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BIORESOURCE PAPER

Biobank Graz: The Hub for Innovative Biomedical Research

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Biobank Graz was established in 2007 as publicly funded, non-profit central research facility of Medical University of Graz, Austria. Biobank Graz is ISO 9001:2008 certified and stores about 7.5 million samples and their associated data, including formalin fixed paraffin embedded (FFPE) and fresh frozen tissues plus fluid samples (serum, plasma, full blood, urine and cerebrospinal, follicular and seminal fluids, etc.) covering 30 years of collection. Samples are handled and stored in semi or fully automated systems to optimally maintain sample quality and retrieval rates. With its broad informed consent, Biobank Graz distributes samples worldwide to ethically and scientifically approved research projects from academia, industry, and cooperative studies in biomedical sciences. This is why Biobank Graz can be viewed as a central hub for biomedical research.

Keywords: clinical biobank; storage automation; ISO9001:2008; sample collection; follow-up samples
Funding statement: As a central research infrastructure of Medical University of Graz, funding for personnel and running costs of Biobank Graz comes from this university. Infrastructure development has been supported by the Austrian Federal Government of Science, Research and Economy (bmwfw) (Konjunkturpaket II) as well as by the Local Government of Styria (Zukunftsfond). Also the city of Graz has supported Biobank Graz as well. Finally, Biobank Graz is supported by a grant from bmwfw to BBMRI.at (GZ 10.470/0016-II/3/2013).

(1) Overview

Project description

Biobank Graz was established in 2007 as a central research infrastructure of Medical University of Graz, Austria. Since 2009 Biobank Graz is ISO9001:2008 certified and runs a quality management system with a document control system for standard operation procedures (SOPs) and associated documents [1, 2]. Today, Biobank Graz has incorporated all major collections within Medical University of Graz including the archive of the Institute of Pathology. This is why Biobank Graz is one of the largest clinical biobanks in Europe, storing more than 7.5 million samples.

The University Hospital Graz is owned by the Styrian Hospital Corporation (KAGes). KAGes and Medical University of Graz jointly take care of medical care within the hospital, while MDs (medical doctors) of the university are also involved in research activities as well as providing teaching for medical students. As a research infrastructure of Medical University of Graz, Biobank Graz has a cooperation agreement with KAGes on how samples are collected, transported and stored. Also, the mutual benefits and obligations of the two partners are regulated with this agreement.

Biobank Graz does not only look at the quantity of samples, but has also developed strategies to maintain sample quality. Automation of liquid handling and (semi-) automated storage of FFPE samples, fluid samples and selected cryo samples has opened the way to standardized processes, optimized sample handling and maintenance of highest sample quality within the workflow processes of Biobank Graz.

Biobank Graz provides a variety of human biological samples such as full blood, serum, plasma, buffy coat, urine, and other body fluids plus fresh frozen tissues and FFPE tissues. Due to the all-in character of the collection of the Institute of Pathology, Biobank Graz contains a cross-sectional collection of unselected pathological samples and clinical data, representing all detected diseases at their natural frequency of occurrence, stored as FFPE samples since 1984 [2]. At the same time, Biobank Graz has set up a disease-specific collection (such as different types of cancer and metabolic diseases) through the collection of a range of different human biological samples of highest quality and detailed clinical follow-up data [2].

Based on a broad informed consent Biobank Graz offers the use of human samples and associated anonymized

clinical data to academic and non-academic research partners worldwide [3]. This is achieved following all ethical requirements and data protection legislations.

Classification (1)
Human.

Species
N/A.

Classification (2)
Clinical biobank: biological samples and associated data, clinical data.

Context
Spatial coverage
Latitude 47°4'48.6228"N
Longitude 15°28'8.4036"E

Description
The biospecimens are collected at the University Hospital Graz, Styria, Austria.
Northern boundary: +/– 47.0559568
Southern boundary: +/– 47.04451272
Eastern boundary: +/– 15.28131448
Western boundary: +/– 15.27161838

Temporal coverage
Biobank Graz was established in 2007 including already existing collections.

FFPE tissue samples: These samples are mostly collected at the Institute of Pathology of Medical University of Graz. FFPE samples are collected based on routine diagnostics (all in). They enter Biobank Graz via routine diagnostic processes including FFPE tissue blocks and slides. Today, Biobank Graz contains FFPE samples (blocks and slides) from samples collected since 1984, i.e. from the last 32 years. Biobank Graz is now planning new automated storage systems to store FFPE blocks covering the next 30 years as well.

Fresh frozen tissue samples: These samples are mostly collected at the Institute of Pathology of Medical University of Graz. Fresh frozen tissues are collected based on specific cooperation agreements and are routed towards Biobank Graz via routine diagnostic processes. Today, Biobank Graz contains fresh frozen tissue samples collected since 1989, i.e. from the last 27 years.

Body fluids: These samples are collected based on specific cooperation agreements with different clinics and departments of University Hospital Graz. When Biobank Graz started in 2007, it has included the serum collection of the Clinical Department of Oncology at Medical University of Graz with first samples collected in 1990, i.e. containing serum samples from the last 26 years. Starting with a serum bank in 2007, today Biobank Graz collects body fluids such as serum, plasma and buffy coat, urine, seminal fluid, follicular fluid and cerebrospinal fluid.

Each year, Biobank Graz registers about 5,000 new incoming fresh frozen samples, about 130,000 aliquots of liquid body fluid samples, about 300,000 FFPE blocks and about 500,000 slides. All these samples are linked to their respective clinical data.

Biobank Graz has no expected date of last inclusion.

Temporal coverage for accessibility
N/A.

Biobank Graz has no indicated date when it has to be destroyed.

(2) Methods

Steps
At Biobank Graz high quality of samples and data is maintained using a professional quality management system (QM-system). Biobank Graz operates a QM-system according to ISO 9001:2008 offering highly sophisticated services for processing and storing samples as well as handling data.

All work processes during handling and storage of samples are based on standard operating procedures (SOPs) and application guidelines for equipment used in the work processes. This includes various tools and software for handheld scanners, semi-automated storage of FFPE samples, automated storage of fluid samples at minus 80°C, cost calculation, and data bases. To enable access of these documents to all authorized staff members, the CQO (chief quality officer) of Biobank Graz oversees the document control system and updates documents if needed, guaranteeing that all authorised employees have access to the latest up-to-date documents in the documents workflow.

Stabilization/preservation
At Biobank Graz the following types of containers and methods are used during collection of samples:

- FFPE tissues: standard formalin fixation of tissue samples in clinical routine of the Institute of Pathology at Medical University of Graz, Austria
- Fresh frozen tissues: shock freezing of tissue samples using nitrogen-cooled methyl butane
- For tissues samples (FFPE and fresh frozen) warm ischemia times are mostly not available, while cold ischemia times are documented for specific tissues.
- Plasma: EDTA (ethylene diamine tetra acetic acid), lithium-heparin or sodium-citrate
- Serum: addition of a clot activator
- Selected fluid samples: Paxgen tubes for RNA stabilisation

Type of long-term preservation
At Biobank Graz the following long-term preservation types are used:

- FFPE tissue samples from 1984 to 2011 are stored at room temperature in a manual storage system.
- FFPE tissue samples since 2012 are stored at room temperature in a semi-automated storage system (YLOG).
- Fresh frozen tissue samples are stored in the vapor phase of liquid nitrogen (–130°C to –180°C) in cryo tanks.
- Specific fresh frozen tissue samples are stored in the vapor phase of liquid nitrogen (–130°C to –180°C) in a semi-automated system with tube handling at –100°C (Askion).

- Body fluids from 1990 to 2011 are stored in –80°C in manual freezers. In 2016 these samples are transferred to a new manual storage system with storage at –80°C and manual single tube handling at –20°C.
- Body fluids since 2012 are stored at –80°C in fully automated storage systems.
  - Storage system with storage at –80°C and automated single tube handling at –20°C (Liconic) (2012–2016)
  - Storage system with storage at –80°C and automated single tube handling at –80°C (Hamilton) (2016-ongoing)

Since 2012 all samples stored at Biobank Graz are labelled with 2D dot matrix codes for a unique identification of samples. All storage systems at Biobank Graz are equipped with alarm systems and monitored 24/7 throughout the year.

Storage temperature

FFPE samples are stored at room temperature, body fluids are stored at –80°C (with tube handling at –20°C or –80°C) and fresh frozen tissues are stored in the vapour phase of liquid nitrogen (between –130°C and –180°C) with tube handling at room temperature or at –100°C for specific fresh frozen tissues.

Shipping temperature from patient/source to preservation or research use

As clinical biobank, Biobank Graz is directly embedded in the routine processes of University Hospital Graz.

- FFPE and fresh frozen tissues are directly transferred from the clinical departments (e.g. surgery) to the Institute of Pathology by the internal clinical transport service. In the institute coworkers of Biobank Graz are waiting to take care of the tissues in collaboration with pathologists (shock freezing or transfer into formalin).
- Body fluids: Body fluids from the clinical departments are transferred via vacuum tube system or by the internal clinical transport service to the central laboratory of the hospital, where the fully automated liquid handling system (Hamilton) of Biobank Graz is located. This unique liquid handler generates aliquots of fluid samples and freezes the aliquots on a single tube level within 5 to 7 min after transfer of the primary tube into the robot system. Fluid samples from larger cohorts are collected in the clinical study center where another automated liquid handler system (Hamilton) of Biobank Graz is located.

Shipping temperature from storage to research use

Body fluids and fresh frozen tissue samples are shipped on dry ice (–80°C) and FFPE samples at room temperature.

Quality assurance measures

The complete workflow of sample and data handling at Biobank Graz is embedded in a quality management system certified by ISO 9001:2008. Process control is based on standard operation procedures (SOPs) that can be found in the central workflow system.

Each FFPE and fresh frozen tissue sample retrieved for a research project is rescreened for diagnosis by a specialized pathologist. Quality assurance of samples such as RIN (RNA integrity number) value of RNA is performed on request. For fresh frozen samples and body fluid samples, temperature profiles of storage are available.

Source of associated data

Biobank Graz is a central research facility of Medical University of Graz. Biospecimens are collected at the site of the University Hospital Graz and hence are associated with their respective clinical data and health records stored at University Hospital Graz. The link between samples and clinical data is conducted by a university-based and biobank-independent custodian. This way, Biobank Graz cannot link the samples stored in its systems with direct person-related data. At the same time, all indirect person-related clinical data stored in the clinical information system can be retrieved and linked to the samples stored at Biobank Graz. This is true for all samples stored at Biobank Graz including the collection of FFPE tissues from 1984 until today.

Ethics Statement

Biobank Graz works in line with ethical guidelines of the OECD (Organisation for Economic Co-operation and Development), the Austrian Bioethics Committee and the local Ethics Committee at Medical University of Graz.

The ethical approval of Biobank Graz as an institution was first given on September 14, 2009 (EK-# 20–492 ex 08/09) and is renewed annually to assure that ethical guidelines are followed at any time. This approval includes a broad informed consent covering the following aspects:

- Use of residual material from visits at University Hospital Graz
- Use of additional 20ml of blood when a routine blood drawing is performed
- Archiving of biospecimens without time limit
- Use of archived biospecimens and associated indirectly person-related clinical data only after approval of the respective study by a new project-related and approved statement of the ethics committee
- Use of archived biospecimens and associated clinical data only in coded form for any biomedical research, including genetic analysis
- Provision of archived biospecimens and associated clinical data in coded form for research in academic as well as non-academic institutions (or cooperation of both)
- Transfer of ownership of samples from donor to Medical University of Graz

The English version of the informed consent of Biobank Graz can be found on the homepage of Biobank Graz at www.medunigraz/biobank.

Biospecimens are archived in Biobank Graz systems only in coded form (2D data matrix codes). These samples are linked to a minimal data set (patient-ID number, gender, age, primary diagnosis, clinical department) in the biobank databases. Access to detailed clinical data in the clinical information system of the

University Hospital is performed by a university-based custodian with the respective rights to access such data. This custodian links indirectly person-related clinical data to sample IDs and sends this information back to the biobank. This way, personnel of Biobank Graz does not have access to any directly person-related data of donors.

Samples stored at Biobank Graz that have been collected prior to 2007 are mostly not accompanied by an informed consent. The Austrian Bioethics Committee of the Federal Chancellery of the Republic of Austria has published a report (May 9, 2007) clarifying the use of legacy samples that have been archived prior to this publication. Such samples, already collected prior to publication, may be used for research if an ethical approval is obtained and the samples have been anonymized.

Constraints

Geographical: Biobank Graz collects mostly biospecimens collected at University Hospital Graz, Austria. The catchment area of this hospital is South-East Austria with a population of about 1.2 million. So far there is one external site where samples are collected, an IVF clinic close to Graz.

Regulatory: Biobank Graz is not allowed to collect biospecimens from children (below the age of 18) and from patients in psychiatry.

(3) Bioresource description

Bioresource name

Biobank Graz, Medical University of Graz, Austria

Bioresource acronym or short name

Biobank Graz

Bioresource location

Biobank Graz is a central research facility of Medical University of Graz, located at University Hospital Graz, Austria. It is owned by Medical University of Graz and thus is a non-profit organisation. Biobank Graz is not linked to any institute or clinic of Medical University Graz/ University Hospital Graz, but is under direct supervision of the head of university.

Storage facilities of Biobank Graz can be found at various sites within the campus of the University Hospital Graz. A new central storage site is set up at the ZWT building in close vicinity to the University Hospital Graz.

Biobank Graz @ Medical University of Graz
Building: ZWT
Street: Neue Stiftingtalstrasse 2B/II
City: 8010 Graz
Country: Austria

Bioresource contact

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Medical University of Graz
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Fax: +43 316 385 72731
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Bioresource URL

http://www.medunigraz.at/biobank

Identifier used

N/A

Bioresource type

Biobank Graz is an all-in clinical biobank. Hence, it stores all types of pathology and disease samples including but not limited to Pathology, Cytology, Gynecology, Obstetrics, Transfusion, Transplant and IVF.

Type of sampling

Biobank Graz is a clinical biobank and central research infrastructure of Medical University of Graz, Austria. Hence, most of the samples are collected in clinical care.

Biobank Graz stores all samples coming from the Institute of Pathology at University Hospital Graz. These FFPE samples are maintained at Medical University of Graz since more than 30 years (since 1984). Hence Biobank Graz contains a cross-sectional collection of unselected pathological samples and clinical data, representing all detected diseases at their natural frequency of occurrence. This part of the collection of Biobank Graz can thus be called population-based. Due to this collection of samples from more than 1 million patients over the last 30 years, samples from the longitudinal collection of FFPE samples in combination with serum samples and associated clinical data are available.

At the same time, based on the specific research foci of clinical scientists at Medical University of Graz, disease-based cohorts are collected as well. Such collections are mostly focusing on body fluids such as serum, plasma, urine and others.

Thus, the type of sampling at Biobank Graz is a combination of population-based and disease-based with longitudinal collections, sampling in clinical care plus sampling in a research protocol.

Researcher may also ask for a specific collection of samples and data in a prospective cohort in collaboration with the respective clinical partners of Biobank Graz.

Anatomical site

Due to the above described type of sampling, biospecimens archived at Biobank Graz cover all anatomical sites of the human body with a wide range of cooperating clinical departments at University Hospital of Graz, Austria.

A large number of clinical and non-clinical departments of Medical University of Graz are engaged in the activities of Biobank Graz based on written cooperation agreements, including Department of Blood Group Serology and Transfusion Medicine, Division of Cardiology, Department of Dermatology and Venerology, Division of Endocrinology and Metabolism, Division of General Surgery, Department of Neurosurgery, Department of Obstetrics and Gynecology, Division of Oncology, Institute of Pathology, Department of Urology

and Division of Plastic, Esthetic and Reconstructive Surgery and others.

Disease status of patients/source
As a clinical biobank, Biobank Graz archives all samples of the Institute of Pathology of Medical University of Graz. Hence, all diseases at their natural frequency of occurrence in the catchment area of University Hospital Graz are archived. Additionally, specific cohorts are collected as well, including cohorts in the areas of diabetes, cardiovascular diseases, oncology and others. Additionally, blood samples from blood donors are collected as well to offer blood samples from healthy donors.

Clinical characteristics of patients/source
Biobank Graz is an all-in clinical biobank, not restricted to any type of disease. All patient related information that is stored in the clinical information system of University Hospital Graz can be linked to the biospecimens stored in Biobank Graz. Restrictions are age (no samples from patients below legal age, <18 years, are offered) and cognitive abilities (no samples from patients from psychiatry are offered).

Vital state of patients/source
The biospecimens are collected from viable patients and donors during routine diagnostics or within study cohorts.

Specific postmortem specimens are collected within specific studies only.

Clinical diagnosis of patients/source
As a central research infrastructure of Medical University of Graz and an all-in clinical biobank, Biobank Graz stores samples derived from University Hospital Graz in coded form (2D data matrix code). Within the IT-system of Biobank Graz a minimal data set including patient-ID number, gender, age and primary diagnosis is stored. Any further and more detailed diagnosis is stored in the clinical information system of University Hospital Graz. This information is linked to the samples stored in Biobank Graz and can be retrieved if needed. Retrieval of detailed clinical data is performed by a university-based custodian with the respective rights to access such data. This custodian, in cooperation with the respective clinicians, links indirectly person-related clinical data to sample IDs and sends this information back to the biobank.

Pathology diagnosis
In addition to the clinical diagnosis of samples, all information from evaluations of the Institute of Pathology of Medical University of Graz is available for FFPE and fresh frozen samples stored in Biobank Graz. This includes diagnoses referring to the ICD-10 and ICD-O codes, the TNM classification as well as referring to receptor status and mutation status.

Control samples
During excision of tumor tissues from patients, normal tissues close to tumor tissues are excised as well and can be used as non-tumor control tissues (fresh frozen and FFPE).

Additionally, blood samples from healthy blood donors are taken to have control samples for serum, EDTA plasma and buffy coat.

Biospecimen type

- Tissues (FFPE blocks) (about 6 million blocks)
- Tissues (fresh frozen) (about 150,000 aliquots)
- Viable cells from leukemia (fresh frozen) (about 1000 aliquots)
- Serum (1ml or 0.4ml) (about 800,000 aliquots)
- Plasma (EDTA, 1ml; Lithium-Heparin, 0.4ml; Sodium-Citrate, 0.4ml) (about 120,000 aliquots)
- Full blood (0.85ml) (about 20,000 aliquots)
- Buffy coat (0.3ml) (about 20,000 aliquots)
- Urine (midstream and 24h, 1ml) (about 50,000 aliquots)
- Liquor (cerebrospinal fluid, CSF; supernatant, 1ml; cells, 0.4ml) (supernatant, about 1500 aliquots; cells, about 500 aliquots)
- Follicular fluid (supernatant, 1ml; cumulus cells, 0.4ml) (supernatant, about 10,000 aliquots; cells, about 1500 aliquots)
- Seminal fluid (1ml) (about 400 aliquots)
- In vitro supernatants of human IVF embryos (0.2ml) (about 700 aliquots)
- Synovial fluid (0.4ml) (about 200 aliquots)
- Biobank Graz associated CellBank of Medical University of Graz with a variety of cell lines and primary cells

Size of the bioresource
Biobank Graz at Medical University of Graz is not a project but rather a central research infrastructure of the university with no end date. The number of full time equivalents working at Biobank Graz is 17, the head count is 35.

Release date
There is no embargo and hence no release date of this biobank. Biobank Graz releases samples and data to research projects worldwide on a regular basis.

Access criteria
Biobank Graz is a bioresource already providing samples and data to researchers worldwide from academic and private partners. It has installed SOPs for retrieval of samples and data within its quality management system.

On its website Biobank Graz offers a project inquiry form for researchers that can be filled and sent to the biobank. Reply to this inquiry will take place within 72h after receipt. Then in most cases an interactive process starts between researcher and biobank ending in the proper definition of samples and data most useful for the project. This interactive and sometimes interdisciplinary discussion process often results in research cooperation.

The next step is to send a project proposal (respective form is available on the website as well) that needs to be accompanied by an ethical approval to show that running the planned methods on the requested samples is ethically sound. Due to the broad informed consent of Biobank Graz, the researchers do not need to collect an informed consent for the samples again.

An Approval Committee (5 researchers from Medical University of Graz) assesses the submitted project proposal. The decision to approve or reject a given project is based on scientific reasons and is accompanied by statements of biobank representatives from those institutes and clinics that provided samples to Biobank Graz. The Approval Committee applies the following decision criteria:

- The project is consistent with the Biobank objectives (research project, no sample and data trade) and a recognizable benefit for the general public.
- Promotion of the research interests of Medical University of Graz, e.g. setting up research cooperation.
- Scientific quality of the project (relevance of research, feasibility).

In the moment Biobank Graz stores more than 7.5 million samples. Costs for projects are based on a transparent cost calculation taking all handling costs of samples and data into account. This calculation includes costs ranging from time of an MD to explain and sign the informed consent to consumables of samples and retrieval of clinical data. Costs vary depending on the type and amount of samples as well as depth of clinical data. There are no restrictions on access to Biobank Graz.

Within Biobank Graz samples are identified by codes and no direct person-related data is available to personnel of Biobank Graz. When samples are distributed to research groups, sample-associated clinical data (indirect person-related data) is sent in coded form and the researchers are not able to link samples to any patient. Hence, for the researchers receiving samples the samples are anonymized.

(4) Reuse potential

Fluid samples: Biobank Graz stores fluid samples at minus 80°C in aliquots. Hence, from a single sample multiple aliquots are available. It is not accepted by Biobank Graz to reuse samples that have been sent research partners for use (freeze-thawing). Biobank Graz uses storage robot systems to maintain handling temperature of frozen fluid samples at minus 20°C or minus 80°C.

Fresh frozen tissue samples: Fresh frozen tissue samples are frozen in small pieces and are distributed as a single small piece rather than the whole sample.

FFPE tissue samples: Sections of FFPE blocks are distributed to researchers to enable use of the tissue block for further studies.

Competing Interests

The authors declare that they have no competing interests.

Author Roles

Berthold Huppertz, Director and CEO (chief executive officer)
Karine Sargsyan, COO (chief operation officer)
Michaela Bayer, CQO (chief quality officer)
Tanja Macheiner, project manager

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