The Hannover Unified Biobank (HUB) – Centralized Standardised Biobanking at Hannover Medical School

BIORESOURCE PAPER

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ABSTRACT

The Hannover Unified Biobank (HUB) was established in 2012 as the central biobank of the Hannover Medical School (MHH) to provide an infrastructure for the standardised collection and storage of liquid biosamples and associated data in the context of research projects and clinical studies. For the comprehensive collection of tissue samples from the clinical routine the HUB cooperates with the MHH Institute of Pathology. All samples are connected with the associated clinical data stored in the ECRDW (Enterprise Clinical Research Data Warehouse) of the MHH. Headed by Prof. Dr. Thomas Illig the HUB developed into one of the biggest state of the art clinical biobanks in Germany and today stores about 2.88 Mio samples (mainly FFPE tissue and blood derived liquid samples) of a wide range of diseases.

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KEYWORDS:

HUB; centralized clinical biobank; broad consent; automation; high quality biosamples

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(1) BIORESOURCE OVERVIEW PROJECT DESCRIPTION

Founded in 1965 the Hannover Medical School (MHH) became one of the leading university medical institutions in Germany with over 7.600 employees and over 530.000 patient contacts yearly (outpatients and stationary, status 2017). In a 2019 published ranking of the best German clinics the MHH was placed on rank 5 [1]. The MHH is one of the strongest research-based medical universities in Germany. The main focus of the MHH is on transplantation and stem cell research, regenerative medicine, infection and immunity research, cancer research as well as biomedical engineering and implant research. The MHH concentrates its research activities to unravel basic mechanisms which are translated into clinical research to develop innovative strategies for diagnosis, prevention and therapy.

The access to high quality biosamples and related clinical data is a basic prerequisite for advanced biomedical research. Therefore, the Hannover Unified Biobank (HUB) was founded in 2012 as the central clinical biobank of MHH [2] to implement comprehensive quality control and standardized procedures during sample collection, processing and storage at the MHH. The HUB has no predefined limitations with respect to sample types or disease areas. Up to now HUB has 25 employees and administers the sample collections of 183 different projects of various sizes from several MHH institutes, clinics and external HUB partners and stores about 2.88 Mio samples of all kinds of biosamples (e.g. body fluids, cells, microorganisms, tissues; status 06.2020) of clinical routine, research projects and studies (epidemiological, clinical and others). Figure 1 shows the Cumulative number of liquid and tissue samples stored in the Hannover Unified Biobank from 2008 to 2019 (Figure 1a, b). Around 73% blood and blood derivatives account for the majority of the liquid samples (Figure 1a) while tissue samples are stored almost entirely as FFPE samples (99.4%) (Figure 1b). The biobank information management system (BIMS) of the HUB is CentraXX, (KAIROS; Bochum, Germany). It complies with the principles of data security and data protection developed by TMF (Technology, Methods, and Infrastructure for Networked Medical Research) and the European data protection regulation [3]. The BIMS is part of the overall MHH IT infrastructure and linked to the clinical data warehouse of the MHH (ECRDW - Enterprise Clinical Research Data Warehouse) [4-6] which holds all consolidated clinical routine data of MHH patients. The infrastructure and biobank processes of the HUB are adapted to the biobank standards and guidelines of the OECD and ISBER [7, 8]. Since 2017, the HUB is a member of the German Biobank Alliance (GBA) [9, 10] and is connected to the German Biobank Node (GBN) and BBMRI-ERIC IT network including the registration in the **BBMRI** Directory.

CLASSIFICATION (1)

Human

SPECIES

Homo sapiens



Figure 1 Cumulative number of samples stored in the Hannover Unified Biobank (HUB). **a)** The cumulative number of liquid samples stored in the HUB from 2008 to 2019 divided in blood and its derivatives, urine, cells and other biomaterials is shown. **b)** The cumulative number of tissue samples stored in the HUB, Institute of Pathology from 2013 to 2019 divided in FFPE and frozen samples is shown.

CLASSIFICATION (2)

Biological samples and associated data

KEYWORDS

HUB, centralized clinical biobank, broad consent, automation, high quality biosamples

CONTEXT

Spatial coverage

Latitude 52.38354734574762

Longitude 9.804591413792282

Description: Hannover Unified Biobank, Hannover Medical School, Hannover, Carl-Neuberg-Straße 1, 30625 Hannover, Germany

The HUB mainly collects samples from patients of the MHH. In addition, the HUB has a close collaboration with the Helmholtz Centre for Infection Research (HZI) in Braunschweig, in particular for its German National Cohort site Hannover [11] for which the HUB stores the local samples. Additionally, HUB arranges the biobanking issues (sample storage and sample data management) for several studies of the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), which is located close to MHH and HUB, and for some multicentre studies with study centres throughout Germany. Another growing field of material storage concerning tissue and blood is provided by huge clinical trials with central reference pathology at the MHH. The majority of samples originate from donors in the region of Lower Saxony (main catchment area of the MHH), Germany. In case of multicentre studies the samples originate from different regions throughout Germany.

Temporal coverage

The HUB was established in 2012. The first collection started in 05/2012. Up to now the HUB has provided and still provides services like sample logistic, pre-analytics, storage and other biobanking services in over 180 different projects (status 06/2020). The duration of the recruitment phase of the different projects varies according to the funding period and the study design. The rate of recruitment varies between the different collections based on the frequency of patients which fulfil the inclusion criteria. In 2018 the HUB started a biobank initiated sample collection based on the broad consent in cooperation with different MHH clinics. Recruitment of patients will be continued without limitation in this collection.

Temporal coverage for accessibility

All samples collected on the basis of the HUB broad consent remain in the biobank until they are used. Samples which are not collected on the basis of the HUB broad consent (e.g. clinical studies) and not retrieved for research projects are stored according to the agreed storage time in the respective consent. After the end of the project funding, the collections of samples and data remain at HUB and are still available for national and international requests. The destruction of samples and deletion of data will only be carried out if a donor has withdrawn his consent or a clear donor assignment of a sample is not possible.

(2) METHODS

In contrast to several other clinical Biobanks the HUB is a mainly project driven Biobank (except tissue collection by the Institute of Pathology). The HUB is commissioned by the respective PIs (MHH) of third-party funded projects to organize the biobanking for the respective project or directly is a funded partner in third-party funded projects. The HUB provides a comprehensive quality management. All steps during sample handling and storage are based on SOPs (according to the German Biobank Alliance (GBA), German Center for Lung Research (DZL), German Center for Infection Research DZIF or ISO standards)[12–14]. For the standardized lab processes HUB uses robot and IT supported sample preparation and aliquoting (EasyBlood, Hamilton; Franklin Massachusetts), DNA extraction (chemagicSTAR, Hamilton) and storage (BIOS, Hamilton) systems. All lab systems are connected to the BIMS. Thereby gapless sample

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tracking becomes possible and retention times as well as preparation steps are documented. *Figure 2.* shows an overview of the monitoring for collection, processing, storage and retrieve of liquid samples. In case of an external sample processing, the HUB provides access to all workflows in the biobank management system required for the documentation of the sample processing.

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STEPS

The recruitment of patients for the different collections is carried out by the respective HUB partners in the MHH institutes and clinics or the study sites. The patients are informed by the responsible physicians and samples are taken by trained medical staff after the donor/patient has given his/her consent. Primary containers labelled with a unique barcode are provided by the HUB. The majority of all samples are collected on basis of the HUB broad consent, for some studies a study specific consent is used. All samples are barcode registered in the HUB IT through a modern and safe web interface by clinics/study sites directly after the collection. This ensures safe linkage of samples to the unique MHH patient identification number or the study patient ID. A harmonized, basic dataset, derived from several standards (e.g. standard pre analytical code (SPREC), Fast Healthcare Interoperability Resources (FHIR)) [15, 16] and projects (e.g. German Biobank Alliance [17]) is collected together with all samples (Figure 3). Samples are picked up by instructed HUB employees (manually for quality reasons) and transferred to the HUB. Pick up of samples on the MHH campus (400,000 square metres) and delivery tracking is managed using a dedicated, in-house developed web application (Figure 4). This ensures a fast transfer of samples to the HUB [18]. In 2019 the delivery of over 16,000 primary samples was managed with the web application (Figure 4a) and samples and over 90% of the samples arrive in the HUB in less than one hour (Figure 4c). In the HUB identity and integrity of all samples delivered is checked and deviations which can influence the quality of the sample (e.g. haemolytic, lipemic and icteric specimens, underfilling) are documented in the BIMS. The samples are processed according to SOPs for the respective biological material by a pipetting robot (serum, plasma, urine, buffy coat) or manually (e.g. sputum, stool samples, swaps, PBMC, liquor). Time stamps for all important steps of the sample processing are documented in the BIMS (time/date of: collection, receive, centrifugation, aliquotation, freeze) to assess sample quality. For blood samples, blood collection tubes from Sarstedt (S-Monovette®) are used as standard. Plasma is mainly collected as EDTA plasma. For PBMC blood is collected and processed using the BD Vacutainer® CPT™ System. Sputum is collected using the Salivette® from Sarstedt. Swabs and Stool samples are stored mainly unprocessed as native samples. Deviations from the SOPs are recorded in the BIMS. In some cases sample transfer of the primary samples to the HUB is not possible due to quality reasons (e.g. external partners). In these cases, HUB can provide electronic workflows for sample processing to partner sites by giving restricted access to the HUB-BIMS through a secure Virtual Private Network (VPN)."

For handling and storage of tissue samples the HUB cooperates with the MHH Institute of Pathology. Samples are collected almost exclusively from the clinical routine (surgical interventions/biopsies) and are processed immediately in the routine laboratory of the Institute of Pathology. Tissue samples are mainly stored as FFPE samples at room temperature and fresh frozen samples at -80°C. Sample processing is carried out by qualified employees according to the SOPs of the Institute of Pathology. Allocation of sample IDs and documentation of all processing steps and sample storage is carried out in the clinical IT systems of the MHH. Currently the Institute of Pathology stores over 1.8 Million FFPE and fresh frozen samples (*Figure 1b*; status 12/2019).

STABILIZATION/PRESERVATION

By default blood samples are stored as EDTA plasma or serum. The buffy coat of all plasma samples is collected and stored as a resource for genomic DNA. A project specific stabilization for certain applications can be implemented for all biomaterials if required. Tissue samples are snap frozen and stored at -80°C or formalin-fixed and paraffin-embedded (stored at room temperature).



Figure 2 Workflow monitoring for collection, processing, storage and retrieving of liquid samples and derivatives in the HUB.



Figure 3 HUB basic data set. The HUB basic data set is collected together with all samples stored in the HUB. Further project specific clinical data are collected.



Figure 4 Statistics of primary sample transports from different sites of the MHH campus to the HUB (2018/2019) managed with an in-house developed web application **a)** Delivery of over 16.000 primary samples was managed with the web application in 2019. **b)** In 2019 over 2.400 deliveries were carried out with an average of 6.7 samples per delivery. **c)** 91% (average of 2018 and 2019) of the primary samples deliveries managed with the sample pickup tool arrive in the HUB in less than one hour.

TYPE OF LONG-TERM PRESERVATION

Routinely, all body fluids are stored in 500 µl – 1ml aliquots. All samples stored at –80°C or below are stored in Matrix[™] ScrewTop V-Bottom Tubes (Virgin Class VI Medical Grade Polypropylene) with data matrix 2D code on the bottom on racks with 1D barcode on the side (ThermoFischer Scientific, Waltham, Massachusetts) for a clear sample identification. Sample storage and all sample rearrangements are documented in the BIMS for a gapless sample tracking. All freezing units are equipped with temperature loggers and connected to an alarm system and a back-up energy supply.

STORAGE TEMPERATURE

Long-term sample storage occurs in safe gas phase of liquid nitrogen tanks (-190°C). For midterm storage samples are stored in an automated -80°C repository (BiOS, Hamilton, Franklin Massachusetts) (except for viable cells) with a -80°C cooled picking station for quality assured and temperature controlled composition of requested and issued samples. Old sample collections from HUB partners which were taken over for storage with samples in tubes without 2D barcode are stored in manual -80°C freezers.

SHIPPING TEMPERATURE FROM PATIENT/SOURCE TO PRESERVATION OR RESEARCH USE

-80°C (on dry ice, fully monitored); 0-4°C (on ice); room temperature (18-25°C)

SHIPPING TEMPERATURE FROM STORAGE TO RESEARCH USE

-80°C (on dry ice, fully monitored); room temperature (18-25°C)

QUALITY ASSURANCE MEASURES

Since the founding of the central biobank at the MHH in 2012, quality management was in the focus of HUB [19]. The infrastructure as well as the biobank processes are adapted to the national and international biobank standards and guidelines of the OECD and ISBER [7, 8]. The HUB has been certified in accordance to DIN EN ISO 9001 in November 2015 by TÜV North. The ISO certified processes of HUB include sample transport, preparation, and storage as well as associated data management. In 2018 the whole MHH has been certified in accordance to DIN EN ISO 9001:2015.

In 2013 the HUB established a local standard for the documentation of liquid samples (*Figure 3* HUB basic data set). About 130.000 (12.6%) liquid bio samples, mostly blood and urine, have been collected (in distributed projects all over the MHH) before the local standard was established. Those samples have been migrated into the HUB and potentially do not comply to the actual HUB quality standards. Processing and documentation of tissue samples was covered all over the by the Institute for pathology SOPs.

In addition, as member of the German Biobank Alliance (GBA), the HUB comply with the GBA quality standard [14] which is based on the new ISO Standard 20387 for biobanking and was developed to prepare biobanks for the ISO 20387 accreditation. Since 2021 the accreditation according ISO 20387 by the German accreditation body (DAkkS) is official possible. HUB will start their accreditation process in 2022. HUB takes part in the audit program of GBA including auditor training and were already twice "friendly audited" according to the GBA quality standard by GBA auditors. In addition the HUB regularly participates in ring trails (GBA) in the context of the improvement and harmonization of the quality management of all GBA Biobanks [20–22].

SOURCE OF ASSOCIATED DATA

The HUB collects a harmonized basic dataset together with each sample (*Figure 3*) and holds all quality data generated in the HUB during sample processing. In addition HUB supports four use cases of storing clinical data storage along with the samples, which can vary and mix among projects. The first use case is anonymized sample storage. The second use case is storage of the HUB basic dataset in the BIMS linked to clinical/patient data in the ECRDW (Enterprise Clinical Research Data Warehouse) of the MHH. The third use case is storage of the HUB basic dataset in the BIMS and clinical/patient data in external study systems. The fourth use case is the storage

of all data in the BIMS. The last use case complies with data protection by pseudonymization and is supported by the biobank team by setting up customized, web based sample capture and data entry forms (eCRFs) per project in CentraXX. This enables researches to set up a seamless process from sample collection and data entry over storing to retrieval and analysis. In all four use cases the HUB data validation policies ensure the existence of high quality data linked to the bio samples through a unique patient identifier. Detailed pathologic descriptions and diagnoses are available from each tissue sample, in a considerable proportion of samples immunohistochemical and molecular profiles have been documented. Kopfnagel et al. Open Journal of Bioresources DOI: 10.5334/ojb.70

ETHICS STATEMENT

The implementation of a central harmonized biobank (HUB) at the MHH was approved by the ethics committee of the MHH in 2016 in accordance to the recommendation for the evaluation of research-related human biobanks by ethics committees, recommended by the Working Group of Medical Ethics Committees (AKMEK) [23]. In addition, any research project/sample collection has to be approved by the responsible ethics committee. The implementation of a HUB initiated MHH-wide broad consent collection (MHH Healthcare Integrated Biobanking (MMH-HIB)) was approved by the ethics committee of the MHH in 2017. Since June 2015 the broad, generic consent model of the AKMEK for donation, storage and use of biomaterials well as the data is implemented. The AKMEK model has been approved in November 2013 by all German Research Ethics Committees (broad consent template, version 3.1 2019) [24]. All samples and data are collected after patients have given their written informed consent. Patients/donors may withdraw their consent at all times. The privacy of all donors and the confidentiality of data or samples for third party analysis) following the generic TMF concept. The data protection concept is approved by the local data security authority.

CONSTRAINTS

n.a.

(3) **BIORESOURCE DESCRIPTION**

OBJECT NAME

As a centralized clinical biobank of the MHH the Hannover Unified Biobank houses multiple biosamples/collections

BIORESOURCE NAME

Hannover Unified Biobank (HUB)

BIORESOURCE LOCATION

Hannover Unified Biobank Hannover Medical School CRC Hannover, Feodor-Lynen-Straße 15 30625 Hannover Germany

BIORESOURCE CONTACT

contact-hub@mh-hannover.de

BIORESOURCE URL

https://www.mhh.de/institute-zentren-forschungseinrichtungen/hannover-unified-biobank-hub

IDENTIFIER USED

BIORESOURCE TYPE

The Hannover Unified Biobank administers over 180 collections covering several sample types, disease areas and disease-severities.

TYPE OF SAMPLING

Samples are collected in clinical routine, research projects, disease based cohorts and control collections and clinical studies.

ANATOMICAL SITE

Tissue samples from all kind of anatomic sites are collected from the clinical routine by the Institute of Pathology of the MHH. The anatomical site is documented.

DISEASE STATUS OF PATIENTS/SOURCE

The disease status is collection dependent. The disease status of the patients in the majority of the collections is within the main focus areas of the MHH (transplantation, stem cell research, regenerative medicine, infection and immunity research, cancer research, biomedical engineering, and implant research.

CLINICAL CHARACTERISTICS OF PATIENTS/SOURCE

Collection dependent

VITAL STATE OF PATIENTS/SOURCE

Alive

CLINICAL DIAGNOSIS OF PATIENTS/SOURCE

Collection dependent

PATHOLOGY DIAGNOSIS

Collection dependent. The pathological diagnosis based on standard nomenclatures of collected tissue samples is determined by the Institute of Pathology, MHH.

CONTROL SAMPLES

Control samples of healthy individuals are collected in some studies and are mainly available as part of a cooperation.

BIOSPECIMEN TYPE

The HUB stores over 80 different sample types. The main sample types are blood, blood derivatives (serum, plasma, buffy coat), urine and tissue samples stored in the Institute of Pathology. In addition the HUB stores a wide range of other body liquids like bronchoalveolar lavage, sputum and salvia, viable cells, swabs and stool samples.

SIZE OF THE BIORESOURCE

Currently, samples from around 690,000 individuals distributed over all studies are stored in the HUB.

RELEASE DATE

n.a.

ACCESS CRITERIA

In case of samples and data collected from MHH patients, the Hannover Medical School (MHH) as the sample owner transmits the authorization to use the biomaterials for medical care and research to the principle investigators (PIs), who collect the samples in

clinical routine, studies and projects [25]. They have the function of gatekeepers, and can use their samples for diagnostics and research (within the scope of the consent). They can also share samples and data with local, national and international as well as industrial cooperation partners. Samples and data (basic dataset, *Figure 3*) can be requested via the HUB and can be used as part of cooperation with the respective gatekeeper. Further clinical data can be requested from the ECRDW as part of a cooperation. In case of the HUB initiated MHH-wide broad consent collection (MHH-HIB) and the 2020 initiated COVID-19 biobank the access to samples and data is regulated by the HUB use and access committee (UAC). HUB will provide a form for the request of these samples. Terms of business are ruled by the by-laws of HUB. Diverse administration and agreement documents for projects and cooperations are also available at HUB (data protection concept, broad consent documents, material transfer agreement (MTA), project responsibility interface agreement etc.).

HUB collections are published in the BBMRI Directory [26] and the GBA sample locator [27].

REUSE POTENTIAL

After the end of the project funding, the collections of samples and data remain at HUB and are still available for national and international requests. All samples can be requested and used by other researchers if a broad consent has been obtained or the use is permitted by the study-specific consent used. The above-mentioned access criteria remain valid. Research data can be requested via the HUB and can be used as part of cooperation with the respective gatekeeper. The approval of the gatekeeper or the HUB use and access committee (UAC) is the prerequisite for a sample transfer.

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FUNDING STATEMENT

The HUB is a core facility of the MHH and receives a basic funding from the MHH. In addition the HUB is a funded partner in several third party funded projects (see table below). Since 2012 HUB is member of the German Center for Lung Research (DZL) and the German Center for Infection Research (DZIF) with the DZIF-Transplant cohort, since 2017 HUB is partner biobank in the German Biobank Alliance (GBA), and since 2019 HUB is member of the excellence cluster "Resist" and "Hearing4all".

CONSORTIA	FUNDER	DESCRIPTION	GRANT REFERENCE NUMBER
German Center for Lung Research (DZL)	Federal Ministry of Education and Research (BMBF)	Network which links scientists at five locations in Germany and focuses on eight disease areas in lung research.	82DZL002A1
German Center of Infection Research (DZIF) Transpant Cohort	Federal Ministry of Education and Research (BMBF)	The DZIF transplantation cohort is part of the research area "Infections in immunocompromised hosts" at the DZIF	DZIF-TTU 07.701
German Biobank Alliance (GBA)	Federal Ministry of Education and Research (BMBF)	Network for the harmonization of Biobanks in Germany. Partners establish uniform quality standards and make their biomaterials available for biomedical research throughout Europe	01EY1706
Collaborative Research Centres (SFB 209)	German Research Foundation (DFG)	Network with the focus on new mechanistic and therapeutic concepts for liver cancer in a solid tumor model	TRR209/1
RESIST	German Research Foundation (DFG)	Excellence cluster with the focus on infections in the immunocompromised host	EXC 2155/1
GAIN	Federal Ministry of Education and Research (BMBF)	Network with the focus on rare autoimmune diseases	01GM1910E
DZIF ZIFCO	Federal Ministry of Education and Research (BMBF)	The ntegrated infection research cohort ZIFCO is an additional study within the German national cohort health study with focus on the correlation between acute, transient infections and chronic diseases	TI 09.903_00
DZIF HBV Cure	Federal Ministry of Education and Research (BMBF)	DZIF cohort with the focus on chronic hepatitis B virus infection	TTU 05.806_01
DIGIT-HF	Federal Ministry of Education and Research (BMBF)	DIGIT HF is a study for the therapy of cardiac insufficiency with digoxin	01KG1303
Neocyst	Federal Ministry of Education and Research (BMBF)	NEOCYST is a multicenter, interdisciplinary network of clinicians and scientists exploring early onset cystic kidney diseases	01GM1903H
KFO 311	German Research Foundation (DFG)	Register of patients who are treated with a support system due to an acute or terminal failure of the heart or lung	IL 53/13-1
Fraunhofer biobank harmonisation	Fraunhofer-Gesellschaft zur Förd.der angewandten Forschung e.V.	The Fraunhofer Cluster of Excellence Immune- Mediated Diseases (CIMD), a strategic network of the Fraunhofer Society with their core institutes IME-TMP, IZI and ITEM, set up a harmonization project to establish a joint biobank infrastructure according to German Biobank Alliance (GBA) standards and modern biobanking demands, supported by the Hannover Unified Biobank (HUB).	n.a.
INDIRA	Ministry for Science and Culture of Lower Saxony	Network with focus on severe RSV infections in children	ZN3437
ImSAVAR	Innovative Medicines Initiative (EU-IMI)	Consortium with focus on the development of nonclinical assessment strategies of immunomodulatory therapies	853988- imSAVAR-H2020-JTI- IMI2
Hearing for all	German Research Foundation (DFG)	Excellence cluster with the focus on improvement of individualized hearing diagnostics and supply of technical	EXC 2177/1
COVID-19 Biobank	Ministry for Science and Culture of Lower Saxony	Implementation of a COVID-19 cohort for SARS-CoV-2 related research projects	14-76103-184 CORONA-1/20

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Verena Kopfnagel: Project Manager, Deputy Head of Laboratory Inga Bernemann: Quality Manager, Project Manager Norman Klopp: Head of laboratory, Deputy director Markus Kersting: Head of IT Nataliia Nizhegorodtseva: IT Manager Jana Prokein: IT Manager Ulrich Lehmann: Manager of Tissuebank Helge Stark: IT Manager Tissuebank Thomas Illig: Director

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