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BIORESOURCE PAPER

# The Multispecialistic da Vinci European BioBank

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The da Vinci European BioBank (daVEB) is a research infrastructure established in 2009 in the Scientific Campus of the University of Florence (Sesto Fiorentino, Italy) belonging to the non-profit foundation FiorGen, which promotes studies aimed at exploiting knowledge on human health. Since 2011, daVEB is ISO9001 certified for collection, storage and distribution of biological samples and the associated data for scientific research. The biobank is currently storing about 9.000 biospecimens (serum, plasma, white cells, tissue, DNA, cells and urine) collected according to specific informed consents by Research Units from healthy donors and patients affected by different diseases - cardiovascular diseases, melanoma, breast carcinoma, non-Hodgkin's lymphoma, cancer in geriatric patients, Krabbe syndrome, rare skin diseases; the biomaterial is available for new research projects.

**Keywords:** research biobank; human samples; SOPs; metabolomics; IT system interoperability and flexibility

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## (1) Overview

### Project description

The daVEB has been designed as a multicenter biobank with a centralized IT infrastructure; the first daVEB repository, equipped with a cutting-edge technology, was established in 2009 and is hosted by CERM (the Magnetic Resonance Center of the University of Florence, a center for NMR in the Life Science; www.cerm.unifi.it) within the Scientific Campus of the University of Florence. The daVEB biobank has been created as a tool for high-quality storage of samples and data for researchers who collaborate with Fiorgen. Given the importance of the metabolomic research component within the Fiorgen Foundation [1-3], most of the adopted protocols for sample collection/handling/storage are focused on assuring quality compatible with the requirements of this analytical method.

In 2011 daVEB implemented the internally created management system suitable for all biobanking activities in a Quality Management System certified according to UNI EN ISO 9001 (CSQ Certificate N. 9122.FFFI; IQNet Certificate N. IT-79101).

With the aim to standardize sample processing and to assure sample reproducibility and quality, daVEB in collaboration with CERM developed validated Standard Operating Procedures (SOPs) and improved preanalytical treatments by metabolomics analysis [4]. SOPs are applied by all the Research Units collecting and processing the samples, before storage in the biobank repository.

In the biorepository different types of sample (serum, plasma, tissue, white cells, DNA, cells and urine) are stored according to the best practices for biorepositories [5], collected from patients affected by various diseases (cardiovascular diseases, melanoma, breast carcinoma, non-Hodgkin's lymphoma, different types of cancer in geriatric patients, Krabbe syndrome, rare skin diseases).

The data concerning the samples are collected both via electronic and manual methods and finally recorded in a electronic database, hosted in a Electronic Data Processing system designed and deployed following the state-of-the-art criteria of Information and Communication Technology, in order to guarantee standards of high availability and security, relying on system interoperability and flexibility of the Information Technology's data model.

### Classification (1)

Human

### Classification (2)

Biological samples and associated data; clinical data

### Context

***Spatial coverage***

latitude 43°49'18.681"N

longitude: 11°11'38.521"E

- Central management infrastructure: Via Luigi Sacconi 6 – 50019, Sesto Fiorentino (Florence), Italy
- Collection centers distributed across Tuscany:
  - Clinical, Preventive and Oncologic Dermatology Section, Department Critical Care Medicine and Surgery, University of Florence; and Azienda Ospedaliera-Universitaria Careggi, Florence, Italy;
  - Plastic Surgery Unit, Regional Melanoma Referral Center, Santa Maria Annunziata Hospital, Florence, Italy;
  - Department of Experimental and Clinical Medicine, University of Florence; and Azienda Ospedaliera-Universitaria Careggi, Florence, Italy;
  - Sandro Pitigliani Medical Oncology Unit, Department of Oncology, Prato Hospital, Prato, Italy;
  - Department of Clinical and Experimental Medicine (Department of Cardiology), University of Florence; and Azienda Ospedaliera-Universitaria Careggi, Italy;
  - Department of Dermatology, University of Siena, Italy;
  - Department of Pediatrics, Obstetrics and Reproductive Medicine, Section of Obstetrics and Gynecology, University of Siena, Italy.

***Temporal coverage***

The daVEB collection activity started in 2010 and the end date is not applicable to the biobank.

The end date of the current collections differs in accordance on the project duration (2012, 2013, 2014).

The oldest collections, dated from 2001 to 2008 have been transferred to the biorepository in 2010 with the available data.

***Temporal coverage for accessibility***

N/A

## (2) Methods

**Steps**

The donors are recruited within approved research protocols by Research Units (RU), namely the collection centers based in hospitals and academic centers across Tuscany, collaborating with daVEB.

In order to standardize pre-analytical procedures and to avoid sample variability, assuring the quality and the reproducibility of assay results, daVEB developed the following validated Standard Operating Procedures (SOPs), some of which in collaboration with CERM:

- SOP01: Collection and transport of fresh peripheral blood samples
- SOP02: Processing and freezing of peripheral blood samples
- SOP03: Long term storage and transport of frozen samples derived from peripheral blood
- SOP04: Bone marrow blood samples
- SOP05: Whole peripheral blood-derived DNA samples
- SOP06: Buffy coat-derived DNA samples
- SOP07: Cultured cells-derived DNA samples
- SOP08: Isolation and storage of total RNA from whole blood
- SOP09: Tissue preservation methods and isolation of total RNA
- SOP10: Tissue preservation for morphological studies
- SOP11: Collection and storage of urine samples
- SOP12: Collection and storage of whole saliva samples for DNA extraction
- SOP13: Cryopreservation of cultured cells

The samples are processed by RU and delivered to daVEB in aliquots; at the same time data are recorded in the biobanking information management system via a secure web link. The dataset generally includes standardized information among which personal data (age, gender, height, weight, body mass index and ethnic origin) and clinical data pertaining the specific disease (e.g.: collection date, sample type, diagnosis, the result of blood test on the donor, drug and/or medical treatment, etc.).

New samples are aliquoted by the RU in 2D barcoded storage tubes, and then registered in the daVEB LIMS, providing secure and traceable sample storage and retrieval. Information about vial locations are periodically transferred from the LIMS to the database and matched to clinical data characterizing each donor.

**Stabilization/preservation**

***Types of container***

Monodimensional and 2D barcoded tubes (volumes = 0.5 ml, 1 ml, 2 ml)

***Preservatives***

- EDTA (for plasma)
- Snap freezing in liquid nitrogen (for tissue)
- RNA Later (for tissue, suitable for molecular biology assays)
- 15% Glycerol and/or 10% DMSO (for cells)

Since the majority of the samples are collected within research projects based on metabolomics studies by 1H-NMR, the preservatives and cryoprotectants that might interfere with the metabolites NMR signals are generally avoided.

**Type of long-term preservation**

Frozen in mechanical freezers or in the vapor phase of liquid nitrogen.

**Storage temperature**

DNA, serum, plasma, white cells, tissue in RNA Later, and urine: -80°C (mechanical freezer).

Cells and tissue: in the vapor phase of liquid nitrogen below -150°C.

Storage duration: not defined.

**Shipping temperature from patient/source to preservation or research use**
Below -150°C (cryoshipper)
-78°C (on dry ice)
+4°C (icebox)

**Shipping temperature from storage to research use**
The shipping temperature from storage to research use is the same as the storage temperature of the specific sample.

**Quality assurance measures**
Given the focus on metabolomics data and the recent results of research activities (see for example the outcome of the SPIDIA project, www.spidia.eu) that identify metabolites as very sensitive reporter molecules of sample quality, 1H NMR profiles are collected on aliquots of urine, serum, plasma and other biofluids at the entry point in the biobank and at different stages of the storage period to monitor possible changes in the metabolomic profile that might be diagnostic for sample deterioration. Available SOPs for the pre-analytical steps of these samples have been implemented on the basis of a similar approach, largely accepted by the international community of reference and now undergo examination of CEN to become European guidelines. A project is ongoing to implement similar measures on tissue quality.

DNA and RNA integrity is generally checked on an agarose gel stained with ethidium bromide (EtBr). A more accurate and sensitive indicator to assess the RNA integrity is the RIN (RNA Integrity Number) based on the entire electrophoresis trace of the RNA sample. This includes the presence or absence of degradation products.

**Source of associated data**
The associated data, collected during the research projects driving to the collection setting up, are coming from hospital medical records and laboratory reports, both paper and electronic; instrumental data obtained from post-processing analysis within the specific research project can be added. The latter is the case of metabolomics data, associated to the samples collected within this kind of projects of the FiorGen Foundation.

**Ethics statement**
Consent is obtained through forms prepared by daVEB both for cognizant adults and fragile subjects or minors, and distributed to the Research Units collecting the samples before they submit the research protocol to their institutional Ethics Committee. Two different kinds of informed consent have been prepared according to the Italian law: one for specific research project, the other for general use (where the donor agrees to be re-contacted in case of a specific research project).

Each sample stored in the biobank is coming from a project approved by the researcher's institutional Ethics committee, which approves also the daVEB informed consent.

In addition the biobank operates having regard to:

- Recommendations issued by the Oviedo Agreement (Convention on Human Rights and Biomedicine signed in Oviedo on 04 April 1997).
- Italian Data Protection Authority (Garante Privacy), Data Protection Code (Legislative Decree No. 196/2003) as published in the Official Gazette of the Italian Republic No. 174 dated 29 July 2003.
- Italian Data Protection Authority (Garante Privacy), General Authorization for the processing of genetic data, No. 8/2013 dated 12 December 2013, as published in the Official Gazette of the Italian Republic No. 302 dated 27 December 2013.
- Italian Data Protection Authority (Garante Privacy), General Authorization for the processing of personal data for scientific research purposes, No. 9/2013 dated 12 December 2013, as published in Official Gazette of the Italian Republic No. 302 dated 27 December 2013.

**Constraints**
Regulatory: none apart for Italian regulation described above.

Managing: limited funds supporting the biobank, mainly related to private funding or via competitive grants.

## (3) Bioresource description

**Object name**
Cardiovascular diseases (cardiomyopathy, hypertension), melanoma, breast carcinoma, non-Hodgkin's lymphoma, cancer in geriatric patients, Krabbe syndrome, rare skin diseases.

*The name is subject to changes, due to the fact that the daVEB collections are from Research Units working on different diseases.*

**Bioresource name**
da Vinci European BioBank
Acronym: daVEB

**Bioresource location**
daVEB: Via Luigi Sacconi 6 - 50019 Sesto Fiorentino (Florence) - Italy

Main collection sites:

- Careggi Hospital, Largo Giovanni Alessandro Brambilla 3 -50134, Florence - Italy
- Santa Maria Annunziata Hospital, Via dell'Antella 58 – 50012 Bagno a Ripoli (Florence) – Italy
- Prato Hospital, Via Suor Niccolina, 20, 59100 Prato, Italy
- Policlinico Le Scotte - University of Siena, Strada delle Scotte, 14 - 53100 Siena, Italy

**Bioresource contact**
info@davincieuropeanbiobank.org

**Bioresource URL**
https://www.davincieuropeanbiobank.org/

**Identifier used**
N/A

**Bioresource type**
Multispecialistic research biobank.

*Samples stored in the daVEB biobank mainly originate from studies aimed at the definition of the individual phenotype and of the molecular signature of different diseases (see the sections "Spatial coverage" above and "Biospecimen type" below). As a consequence, daVEB collects different types of biological specimens from cohorts with various diseases, as well as from healthy donors.*

**Type of sampling**
The samples are usually collected in clinical care from donors affected by different diseases, within research projects protocols.

**Anatomical site**
Presently it is possible to describe the anatomical site only for the tissue samples of the melanoma collection: head, nose, leg, foot.

**Disease status of patients/source**
Patients affected and healthy controls.

**Clinical characteristics of patients/source**
Males and females.

Sure status and diagnosis.

Inclusion criteria are different according to the specific collections (and the related research protocols).

**Vital state of patients/source**
Alive at the sampling.

**Clinical diagnosis of patients/source**
daVEB collects samples from patients affected by several significant diseases, presently: cardiovascular diseases (cardiomyopathy, hypertension), melanoma, breast carcinoma, non-Hodgkin's lymphoma, different type of cancer in geriatric patients, Krabbe syndrome, rare skin diseases.

**Pathology diagnosis**
All disease are recorded according to ICD-10 classification.

**Control samples**
Healthy individuals at the sampling, preferably recruited in the same site and aged as the patients.

**Biospecimen type**

- Frozen tissue: approximately ≤ 0.5 cm, 1-2 per donor, if possible (both healthy and damaged fragments).
- Tissue in RNA Later: approx. ≤ 0.5 cm, 1-2 per donor, if possible (both healthy and damaged fragments).
- Plasma: 8 aliquots per donor, 0.5 ml each.
- Serum: 8 aliquots per donor, 0.5 ml each.

| Disease | Donors |
|---|---|
| Cardiomyopathy | 291 |
| Hypertension | 126 |
| Breast cancer | 209 |
| Melanoma | 169 |
| Geriatric patients affected by different type of cancer | 257 |
| Skin diseases | 219 |
| Healthy subjects | 175 |
| Non Hodgkin's lymphoma | 73 |
| Krabbe syndrome | 13 |

**Table 1:** Number or recruited donors, per disease or healthy status.

- White cells for future DNA extraction: 2 aliquots per donor, 0.5 ml each.
- Urine: 6 aliquots per donor, 1.0 ml each.
- DNA from blood/cells: 2 vials per donor (at least 20 $\mu$g).
- Cells: 1-2 vials, 1.0 ml each.

**Size of the bioresource**
About 1450 recruited donors (9000[1] samples / 25000 aliquots at 31 August 2014) distributed as in **Table 1**.

**Release date**
Data and samples are currently available.

**Access criteria**
Basic rules are applied to all researchers, including FiorGen staff, according to the following criteria.

After browsing at the link https://www.davincieuropeanbiobank.org/public_search/davebtables/search.html, where applicants can access the public section of daVEB database, and contacting the biobank to get more detailed information, researchers are required to fill in and sign a form describing types and number of the required samples, scientific project, project sustainability, expected results, etc.; this form contains a MTA section; further, the applicant must demonstrate to have obtained approval to the proposed research from the institutional Ethics Committee.

The daVEB Technical and Scientific Committee will consider the impact and feasibility of the proposed study and approve it or not, referring to the authorization to sample transfer in the daVEB repository originally given to the researcher by the institutional Ethics Committee, and having received the positive opinion from the daVEB Ethics Committee to the proposed research project. In the scientific evaluation of the project, if necessary, it is foreseen to consult external referees. In the case of positive evaluation, an economic quotation is sent (covering shipping costs and partially costs for biobanking-related services - sample handling, consumables). No patient samples or data are sold for profit.

## (4) Reuse potential

All the biomaterial stored in daVEB is available for other research project.

In particular, left over aliquots of samples collected within a project focused on a given pathology can be transferred to third party scientists only for scientific aims directly connected to those for which they have been originally collected, lacking of identification data in accordance with the Italian Data Protection Authority regulations (as specified in the informed consent).

Biological samples or their sub-products cannot be used for commercial purposes but only for the scientific research purposes specified in the application form.

As a condition the applicant must acknowledge the daVEB in all publications resulting from the use of these samples and provide a copy of the published paper to daVEB.

### Author roles

- Marcon Giordana, daVEB Technical Director
- Nincheri Paola, Sample Manager

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Patrizia Funghi, daVEB bioethics consultant;

daVEB Technical and Scientific Committee.

### Notes

[1] This number is due to the different sample types and collections dates distributed also in the follow-up phase (at 3, 6, 12, 18 or 24 months depending on the project).

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