

OECI TuBaFrost tumor biobanking

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ABSTRACT

TOECI TuBaFrost harbors a complete infrastructure for the exchange of frozen tumor samples between European countries. OECI TuBaFrost consists of:

- A code of conduct on how to exchange human residual samples in Europe,
- A central database application accessible over the Internet (www.tubafrost.org) where data can be uploaded and searched from samples that can be selected and ordered
- Access rules with incentives for collectors,
- Standardization needed to enable the analysis of high quality samples derived from different centers
- Virtual Microscopy to support sample selection with difficult pathology

The entire infrastructure was, after completion, which was entirely financed by the European Commission, implemented in the OECI. But so far it has not been used to its capacity. A recent survey held amongst the OECI members shed light on the causes. The main conclusion is that all responders see OECI TuBaFrost as a good platform for exchange of samples, however, the biggest bottleneck found was that potential users are too unfamiliar with the communication between their own biobank tracking system and the TuBaFrost central database application. Therefore, new future plans are drawn. In addition, new infrastructure plans have been developed and the first preparatory steps have been set. For biobanks the BBMRI project has started aiming for Pan-European Biobanking and Biomolecular Resources Research Infrastructure.

Introduction

The TuBaFrost project started out as a framework 5 European project, that had the goal to set up a network of frozen tumor banks amongst the consortium members¹. It was based upon the idea the treasure of information hidden in human tumor samples^{2,3,4} could be more efficiently used for cancer research⁵. The consortium members or institutes are all active in the OECI and/or EORTC. From the start it was clear it had to be an infrastructure that had a low operation cost, because after three year funding from the European commission there was no sustainability. Therefore, processes requiring personnel were avoided, which in turn resulted in a database application that where feasible automated most of the different processes involved in the communication amongst collectors and requestors of samples.

The success of the network is depending mostly on voluntary contributions of the collectors, as a consequence, low invasiveness at implementation and incentives for collectors need to be implemented in the infrastructure and unnecessary measures avoided wherever possible. This appeared to be a big challenge when trying to determine the standardization and quality assurance⁶. In addition, the access rules of the network should have no or only limited consequences on the normal local exploitation of the samples⁷.

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The infrastructure

During the project the vision developed that the access rules of the biobank were in fact correlated closely to the incentives. Specific awareness developed on possible future conflicts when installing a review board that would evaluate the participation in a request could have a large negative impact on the incentives. Therefore, it was chosen to let the collector keep the full custodianship over the collected samples. This leaves room for complete autonomous negotiation between collector and requestor on cooperation, publication and compensation in costs in exchange of the samples. For issuing samples can be followed. In addition, the local biobank rules for access with local decision protocols and responsibilities⁸ can fully applied without interference of the network. This would in turn stimulate cooperation in multi-center translational cancer research, whereas in addition, the collector has the local collection at their own disposal as usual, which can now be topped off by requesting samples from the network. The chances of obtaining cooperation on the basis of the collection with for instance at that moment cutting edge technology, which forms a strong incentive, permits and stimulates even the upload of scientific highly valuable collections

The low operating costs also imply the samples to stay at the local collector until they are needed for use. The data of the samples are collected in a central database⁹. Luckily, this was also in complete concordance with the most favorable access rules described above, where the local collector should be able to use its own collection as usual. The central database needed to automate several protocols. The collector is asked to register and upload the data of every sample (in batch or per sample) and keep this data up to date. The database application has the sole purpose to set up communication between the collector and the registered requestor on basis of the sample data that is presented to the requestors, so they can request the samples by searching and selecting the collections. The request process asks the requestor to describe several subjects to make a sound evaluation of the request possible, e.g. full name and complete address of the requestor, the experiments planned, Internal review board (IRB) or Medical Ethics Commission (METC) approval number, the already reached results, recent publications, involved grants, the requestors recent scientific activities etc etc. When the request is submitted e-mails will be generated automatically to the involved collectors with the requestors e-mail address as sender. This way only those that have registered properly with their actual e-mail address will get the communication going. In addition, the administrator checks all new collector and requestor registries on their involvement in medical research or biobanking for medical research before the registration is actually activated. The communication can then be focused on the conditions

of exchange as laid down in the access rules. It is clear that transport costs need to be reimbursed by the requestor, however, negotiations between the stakeholders might give another end result. A complete Material Transfer Agreement and a Code of Conduct for exchange of residual samples support the transfer of samples across the borders of European countries. The code of conduct is embedded in European law¹⁰ and is actually simple to use. The basic rule is: 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 in that other country has other regulations in force for residual tissue research collected from patients under their jurisdiction.

In a biobank network it is of the utmost importance to be able to acquire samples from more than one institute, which can be compared within the results of one experiment. Hence, standardization measures for the collection and storage of frozen samples are needed to share samples of equal high quality. However, standardization cannot be one Standard Operating Procedure (SOP) that has to be implemented at all participating institutes, because that would have too large an impact on the invasiveness of the network on the volunteering institutes. Therefore, it was necessary to identify all steps needed for obtaining a high quality sample and weigh the impact of that step on the quality of the sample and determine the alternatives possible that lead to equal quality. This way the TuBaFrost consortium could describe a minimum standard protocol and quality assurance for fresh frozen tissue samples that results in samples that can be used in future multi-center experiments⁶. In addition, the obtained quality is high so the samples can be used in sensitive experiments. To give examples of the choices offered in this protocol, the protocol used by Erasmus MC tissue bank was published to show an example SOP compliant to the TuBaFrost standardization and Quality assurance¹¹.

Exploitation of TuBaFrost

Although, the OECI TuBaFrost platform is receiving a lot of attention, it is not yet used for exchange of samples, as foreseen. A recently held survey amongst OECI members shows that all the responders see TuBaFrost as an excellent platform for sample exchange. However, the potential users feel not very confident using the central database and are in need of support uploading sample data. This shows there is a serious bottleneck between the local database and the central database. It is for biobank staff too much work and more importantly also too difficult to efficiently do a time consuming translation of the sample description for a batch upload

of sample data also without really knowing the benefits of the system for the local biobank.

Plans to change the data (batch) upload procedure from a sample-to-sample basis to filling out a questionnaire instead are in preparation. This questionnaire asks information about the general local collection and needs to be updated only if major changes have occurred in the collection with a minimum of once a year.

The sample-to-sample data works much better in a multi center project driven environment like designed for the European project EuroBoNeT. This 6th framework European project uses the infrastructure of TuBaFrost with additions to the database application specified by the EuroBoNeT consortium to exchange samples in a closed environment to support their multi-center studies on bone tumors. The database application has been adapted to the wishes of the consortium to also handle FFPE, cell lines, xenografts and blood/serum samples with different isolation methods. In addition, stocks of derivatives from the sample can be traced and prospective collections started. Furthermore, searchable facts originating from experimental results can be added as well as links to the large result files. These additions, however, have been designed such that they can be successfully exploited for other projects as well and it has become a very usable application also for other projects to support sample exchange. The whole EuroBoNeT application can be easily adapted to create an environment in TuBaFrost to support more than one project in their closed environments and where the open TuBaFrost environment is served by the questionnaire format, allowing already the desired communication on requests. This would also be the environment of choice to look for partners when starting to think on the submission of an International/European project proposal involving translational cancer research.

Future European plans

Although the planned changes for TuBaFrost look absolutely necessary, logical and straightforward, it is not easy to find European resources to finance and realize these ideas. National funding will not provide a budget for European oriented plans, whereas European calls for biobanking infrastructure seem to be focused entirely around the new ambitious roadmap provided by the European Strategy Forum on Research Infrastructures (ESFRI)¹².

From the ESFRI roadmap many infrastructure projects are starting their preparatory phase. This phase is meant to prepare the basis for the creation of the real infrastructure. The biobanking facility described by ESFRI should become a (quote) "pan-European and broadly accessible network of existing and de novo biobanks and biomolecular resources. The infrastructure will in-

clude samples from patients and healthy persons, molecular genomic resources and bioinformatics tools to optimally exploit this resource for global biomedical research." From this basis the BBMRI proposal was submitted and approved for financing. BBMRI is a project that has the aim to create a Pan-European Biobanking and Biomolecular Resources Research Infrastructure. The BBMRI project plans to network the important existing European biobanks of different research strategies. These strategies can be divided in two important streams:

1. Population biobanks containing the longitudinal population-based cohorts and twin registries
2. Disease-oriented or clinical biobanks containing clinical case/control studies

Both streams are expected to have huge impact on future target and biomarker discovery and therewith change the landscape of personalized medicine by identification of new subgroups and new drug development. The OEI TuBaFrost network and its members are, of course next to many others, represented in the BBMRI work package 3 on disease-oriented biobanking. This way the gained experience and the future plans can be used in BBMRI and OEI. The future resource centers in the network will need to comply with guidelines as published by the OECD¹³, ISBER¹⁴ and IARC¹⁵.

There are still many challenges left to solve for networking biobanks on an International or even global level. Subjects concerning global harmonization have been discussed within the Marble Arch group and even attempts were undertaken to couple the three networks CTRnet from Canada with TuBaFrost and the Alleanza contra il Cancro in Italy. However, also on this level of networks, similar bottlenecks are encountered as from the local institute to central database level: Local or National multiple (self-designed not standardized) database systems in use for sample tracking and different languages used for description, multiple coding lists (e.g. Snomed, ICDO-10) that in addition ask licensing costs per user both forming a barrier to design a general automated interface to upload data. The dynamics of local laws and ethics on the use of human samples for medical research jeopardizes exchange within European countries. This same problem of course occurs on the global level at an even larger scale.

The strength of these ESFRI projects is that they involve National fundraisers and ministries of health to synchronize the European plans with the National ones and in this way creating a more sustainable environment. In addition, the planned infrastructures BBMRI, EATRIS, ELIXIR, INSTRUMENT and IMI form each of them an important part with overlap into the different projects in the complete roadmap for better biomarker and drug discovery.

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