Bimetra Biobank: A High Quality Biobank Facility to Stimulate Translational Biomedical Research

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Bimetra Biobank is the central high quality biorepository of University Hospital Ghent in collaboration with Ghent University (Belgium). Fully operational since 2015 in a new state-of-the-art biobank facility, Bimetra Biobank acts as a core facility for researchers and third parties looking for high-quality annotated clinical biospecimens. Bimetra Biobank stores about 120,000 clinical samples, both historical collections and prospective collections (disease-based collections, population-based collections and basic research collections) within well-defined and ethically approved research projects. Through a clear governance structure compliant with applicable laws, collections are operationally managed by Bimetra biobank personnel and samples releases are coordinated through collection specific coordinators and advisory boards. Biobank collections are open for collaborations to the international scientific community.

Keywords: hospital integrated biobank; clinical biobank; population biobank; high quality samples; service provider

Funding statement: The Bimetra Biobank facility was established with a one-off FFEU infrastructure fund (Flemish Government) and matching funds from Ghent University Hospital. The facility is operationally managed through a fee-for-service model complemented with an annual fee tumour biobanking (National Cancer Plan Minister Onkelinx, action 27).

(1) Bioresource Overview

Project description

The Bimetra Biobank is the central high-quality biorepository of Bimetra, the Clinical Research Centre (CRC) [1]. Bimetra was established in 2010 as central point of contact (CPOC) for facilitation of translational biomedical research within Ghent University Hospital in collaboration with Ghent University. The mission of Bimetra is to reinforce the translation from basic research discovery studies to validation studies and clinical trials by creating an effective ‘discovery-to-care continuum’ towards health care innovation. Being able to build upon resources is key in accelerating translation and strengthening the position of Academic Health Centres. To achieve this goal, Bimetra is organised in five specialized platforms to facilitate specific research aspects (Figure 1).

Bimetra Biobank is a central biorepository at Ghent University Hospital, facilitating all aspects related to high quality sample processing, storage and distribution. Bimetra biobank acts as a core facility for local researchers and third parties in need of high quality biobanking. Local strategic prospective collections, important historical collections and interuniversity focus collections are operationally managed within the biobank. The collections in the Bimetra Biobank are diverse, ranging from disease-based clinical to population-based cohort collections, besides a cell line catalogue. A detailed overview of collections hosted at Bimetra Biobank can be found below under bioresource type.

The day-to-day operational management of Bimetra Biobank is performed by the biobank manager under supervision of the Head of Department of Bimetra. Sample processing, storage and associated data management is performed by the lab technicians. For each particular primary collection a coordinator (MD) is appointed, responsible for interactions with donors (ICF, sample prelevation, incidental findings, secondary use). For general/central collaborative collections, the coordinator confers with an advisory committee of specialists regarding sample requests. E.g. for the tumour biobank collection, the tumour biobank coordinator confers with the multidisciplinary cancer-specific oncological advisory committee. The biobank manager facilitates sample requests handling in interaction with collection coordinators to ascertain approval for sample release. A general hospital biobank coordinator was appointed to oversee compliance with all applicable laws, policies and regulations.

An overview of the governance structure of Bimetra Biobank is described in Figure 2.
Bimetra Biobank is part of the Flemish Biobank Network (Centre for Medical Innovation (CMI)), within the Belgian node BBMRI.be of the European Biobank Network BBMRI-ERIC. The Flemish Biobank Network was officially founded in December 2009 through a collaborative effort between the Flemish Government, the Flemish Ministry of Economy and Scientific Affairs, the 5 universities and the 4 university hospitals and representatives of the Healthcare Industry. Bimetra Biobank together with each university hospital in this Network was able to set up a central high quality repository facility by 2015 through a one-off governmental funding (8 M EUR for all collaborating centres in total and matching funds from the participating institutions). The initiation of the Flemish Biobank Network and available funding led to jointly set up local biobank infrastructures within a harmonized quality framework, according to ethical and legal requirements, with common access procedures and an integrated interuniversity catalogue [2] of available samples. A uniform quality management system was implemented within this Network according to the International Society for Biological and Environmental Repositories (ISBER) Best Practices for Repositories Guidelines [3] and Organisation for Economic Co-operation and Development (OECD) guidelines for biorepositories [4] and is adapted for storage of
different sample types in controlled and temperature monitored Ultra Low Temperature (ULT) devices and isothermal freezers. Besides cryogenic storage capacity, Bimetra Biobank has established a laboratory for sample processing (e.g. serum separation, buffy coat preparation, Quality Control (QC), Formalin-Fixed Paraffin Embedded (FFPE) slide and cryosection preparation, isolation of nucleic acids) which follows Good Laboratory Practices (GLP). The laboratory is located next to the storage facility, in order to minimize critical transportation time of samples. All samples are registered in the biobank management system, SLims (from Genohm) [5] with an associated minimal dataset, including International Statistical Classification of Diseases and Related Health Problems codes (ICD-10) and International Classification of Diseases for Oncology (ICD-O3) codes, both established by the World Health Organization (WHO). This is supplemented with the sample pre-analytical data to automatically generate the Standard PREanalytical code (SPREC) [6]. The flexibility of our biobank management system with integrated Electronic Lab Notebook (ELN) system allows for easy automated collection of the parameters needed for the SPREC coding linked with information from various other databases. Throughout all collections minimal datasets are used, often linked to larger collection specific datasets making the datasets very valuable. In addition, the quality management system is provided with a document control system for Standard Operating Procedures (SOPs). Bimetra Biobank is partner of Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) with an associated minimal dataset, including International Statistical Classification of Diseases and Related Health Problems codes (ICD-10) and International Classification of Diseases for Oncology (ICD-O3) codes, both established by the World Health Organization (WHO).

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to 5 ml, straws, stabilizer tubes (Paxgene tubes) or biobanking tubes of 300 or 600 µl. The type of storage is dependent on the specific needs of the research project and requests from the researchers.

**Type of long-term preservation**

Frozen samples: in access-controlled and temperature-monitored facility with locked –80°C freezers and isothermal freezers (LN2).

FFPE tissue samples: in access controlled and temperature-monitored storage cabinets.

**Storage temperature**

Isothermal freezers (−170°C to −190°C), −80°C, −35°C, −20°C, 4°C, room temperature (18°C–25°C).

**Shipping temperature from patient/source to preservation or research use**

0–4°C (on ice); room temperature (18–25°C).

**Shipping temperature from storage to research use**

−170°C to −190°C (liquid nitrogen), −80°C (on dry ice); 0–4°C (on ice); room temperature (18–25°C).

**Quality assurance measures**

Samples are processed according to harmonized procedures (SOPs), by trained staff. All process steps are recorded into the ELN of the sample- and data management system, automatically generating the appropriate SPREC Code. The SPREC codes are a general indicator of the sample quality and the appropriateness of a sample to be included in specific types of analysis.

Yearly, a quality check of general tissue and liquid samples is performed. Specific care is taken into account for selection of the samples to be sacrificed for the quality control procedure, so that unique and rare samples are never accidentally selected.

Principal measures for ensuring the quality of samples:

### Table 1: Generic processing protocol data.

<table>
<thead>
<tr>
<th>Type sample type</th>
<th>liquid sample</th>
<th>serum, plasma, plasma low platelet, plasma and RBC rest, buffy coat, viable PBMC, cell lines, urine, semen, reproducitive material, stool, frozen tissue, tumor, frozen tissue, normal, frozen tissue, other, FFPE tissue, reproducitive material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary collection tube</td>
<td>serum separation tube with clot activator, Potassium EDTA tube, Potassium EDTA tube, NA, 30 ml PP tube, straws, cryovials and straws, 30 ml PP tube and 1.5 ml PP tube, NA, NA, NA, NA, NA</td>
<td></td>
</tr>
<tr>
<td>Processing</td>
<td>1500 g at RT, 10 min, 815 g, 4°C, 10 min and 2500 g, 4°C, 10 min, 3200 g at RT, 12 min and 2000 g, 4°C, 10 min, 815 g, 4°C, up to 20, NA, NA, controlled rate freezing, controlled rate freezing, weighing and aliquoting, macroscopical dissection and freezing, macroscopical dissection and freezing, macroscopical dissection and freezing, formalin fixation and paraffin embedding, macroscopical dissection and freezing</td>
<td></td>
</tr>
<tr>
<td>Freezing</td>
<td>slow rate freezing, ULT, slow rate freezing, ULT, slow rate freezing, ULT, controlled rate freezing, ULT, controlled rate freezing, device, slow rate freezing, ULT, snapfreezing isopentane, snapfreezing isopentane, snapfreezing isopentane, controlled rate freezing, device, controlled rate freezing, device</td>
<td></td>
</tr>
<tr>
<td>Aliquots</td>
<td>3 to 6, 3 to 6, 3 to 6, up to 20, 1 to 10, 1, multiple, multiple, 1 to 5, 1 to 5, 1 to 5, multiple, multiple</td>
<td></td>
</tr>
<tr>
<td>Storage (main storage)</td>
<td>−80°C, −80°C, −80°C, isothermal freezer, −80°C, −80°C, −80°C, −80°C, −80°C, −80°C, −80°C, −80°C</td>
<td></td>
</tr>
</tbody>
</table>
preparation of a cryosection with Hematoxylin and check of the SPREC code and appropriateness with check of required volume and amount of aliquots
• Maintain the database up-to-date.

Checks that are performed:
• DNA extraction, quantification and integrity check with DNA Integrity Number (DIN) assessment
• RNA extraction, quantification and integrity check with RNA Integrity Number (RIN) assessment
• Buffy coats: viability checks

When samples are requested, dependent on the type of sample, additional checks are performed.

• all samples:
  ◦ location check
  ◦ check of required volume and amount of aliquots
  ◦ check of the SPREC code and appropriateness with regard to the specific analysis
• tissue samples:
  ◦ preparation of a cryosection with Hematoxylin and Eosin (H&E) staining
  ◦ evaluation performed by a pathologist

In 2016, the Bimetra Biobank participated in the Integrated Biobank of Luxembourg (IBBL) proficiency testing (ISBER endorsed) for DNA extraction from tissues, DNA quantification, RNA extraction from tissues, RNA quantification and buffy coat preparation. The Bimetra Biobank performed very satisfactory in all categories.

Source of associated data
As mentioned before, the Bimetra Biobank has implemented several minimal datasets:

• for tumour related material: tumour biobank minimal dataset with ICD-O-3 coding and TNM Classification of Malignant Tumours (TNM) coding
• for other collections: Flemish Biobank Network minimal dataset with ICD-10 coding for diseases

Both minimal datasets also include all parameters needed to generate the SPREC coding. All this data is recorded and kept in the sample- and data management system, SLims. The system is customised according to the Bimetra Biobank specific needs. Furthermore, the minimal dataset can be extended to project specific datasets. Patient and disease related data is collected through automatic data retrieval from several linked databases, such as the electronic patient health records and pathology records. These database connections are strictly project specific and established after all legal and ethical approvals are obtained. The automatic data retrieval minimizes the risks in mistakes or misidentifications. This data can be completed with data from questionnaires and laboratory analysis, inputted manually or through coupling with electronic Case Report Form (eCRF) modules.

To improve accessibility and visibility of the samples and data sharing for translational clinical research, the Flemish Biobank Network has recently set up a catalogue of biobank samples [2]. The catalogue maps different data sets and subsets from autonomous database systems enabling aggregated query results and threshold induced notifications for participating researchers (Figure 3). At each Partner Biobank within the Network, harmonized datasets are uploaded to a local Opal database. Aggregated results of a subset of the variables is made available to the central catalogue, Mica (referred to as the central backbone in figure), which is query able in real-time through the online catalogue. A verified email address suffices for querying the Minimal Data Set of 12 variables. Query terms can be added using real-time filtering of ontologies (ICD-10, ICD-O-3) or aided by statistics of the variable. No individual-level data passes through Mica (the central backbone), yet researchers can assess the suitability of a dataset for their needs. The results are shown as grouped data with a total result of matching samples to query data. The sample can be requested through sample access flows, specific to each partner of the Flemish Biobank Network.

**Ethics Statement**
All collections managed within the Bimetra Biobank have been established in the context of a predefined research project for which an Institutional Ethical Review Board approval was obtained. All projects comply with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the Good Clinical Practice (GCP) regulation and Data protection regulations.

Primary use of samples is accepted only within the predefined research goals, secondary use is subject to a revised Ethical Board approval and in addition the donors need to be recontacted to reconsent to the secondary purposes. All data related to the donor collected in the database system, are pseudonymised. The database system, SLims, implies a coding strategy which is compliant with current privacy regulations, and will be updated for implementation of GDPR.

**Constraints**
N/A

**Bioresource description**

**Object name**
Bimetra Biobank

**Bioresource name**
Bimetra Biobank UZ Gent

**Bioresource location**
Bimetra Biobank UZ Ghent
De Pintelaan 185-1DWR
9000 Ghent
Belgium

The Bimetra Biobank is located at Ghent University Hospital. The central biobank facility is located at DWR, -1 (basement). There are multiple sample collection points at the University Hospital, such as the Pathology Department for tissue samples and the central clinical lab for blood, serum and plasma samples.

Bioresource contact
bimetra.biobank@uzgent.be

Bioresource URL
www.bimetra.be/biobank

Identifier used
BE_71067049; Bimetra Biobank @ UZ Gent, BBMRI-ERIC

Bioresource type
The Bimetra Biobank is a central hospital integrated biobank, comprising of a number of disease-oriented biobanks, population-based biobanks and basic research collections.

- Disease-oriented biobanks:
  - Hepatotropic pathogens: HCV and HBC
  - Inflammatory Bowel Diseases: Colitis Ulcerosa, Crohn’s disease
  - Rheumatoid arthritis
  - Chronic Obstructive Pulmonary Disease (COPD)
  - Chronic Renal failure
  - Neurodegenerative diseases: Multiple Sclerosis
  - Cancer related collections
    - Cancer tissue bank (solid tumours): prostate cancer, breast cancer, urothelial cancer, cervix cancer, lung cancer...
    - Cancer serum collection
    - Pediatric hemato-oncology biobank
  - Population based biobanks:
    - Asklepios collection (cardiovascular risk factors and aging (longitudinal cohort))
    - Twin registry (East-Flemish Twin register)
    - Hepatotropic pathogens: population serum collection
  - Basic research collections:
    - Human embryonic stem cells and iPS cells for stem cell research
    - Reproductive health collections
    - Cancer cell line collections (human): primary and immortalized

Type of sampling
Operational management of multiple type collections:
- population-based cohort collections with longitudinal follow-up
- disease-based collections
- hospital-based clinical collections (residuary material after diagnosis)
- hospital-based clinical trial collections
- tumour biobank collections

Anatomical site
Several anatomical sites in the body are covered, depending on the focus of the collection.

Disease status of patients/source
Available.

Figure 3: Overview of the data-structure of the Flemish Biobank Backbone.
Clinical characteristics of patients/source
As mentioned in the associated data, a minimal dataset is accessible for each sample in the Bimetra Biobank, with inclusion of ICD-10 or ICD-O3 and TNM Classification of Malignant Tumours codes (for tumour related samples). Project specific extended datasets with multiple clinical parameters and questionnaire information can be made available in the research collaboration, depending on the type of collection and the criteria followed for sample and data collection.

Vital state of patients/source
Alive at time of sampling.
Small collection of post-mortem samples.

Clinical diagnosis of patients/source
Available in dataset: ICD-10 or ICD-O3 classification. Healthy collections and disease-based collections.

Pathology diagnosis
Available in dataset when applicable.

Control samples
Control samples are available in multiple specific collections. Most frozen residual tumour samples are stored with matching normal tissue. Several collections have healthy control samples available.

Biospecimen type
A different variety of samples is available, depending on the specific project and related research settings, such as serum, plasma, platelet low plasma, viable Peripheral Blood Mononuclear Cells (PBMCs), tissue, cells, DNA, RNA, cell lines, urine, stool...

Size of the bioresource
Bimetra Biobank is not a project, but is part of the CRC Bimetra and has no fixed expiry date. The size of each project collection within the Bimetra Biobank varies. In general, about 120,000 samples are currently present in the Bimetra Biobank, originating from different research projects and in collaboration with multiple researchers, comprising both prospective and historical collections. In Figures 4 and 5, an overview of the amount of stored samples and distribution of samples can be found.

Release date
Data and samples in the collections are available within the context of well-defined research collaborations in consensus with all parties involved.

Access criteria
Samples and associated data from collections within the Bimetra Biobank can be applied for further biomedical research. A sample request can be launched through the Flemish Biobank Backbone [7], through the sample locator of BBMRI (national node BBMRI.be) or by filling in the sample request form on the Bimetra biobank website [9], using a set of minimal parameters. Every researcher worldwide can send in a request to the Biobank.

Bimetra Biobank will facilitate downstream processes regarding the sample request (such as contacting the coordinator of the collection and sample flow release, assistance and (p)review of an IRB approval to ensure that the planned methods on the requested samples are ethically sound, research agreement negotiations, QC control of the requested material and sample transport). In addition, Bimetra Biobank has implemented and executed SOPs for retrieval of samples and data within its quality management system. The Bimetra Biobank will act as a trusted third party collaboration, ensuring patient/donor coding/anonymity.

The costs will vary related to the type and amount of samples that are shipped and the specific data that is requested, as is set out in the research agreement with integrated Material Transfer Agreement (MTA)/Data Transfer Agreement (DTA).

(4) Reuse potential
Samples and data in the Bimetra Biobank collections can be used in different scientific projects. A sample request can be launched by filling in the sample request form on
the Bimetra biobank website [9]. Additional clinical data related to Biobank samples can be traced through the electronic health record systems via the treating physician or the medical ‘controller’ (as following Belgian legislation concerning the requirements for collection, storage and use of human bodily material for research purposes), and aligned with the IRB approval and the provisions in the research collaboration agreements on the sample and data use.

In sample distribution, Bimetra Biobank acts as a trusted third party, ensuring donor anonymity by coding of the samples. The applicant must follow the agreements made in the MTA/DTA with the primary researchers of the collection and acknowledge the Bimetra Biobank, according to the COBRA guidelines [10] for standardised biorepository citations. The actual citation for each collection, with unique reference number, is specified in the MTA agreement.

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We explicitly want to acknowledge all partners in the Flemish Biobank Network and their liaison officers in particular, Prof. Nadine Ectors, Prof. Peter in ‘t Veld, Prof. Elke Smits, Prof. Veerle Somers. In addition, we acknowledge the Pathology Department of UZGent with Prof. Marleen Praet and Anne Hoorens in particular and the UZGhent Biobank Medical Director, Prof. Dr. Catherine Van Der Straeten.

Competing Interests

The authors have no competing interests to declare.

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References