sent to the requestor separately by e-mail or with the shipment of the samples.

8. Conclusion and future perspectives

The TuBaFrost project's primary aim is to develop a virtual European network of frozen tumour tissue banks for the whole scientific community working on human diseases. One of the cornerstones of this network is the online central database management system allowing institutes that collect and store frozen tumour tissue samples to manage the infor-

mation regarding these samples. In addition, the system has the tools to function as a broker between those collecting and those in need for tissue for their research projects. Moreover, the business rules of the exchange process are built in the system.

This will encourage and promote cancer research within the European Community.

The future vision of TuBaFrost focuses upon the expansion of the network to include other types of repositories and tissue banks (e.g. paraffin embedded samples, liquid samples, tumour cell line, and xenografts repositories). In addition, links could be established with regional and national cancer registries, epidemiology data, European Organisation for Research and Treatment of Cancer (EORTC) clinical trials, patient care and translational research groups. With the expansion of the European Community, legal and ethical considerations will be extremely important and the TuBaFrost network must maintain the European Code of Conduct and develop other policies and regulations for tissue banking and research within Europe.

With the extension of the network, other faster and more efficient methods of entering data into the central database will be required, for example, local and central database auto-synchronisation or software that can extract requested data from a local database and transfer it to the central database over the Internet (with the appropriate permission of the database owner). The database structure will require considerable expansion to enable these new types of repositories and data types to be ordered and grouped. Accordingly, the online search engine and tissue request system must be expanded and stream-lined to allow scientists to efficiently locate tissue or liquid samples for their research projects within the multiple tissue bank types within the expanded network.

Conflict of interest statement

None declared.

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