BONEBANK

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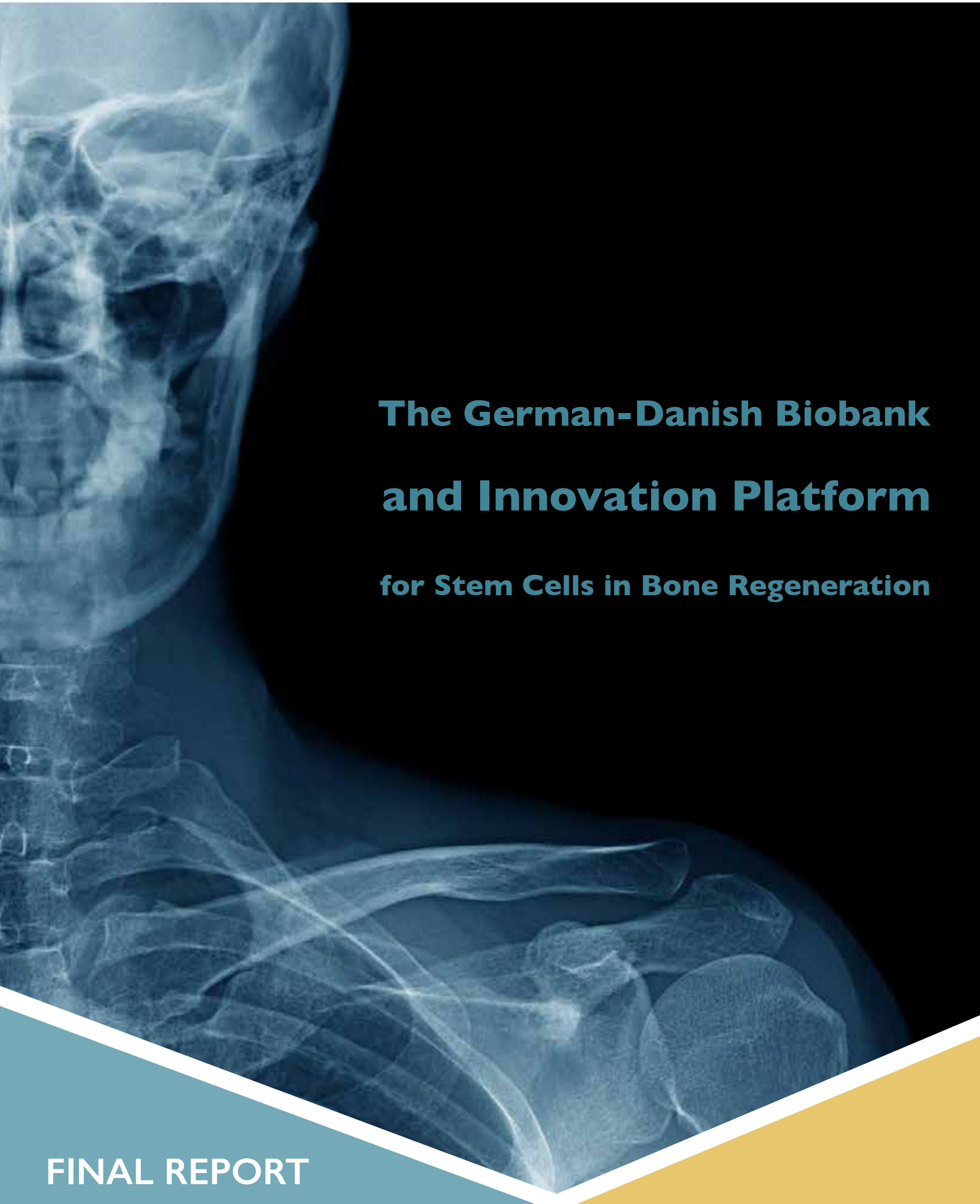
EUROPEAN UNION



The German-Danish Biobank and Innovation Platform

for Stem Cells in Bone Regeneration

FINAL REPORT

PUBLICATION CREDITS

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TABLE OF CONTENT

EDITORIAL

One day I talked to my friend Nils Reimers, who was about to have major dental surgery. We got to wondering, whether it would be possible to rebuild his jaw with the help of stem cells and thereby considerably simplify his treatment. That triggered my interest in the topic, and I began to research.
I found out that bone healing through stem cells is in fact possible, but as of now it is rarely employed, due to the difficult access to stem cell-containing material. That made me startle.

As a surgeon I throw bone marrow and bone pieces containing this valuable resource in the bin on a daily basis. What a waste!
I looked for competent partners to cooperate with in finding solutions for collecting the biomaterial, storing it and providing it to researchers. This is how the German-Danish cooperation project BONEBANK kicked off.

This report documents the results we have achieved in the past three years of the project's existence, and offers an overview of the developments still to come.

Prof. Arndt Peter Schulz, Lead Partner, University Hospital Schleswig-Holstein

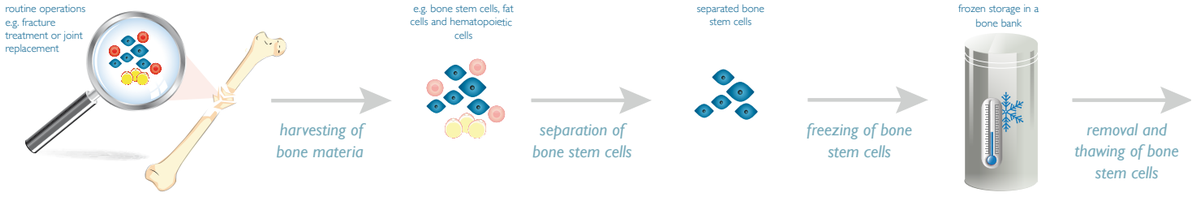
PROJECT FACTS

Duration: Sep. 2015 - Feb. 2019
Total budget: 2.4 million Euro, thereof 1.34 million Euro funding
Partners: 5 project partners, 2 network partners

BONEBANK is supported by **Interreg Deutschland-Danmark** with funds from the European Regional Development Fund.

Project partners:
- University Medical Center Schleswig-Holstein, Campus Lübeck
  Laboratory for Biomechanics and Orthopaedic-Traumatological Research, Deparment for Orthopaedics and Trauma Surgery,
  Interdisciplinary Center for Biobanking-Lübeck (ICB-L) & Section for Translational Surgical Oncology and Biobanking, Department of Surgery, University of Lübeck
- Life Science Nord Management GmbH
- Odense University Hospital
- soventec GmbH
- Stryker Trauma GmbH

Project extension: Mar 2019 - Aug 2020



SUMMARY

Currently, bone and bone fragments with valuable stem cells are disposed of as waste material during fracture-related routine operations. However, these stem cells have a high potential for regenerative therapies, for instance in the treatment of bone fractures.

The BONEBANK project partners harvest these stem cells. In the next phase, the cells are transported to the hospital sites in Lübeck and Odense, where they are isolated from the bone marrow material. Finally, the extracted cells are being stored in a cross-border biobank. BONEBANK's aim is to provide these stem cells for research purposes, and to create an organisational and exploitation model for the biobank, so that patients, research and companies can benefit from it.

The BONEBANK project generates a unique new value chain that offers an innovation platform for research based companies to develop new medical products and therapies for regenerative medicine. As a result, a surgical instrument which allows collecting a sufficient amount of biological vital stem cell-containing material during fracture surgeries has been designed. Besides developing a method for the safe and effective extraction of a blood-fat-marrow material mix, the project has provided the technical and spatial infrastructure for the transnational transportation, preparation and storage of the stem cell material. The collection of high-quality biomaterial and its related clinical data is then used for fundamental disease research for the benefit of the general public.

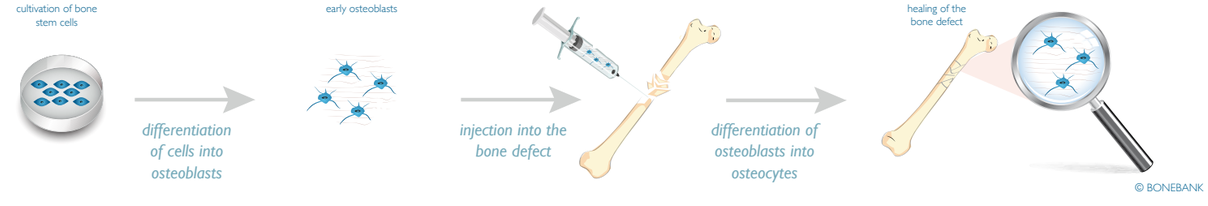
BONEBANK PROCESS

BONEBANK thereby creates the preconditions for a field of diverse applications of stem cells in the process of bone healing. In future, the collected material could be reinjected into the donor patients themselves, donated to other patients, or used in the development of personalised diagnostics, drugs and therapies.
The results of BONEBANK are interesting for various target groups:
- Clinicians and hospitals implement the BONEBANK approach to harvest bone marrow stem cells during routine operations.
- Public and/ or private biobank operators are part of the BONEBANK value chain to store, use and/ or market stem cells.
- Academic researchers use bone marrow stem cells for research purposes.
- Life Science Industry (medtech, biotech, pharma) companies purchase bone marrow stem cells for research and the development of therapies.
- Politicians and the general public understand the potential of bone marrow stem cells for regenerative medicine, and the value of the BONEBANK network for the cross-border region.

The partners are developing an organisation and business model for the use of bone marrow stem cells by donors, patients, research institutions as well as life science companies and SMEs.

PROJECT EXTENSION

Building on the results achieved so far, the BONEBANK extension phase is set to further develop and implement the legally authorised cross-border harvesting, storage and usage of bone material. During this phase, the partners plan to establish a BONEBANK organisation by involving additional organisations such as donor and implantation hospitals, biobanks and companies.
The aim of developing a GMP-conform cell product is to enable the usage of stem cells in regenerative therapy. To achieve this, BONEBANK intends to launch an entirely new cell product. Upon successful completion, the project partners will have established a competence cluster in the field of bone stem cells within the programme region Germany-Denmark.



BONEBANK process chain

WORK PACKAGE

„HARVESTING OF BONE MARROW STEM CELLS“

CONCEPT DEVELOPMENT OF A DISPOSABLE MEDICAL DEVICE

GOAL

The concept of BONEBANK starts with the availability of a special disposable instrument for surgeons, which allows collecting a sufficient amount of biologically vital and high-quality stem cell-containing material during fracture surgeries. Therefore, the goal of this work package was to develop a concept for the safe and effective extraction of a bone-blood-fat-marrow material mix. The device is planned to be provided in a sterile application set with all required equipment which allows to re-pack and seal the harvest for shipping to the biobank.

RESULTS

In a first step, the project team drew up a list of requirements for the surgical instrument. These included the clinical and operational requirements, as well as the geometric and material specifications. In a next step, the medical device manufacturer identified additional functional requirements by testing the device with fluids of different viscosity in cadaveric bones. The tests confirmed efficient function of the BONEBANK harvester as well as an intuitive handling for the surgeon in typical deployment scenarios.
It was shown that the safe collection and transportation of the extracted material presented a key challenge, due to its high viscosity (high fat content), its granules content, and adhesion characteristics. In the process, highest demands were set regarding the safety of the apparatus in surgical practice, as the instrument might be inserted deep into a patient‘s long bone. During feasibility assessments, various mechanically, manually, and electrically-driven procedures were tested and evaluated. In order to keep efforts and time-to-market feasible, the focus was placed on the use of approved materials, the realisation of robust designs, and the implementation of quick clinically accepted working steps.

Finally, the team developed and presented a mature pre-series product, including a full application kit, proven technical feasibility and advanced regulatory assessment. Design, handling and usability of this future product is linked and synchronised with subsequent BONEBANK process steps. The BONEBANK harvesting device development is oriented at ISO13485 documentation.

3D view of the BONEBANK extraction device for stem cell containing tissue material.

CONCLUSIONS & OUTLOOK

The BONEBANK harvesting device provides the initial hardware concept within the new exploitation chain. Due to regulatory requirements, the product is not yet CE-certified. The concept, however, has been shown to be intuitively usable, and reduces the disruption of the surgical procedure to a minimum. Therefore, the new product may allow the wide dissemination of this idea and provides the basis for the entrepreneurial success of BONEBANK.

PROCESS CHAIN: HARVESTING AND BIOBANKING

GOAL

The BONEBANK project requires the development of a cross-border procedure for the harvesting of bone marrow stem cells, and the implementation of logistics for the transport of the stem cells to the biobank. Thus, a central goal was to develop a process for the storage and transport of the harvested tissues, as well as the implementation of a system for quality assurance in the operating room and in the trauma centres.

RESULTS

A complete BONEBANK process chain of the harvested bone material from the operating room to labs/biobanks in Denmark and Germany was developed. This included consulting all necessary EU directives for international transport of human specimens, and internal regulations for receiving and storage of human cells and tissue.
Besides the joint process for the cultivation of the stem cells, a process for the quality control with regards to the ability of bone formation was developed. The BONEBANK project successfully tested the storage conditions necessary to ensure the quality of biomaterial samples throughout their storage life until later use. The quality control aims at excluding any risk for the recipient.

Patient consent, medical history and physical examination

The BONEBANK process chain starts with the admission of a patient to a hospital in Denmark or Germany, with an indication for a surgery on bone in which bone material is discarded. If the patient is able to consent, he/she will be informed about the possibility to donate his/her bone material. If the patient agrees to the donation, he/she signs a consent form. The BONEBANK process chain will only continue with written patient consent, otherwise the surgery will be performed without the harvesting of bone material.
The next step of the process chain is to check whether the patient could be a possible donor. The suitability is determined on the basis of the medical history and the physical examination. This is intended on the one hand to protect the patient from possible risks of the donation, and on the other hand to protect the recipient in case of an allogenic donation, as well as the worker or researcher from possible infections.
The medical history of a prospective donor is determined on the basis of an anamnesis questionnaire that asks the potential donor about diseases he/she might currently be suffering from. In addition to the anamnesis questionnaire, the feasible donors are examined by a doctor, in order to assess the general condition of the patient. During clinical routine, blood samples are taken from the potential donor in order to perform biological tests.

Harvesting of bone material during the surgery

If bone material shall be collected during the bone surgery, the surgical nurse provides the BONEBANK set in the operating room before starting the surgery. The BONEBANK set includes the harvester with a suitable container lid, packaging and labelling material. During surgery preparation, the nurse removes the individual parts and checks the sterility. In the case of defects, the BONEBANK set is immediately replaced by a new one.
During the surgical procedure, the surgeon collects bone material with the use of the harvester, and transfers it to the sterile container. The harvesting process is documented in a harvesting report. At the end of the surgery, the container is sterilely closed, and transferred to the secondary packaging after the surgeons' approval.

Sample registration and processing at the biobank

After arrival of the sample at the biobank, the packaging of the sample and the associated documents (donor file, sample report, transport report) must be checked.
If the documentation is complete and the packaging undamaged, the sample is included in the respective biobank register, which is linked to the cross-border BONEBANK database.
The bone material is then processed at the biobank/ laboratory infrastructure of the partners sites in Lübeck and Odense. The bone stem cells are isolated from a portion of the bone material, according to standardised work instructions. The remaining bone material and the isolated bone stem cells are then transferred into designated barcoded freezing tubes, together with special freezing liquids. The samples are thereafter stored in (semi-) automated nitrogen tanks at temperatures below -150°C in the respective biobanks by specialised personnel.
For further examination, the stored isolated bone stem cells and the bone material are thawed. Here, the focus lies on whether it is possible to isolate stem cells after freezing. In order to check the quality of the samples after storage in the biobank, the stem cells are examined for their differentiability and their growth behaviour.

Request and retrieval of biomaterial

After an incoming request, a BONEBANK committee reviews the feasibility and ethical appropriateness of the request. Only after a positive vote by the committee can samples be made available. The software CentraXX is used to manage sample storage and associated clinical and research data, thus allowing retrieval of specifically requested samples from the liquid nitrogen tanks. All this information is documented in a retrieval report and record in CentraXX and the BONEBANK database. After removal from storage, the sample is packaged and labelled in accordance with transport regulations, and transported under controlled conditions which guarantee the quality of the sample.

CONCLUSIONS & OUTLOOK

From the beginning of the project until 28th of February 2019 114 bone samples have been collected. The first results show that viable stem cells could be isolated and cultured as described in the next chapter. A further goal is to allow isolation and culture also from initially frozen bone material. Indeed, findings show that this might be possible since isolated stem cells from primarily frozen bone material were vigorous and cultivable.
The next step will be to check whether long-term storage in the biobank has an influence on the differentiability of the stem cells, and how far one can optimise the freezing and thawing process.

(semi-) automated nitrogen tanks: BioStore (TM) III 1500 Cryo (Brooks Automation Inc.), C-line® HS200 S (Askion GmbH), Smartfreezer® V180-20 (Sysmex Suisse AG)

PRE-STUDY: ANALYSING THE ISOLATED STEM CELLS

GOAL

The main research goal of the project was to determine whether bone material collected during routine orthopaedic surgeries can be a sufficient source of mesenchymal (stromal) stem cells (MSCs). After successful isolation, we would further focus on the quality of the isolated cells and therefore apply various in vitro assays to assess their biological properties.

RESULTS

During the BONEBANK project, we collected bone material from donors undergoing various routine orthopaedic surgeries at Odense and Lübeck. Our donor cohort included males and females with different anthropometric characteristics and health profiles. The collection of such a comprehensive material cohort provided us with a basis, on which the stem cells from a broad cross section of the population could be investigated.

From the beginning of the project until 28th of February 2019 114 bone samples have been collected. The procedure for obtaining MSCs was initiated at the hospital in the operation theatre, where the surgeon collected bone material during various orthopaedic surgeries. The aspirated material was immediately transported to the laboratory/biobank, where MSCs isolation was attempted. We succeeded in isolating MSCs from 89% of all samples, and the cells were cultured and subsequently analysed by researchers. The biological properties of the cells were assessed by applying classical and novel in vitro assays to investigate the cell clonogenicity, proliferation, expression of cell membrane markers and differentiation potential. These analyses provided an overview of the MSCs quality, and more than 76% of the cells showed good differentiation potency. We conducted further studies on these cells with a view to identifying indicators of MSCs potential for clinical applications.

The successfully isolated MSCs exhibited a heterogenous character in respect to their ability to proliferate and form colonies. We also found that the expression of several cell membrane markers associated with the cell multipotency also varies between donor samples. Furthermore, the in vitro osteogenic and adipogenic differentiation assays revealed that most of the isolated cells had a bipotential character, as they were capable of forming osteoblasts and adipocytes.
The MSCs are currently cryopreserved in liquid nitrogen tanks in a biobank for further cellular, molecular and cryopreservation analyses.

The main findings of the research are:
• Bone material collected from donors during routine orthopaedic surgeries is a good source for isolation of biologically potent MSCs.

• The cells isolated from bone samples were plastic-adherent cells, which expressed standard cell membrane markers fulfilling criteria of mesenchymal stem cells, as well as markers associated with the multipotency of MSCs. The cells demonstrated a heterogeneous ability to form colonies, to proliferate and differentiate into osteoblasts and adipocytes.

CONCLUSIONS & OUTLOOK

Our research goal was met, as our study indicates that the bone samples harvested during routine surgeries are a promising alternative for the current practice of volunteer donations. This method could possibly increase the number of MSCs for potential future clinical applications. Our analyses demonstrated that MSCs from surgical material exhibit a heterogeneous character in their biological functions, which is similar to samples from volunteer donors. This in turn may indicate that the donor characteristics may have a crucial influence on the biology of the MSCs. Therefore, the current focus is to identify donor and cell features that may serve as markers of cell lineage commitment. These potential predictive factors may facilitate the selection of potent MSCs for future clinical treatment in the orthopaedic field. Thus, in the second part of the BONEBANK project we will aim to apply our findings in clinical practice.

REQUIREMENTS ON PATIENT CONSENT

GOAL

Development of a concept for the patient consent for the full process of the BONEBANK project for Germany and Denmark, including the different range of applications: currently only for research purposes and in the future for therapeutic (allogeneic or autologous) purposes.

RESULTS

In its current form, a concept for patient consent was developed and applied for research purpose only in Denmark and Germany. The concept is based on the current guidelines from Germany and Denmark. Patient consent is required for the donation of bone material. The patient information sheet and the consent form were developed according to the legal requirements, the "Guideline for Good Clinical Practice (GCP)", the ethical principles which have their origin in the Declaration of Helsinki, and were updated according to the EU data protection regulation (GDPR). The patient information and consent have been approved by the responsible ethics committees and Data Protection Officers.
The patient must be informed by a qualified person about the study. To ensure the patient understands the information, simple language without technical terms is used, and the patients shoud have sufficient time for consideration to participate and for aking questions. Also, the potential donor must be informed of the right to refuse participation, or to withdraw their consent at any time, without incurring any disadvantages for clinical routine treatment. The patients must not be influenced in their decision, and must give their consent voluntarily. In the case of the donor withdrawing their consent after harvesting the bone material during the routine surgery, the sample is to be destroyed and the patient data to be deleted. The samples and associated clinical data which were already used, e.g. for publication purpose, cannot be revoked. All limitations of withdrawal are clarified in the consent form. In addition, as declared by the European parliament, the potential donor must be informed about

"the purpose and nature of the procurement, its consequences and risks, analytical tests, if they are performed; recording and protection of donor data, medical confidentiality; therapeutic purpose and potential benefits and information on the applicable safeguards intended to protect the donor".

In the following sections these aspects of the consent will be described in relation to the BONEBANK project.

The purpose and the nature of the procurement is the harvesting of bone material during surgery on bones. The surgery is not a part of the BONEBANK project, and collection of material for BONEBANK is performed during medical treatment using a specially designed surgical device. A condition for the use of the device on the patient is CE certification. The requirements for CE certification include a risk analysis including all possible risks for the donor.

The next aspect would be the *analytical tests,* which are required for therapeutical purposes (allogeneic and autologous transplantation). The donor must be informed about the necessity of a blood collection for these tests, and about the associated risks. To protect both donor and recipient, also a physical examination of the donor must be performed, and the results and the medical history must be documented.

Another main part of the consent is the *therapeutic purpose and the potential benefits.* These differ depending on the intended research or therapeutic use. With an autologous donation, the isolated stem cells would be used for exactly the same patient when future diseases like pseudo arthrosis occur. Sample donation for allogeneic transplantation or donation for research purposes will not allow benefits for the donor himself. However, either other patients might directly benefit from the donation, or the general public benefits through the development of new stem cell therapeutics.

Another point is the information on *applicable safeguards intended to protect the donor.* As described above, the only risks concern the harvesting device and the data protection. The intended safeguards are therefore the development of the device with all necessary safety precautions, and proper data

protection measures and concepts approved by the responsible authorities.
After informing the donor of these aspects, the donors give their consent by signing the consent. In addition, the person who conducted the patient information must also sign the written consent form.
Only after the consent has been signed by the donor may bone material be collected for research or therapeutic purposes.

CONCLUSIONS & OUTLOOK

This concept developed for patient information and consent contains the main important aspects, which must be included for a bone material donation for a different range of applications.
The next step will be to not only further apply the approved consent procedure for reserach purposes but to set the stage for patients' donations in BONEBANK also for therapeutic purposes.

WORK PACKAGE

"GERMAN-DANISH BIOBANK FOR BONE MARROW STEM CELLS"

STORAGE MANAGEMENT

GOAL

In order to establish and operate a cross-border biobank and innovation platform for human bone (marrow) stem cells (MSCs) from fracture-related routine operations in bone regeneration at the sites Odense and Lübeck, it was necessary to develop and implement a concept for the process of sample collections, reconditioning and physical storage. Besides these infrastructural aspects, another goal was the description of the legal framework and current EU data protection regulations for the Danish and the German stem cell biobank. This description included a harmonised set of parameters for the common BONEBANK database, regarding all processes within the project (i.e. sample collection, processing and storage as well as the clinical and sample related phenotypic data).

RESULTS

The preparation and storage process as well as sample retrieval from the biobank system were performed in harmonised standard operating procedures (SOPs) with respect to the data protection requirements of the EU legislation in both countries.

MSCs were extracted and separated from bone pieces at the University Medical Center Schleswig-Holstein (UKSH) and from bone marrow at the Odense University Hospital (OUH). For this reason, OUH's SOPs had to be adapted at the UKSH, in particular concerning the differentiation time, based on the different sources of MSCs. After the identification as human MSCs, cells were differentiated into mesenchymal tissues like osteocytes and adipocytes in vitro.

At UKSH, MSCs are still vital and still have the potential for osteogenic differentiation after being frozen at cryogenic temperatures. Also, isolated MSCs from frozen trabecular bone pieces are still vital, and have the potential for osteogenic differentiation with a lower output of human MSCs. Both facts confirmed a successful implementation of OUH's SOPs for isolation and differentiation of human MSCs in Lübeck.

(semi-) automated nitrogen tanks: BioStore (TM) III 1500 Cryo (Brooks Automation Inc.), C-line® HS200 S (Askion GmbH), Smartfreezer® V180-20 (Sysmex Suisse AG)

CONCLUSIONS & OUTLOOK

The establishment of a harmonised cross-border German-Danish biobank infrastructure enables the use of synergies between the various areas of expertise and infrastructures. BONEBANK thus enables substantially improved interdisciplinary cross-border research opportunities on MSCs for the optimisation of regenerative medicine.

TECHNICAL INFRASTRUCTURE OF THE BIOBANK

GOAL

The goal of developing the technical infrastructure of the cross-border biobank for bone marrow stem cells for non-human use at the sites Odense (OUH) and Lübeck (UKSH) was to ensure stability and operation of the stem cell biobank.

RESULTS

A concept was produced allowing collection, transport and preparation of high quality stem cells from the operating theatre to the biobank. Methods were established to test and assure osteocyte and lipocyte differentiation potential of the stem cell.

The technical infrastructure (figure 1) comprises:

- Local orthopaedic surgical wards collaborating with the biobanks by collecting samples using SOP-guided procedures.
- Research laboratories separating and purifying and culturing the stem cells, while applying functional tests to assure the quality and differentiation potential of the cells.
- Facilities for controlled freezing and storage in liquid nitrogen of the cells prior to shipment.
- IT facilities and user interfaces allowing distribution of frozen cells to laboratories or customers.

In the infrastructure developed for BONEBANK, local operating theatres at UKSH and OUH deliver freshly-sampled bone marrow material or bone pieces to the local BONEBANK laboratory/ biobank, in which stem cells are recovered, prepared and stored frozen.

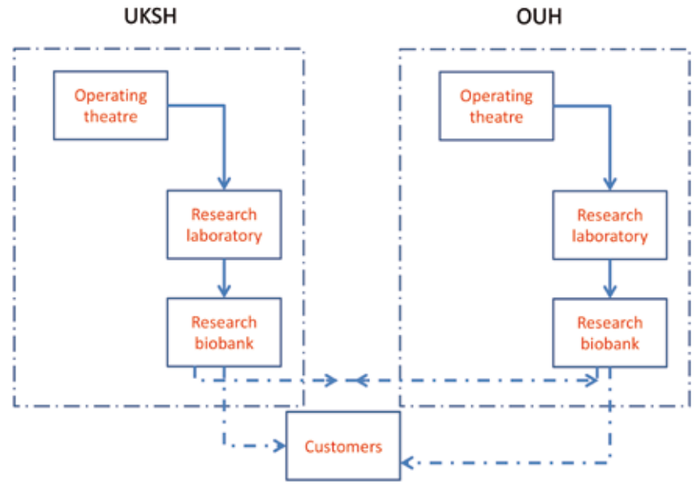


Figure 1: The current infrastructure of BONEBANK (Full arrows illustrate the usual traffic of samples and cells. Hashed arrows represent possible routes for frozen stem cells in transit for other laboratories or future customers.)

The procedure comprises:

1. Patient recruitment including consent to the procedure and future use of the cells.
2. Standard forms for patient/sample information.
3. Standard procedure for recovery of bone marrow or bone pieces.
4. Temperature-controlled, fast transport to the local BONEBANK laboratory.
5. SOP-controlled procedures for cell recovery, culture and testing.
6. SOP-controlled procedures for cell freezing and storage.

CONCLUSIONS & OUTLOOK

Users of the results will be the consortium members and other European biobanks (academic and industrial), as well as the sector of industry active in the biobank business (cryotechnology, medical technology, life science, medical computing, etc.). In the future, the infrastructure may be expanded to a Good Manufacturing Practice-compliant concept, allowing clinical use of the cells.

A fully-developed commercial BONEBANK will also need subsequent steps enabling marketing and distribution of frozen cells to customers. However, BONEBANK thus far only includes local usage for research and quality assurance purposes. Therefore, permissions from local (German and Danish) ethical committees and data

authorities suffice to establish a legal framework for the concept. Trans-border traffic of tissues and products is also feasible, but will require a data treatment agreement ('databehandleraftale') regulating proper treatment of sensitive patient data at the various localities. The GDPR does not preclude this, as long as both parties are EU members. Even traffic to third-party countries is likely to be possible, because such traffic is already widely used e.g. in organ and haematopoietic stem cell transplantation.

A possible infrastructure for a future clinical grade BONEBANK is illustrated in figure 2. Such a BONEBANK exceeds the scope of this report, and will require further permissions and accreditations in order to comply with Good Manufacturing Practice standards. If stem cells are cultured, they will probably constitute Advanced Therapy Medicinal Products (ATMPs) and must adhere to the EU Regulation No 1394/2007 and other rules applying to pharmaceutical products.

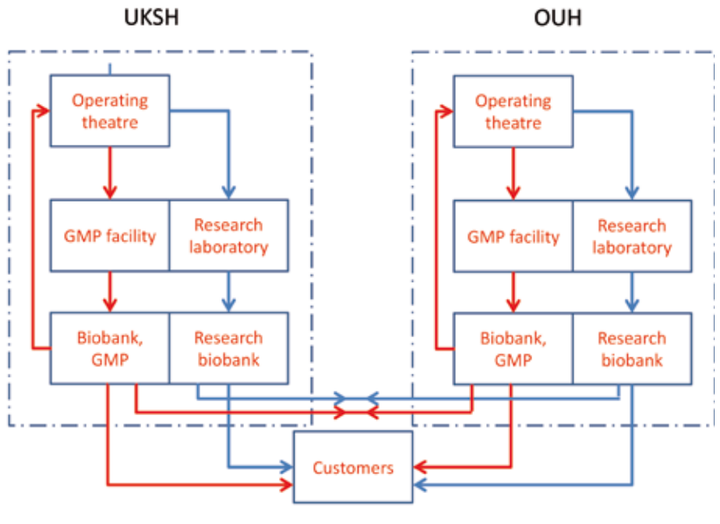


Figure 2: Example of a possible future extension of the structure allowing clinical usage of the cells.

Liquid nitrogen freezers at the Department of Clinical Immunology, Odense University Hospital

IT INFRASTRUCTURE OF THE BIOBANK

GOAL

One of the central prerequisites for a cross-border biodata database is the uniform specification of the parameters that the participating partners document for the characterisation of the samples, or for finding the samples for further processing.

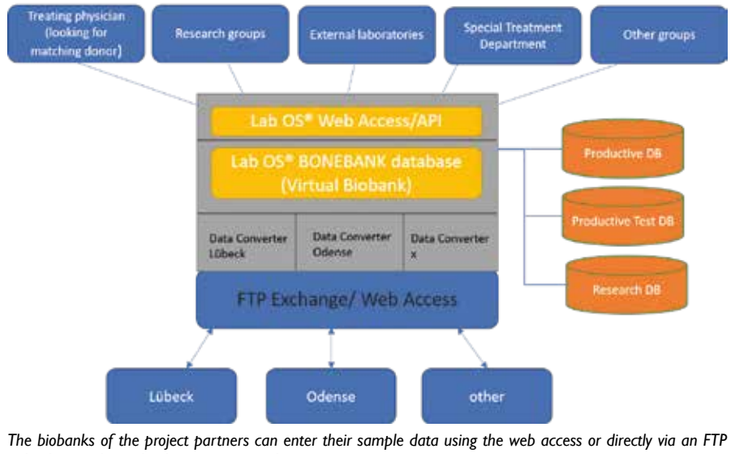
A subgoal of BONEBANK therefore is to connect the IT infrastructure of the locations involved, for easy access to the joint data. This is also necessary for the efficient operation of BONEBANK's biobank for stem cells.

The sample data shall be managed by a central IT solution (hereafter: BONEBANK DB), to fulfil the requirements relating to data management within the project phase on the one hand, and to provide a sustainable foundation for productive use in future on the other hand. In both cases, high standards must be applied for data privacy protection and security.

RESULTS

The project partner soventec has developed the BONEBANK DB software. At BONEBANK, the extracted bone material is collected and processed by one team in Odense and one in Lübeck, respectively. The IT solution enables the data of these samples from different locations to be entered into the virtual sample database. With web-based access, the samples can be managed across teams and identified at any time.

For this purpose, the German and Danish partners agreed on uniform parameters. The parameters set for the sample database take equal account of German and Danish interests with regard to common standards. In particular, the matching of different medical coding systems used in the Danish and German healthcare systems presented a challenge.



The biobanks of the project partners can enter their sample data using the web access or directly via an FTP upload or similar technologies to import data.

Technical concept overview of the BONEBANK DB

The BONEBANK DB contains patient-related data. Therefore, the highest level of security must be applied. Pseudonymised data is provided by the data deliverers (UKSH, OUH) through an encrypted channel. The data can be entered using a web interface.

The web interface is also used to search for samples according to given criteria. For interesting samples, the data delivering partners (UKSH, OUH) can be contacted to get more detailed information or the samples themselves.

Legal responsibility for the sample data

A legal contract framework concept has been developed for data exchange between the partners. The data delivering partners (UKSH, OUH) are responsible for delivering high-level pseudonymised datasets. They are legally responsible in the event that the agreed minimum dataset can be traced back illegally to the original patient.

As the developer of the BONEBANK DB system, soventec has taken measures to ensure a state-of-the-art security level. In the project phase, soventec is responsible for the data security in BONEBANK DB, and thereafter the future BONEBANK organisation.

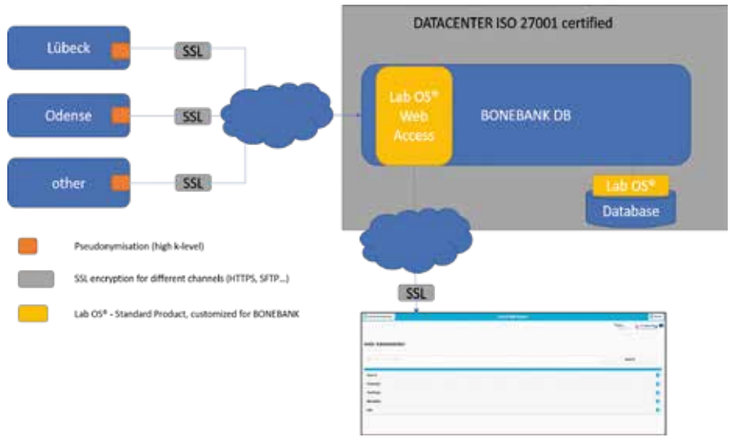
A data centre with an ISO/IEC 27001 certification in Germany is being used during the project phase. Therefore, EU's General Data Protection Regulation (GDPR) is applicable.

CONCLUSIONS & OUTLOOK

Beneficiaries of the results will be the consortium members and other European biobanks (academic and industrial), industry partners which are active in the biobank business (Life Science, medical informatics etc.), as well as the clinics for patient care.

In the long run, the approach of this cross-border IT concept should enable a location-based sample query, also giving external users the possibility to search for suitable stem cell samples, and to request these.

In order to reach a high and safe legitimation level, a legal framework must be established between the partners, and between the partners and consumers.



Pseudonymised data is provided by the data delivering local biobanks/hospitals through an encrypted channel. SSL-encrypted data is then stored in a data centre with an ISO/IEC 27001 certification located in Germany.

WORK PACKAGE

"EXPLOITATION AND ORGANISATION MODEL"

FEASIBILITY AND APPLICATION FIELDS

GOAL

The goal of this activity was to present the state-of-the-art of the stem cell market, and the possibilities for the BONEBANK project and the BONEBANK biobank. Here, various functions and tasks, such as quality assurance and control, data annotation, biospecimen inventory and storage management, administration and facilities are essential elements to be considered when constructing a biobank.

RESULTS

After the consortium explored the potential of isolated mesenchymal stem cells (MSCs) from routine surgeries, it became clear that the isolation of the stem cells and the development of a business model in the next step, which aims to use these cells for therapy, is not achievable within the project's lifetime. However, there was agreement on the possibility of using the cells for research aspects in different ways.

Regarding application fields, we found that for research purposes big pharma companies primarily use induced pluripotent stem cells. That could be a niche for BONEBANK replacing iPS cells. Moreover, there is a debate about the quality of medium-sized companies, which promise large-scale production of stem-cells. Selling MSCs of high quality could be an option for BONEBANK. Otherwise, there are promising approaches to overcoming problems regarding large-scale production of MSCs.

The most obvious example of how the isolated cells could be used is for the analysis of genetic mutations and disorders. Isolated cells, or the entire human biological material, could be used internally or externally for academic research.

Talks and meetings with stakeholders on a national and international level revealed that there is a strong interest in genetic mutations, individual medicine or epigenetic analyses. However, it became clear that the BONEBANK project has to do some effort in the future to become market relevant, which will be further elaborated in the future. Furthermore, there are already existing biobanks storing tissue, cells and DNA like EuroBioBank and others mentioned above, which focus on rare diseases. Therefore, for long-term sustainability of BONEBANK, and to reduce dependence on public funding, development of a cost-reimbursement or recovery strategy is required.

In this context, there are two different options for using the donated material for therapy. The first option is that the patients donate and store the material for their own use. In this case, the patient bears the costs for storage, preparation and logistics. The second option is that the patient donates the material for use by other patients. In that case, the costs incurred must to be covered by the recipient's health insurance or the patient himself. For this scenario, there are also two ways of processing the material. The first scenario is to use the donated material directly in a patient, similar to bone marrow stem cell donation/transplantation. The second scenario is that the donated material is processed (cultivation and multiplying cells in vitro) by a treatment manufacturer. Since this option represents an advanced therapy medical product (ATMP), it needs regulated and approved processes. Cost reimbursement is conducted by the patient himself or his health insurance, depending on the status of the ATMP and the scope of insurance cover.

CONCLUSIONS & OUTLOOK

At present, the isolated cells do not meet the requirements for therapeutic use. However, the application field "cells for research" has been defined.

In discussions with experts, we learned that there is a need for MSCs, for example to enable better clinical outcomes regarding orthopaedic diseases and injuries. The current achievable result 'cells for research' could serve as a basis for developing a strategy to use the cells for therapy in future. The findings from the analysis of the feasibility and application fields were used to develop the business model.

COMPARISON OF THE DANISH AND GERMAN HEALTH AND REIMBURSEMENT SYSTEMS

GOAL

The goal of this activity was to give an overview of the Danish and German health and reimbursement systems with stem cell thematic relevance. Furthermore, the goal was to investigate the legal, ethical, social, infrastructural and financial conditions, which currently prevail in the programme region.

RESULTS

Discussions with experts such as clinicians, researchers and operators of stem cell banks were used in this activity, and the relevant literature and information material was evaluated and compiled. On the one hand, the information on the existing applications of stem cells, and on the other hand, the associated conditions, together provide a solid basis for the elaboration of the business plan for the recovery and organisation model of a German-Danish stem cell biobank.

An overview, including a comparison of the health and reimbursement systems with relevance for stem cell recovery in the form of a status quo report, was published as a public dossier to compare the reimbursement systems.

Comparing the framework conditions within the project region, our findings show considerable differences between German and Danish healthcare systems. These are not to be disregarded in the implementation of the BONEBANK project. Germany has over 200 health insurance companies. In contrast, Denmark has only one, and the Danish hospitals are also centrally monitored and managed. Furthermore, the high use of Information and Communication Technology (ICT) in Denmark allows easier monitoring of processes. On the one hand, these framework conditions mean, that BONEBANK will have to include many different entities in negotiations regarding reimbursement. On the other hand, they imply that there is no one concept that can cater to the entire project region. Rather than that, strategies will have to be fine-tuned to the specific conditions of the two countries.

Regarding the cell therapy and innovation landscape within the project region, our assessment reveals that a lot of fundamental and clinical stem cell research is being done in the two countries. The research focus is on areas such as differentiation or regulatory mechanisms, which are linked to specific diseases. The group of Professor Moustapha Kassem (Research Unit for the Department of Endocrinology (KMEB) in Odense) was established in 2001, and is also a partner within the BONEBANK project. The group primarily conducts fundamental and clinical research into mesenchymal stem cells (MSCs), with a focus on MSC differentiation into osteoblasts and bone formation.

Innovative and new therapies can be more cost-intensive than conventional therapies and drugs. It is even more expensive to produce stem cells for allogeneic therapy than for autologous therapy. Moreover, logistics are challenging, as products available on the market have a life-time ranging between 24 and 40 hours. Technical innovation (e.g. stem cell reactors), growing markets and increasing competition will likely decrease costs in the future, and full regulatory oversight will also increase the pressure on companies to reduce costs.

CONCLUSIONS & OUTLOOK

The findings show that development of stem cell products with high market share which replace conventional therapies are in need for the future – current therapeutic effectiveness is often still low or not completely proven, and costs for production are high. However, the BONEBANK project and its future activities will follow the aim of supporting and achieving efficiency of therapeutic usage of these cells.

We consequently see a strong need to provide more public information on stem cell therapy, especially regarding reimbursement. Stem cell therapy offers excellent potential for better bone healing, and reducing costs for patients and the entire healthcare system. With the BONEBANK project and further activities, we will be able to raise awareness for the potential of MSCs for research purposes and therapeutic use to further improve healthcare including reimbursement changes in the future.

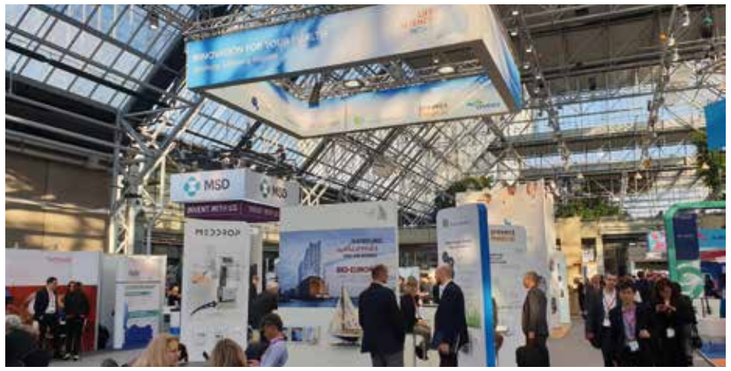
BUSINESS PLAN

GOAL

The goal was to develop a business plan and an organisation model for mesenchymal stem cells isolated from harvested material during routine surgery. The business plan had to be flexible – therefore, fundamental research and input from project partners served as an essential source, and a basis for developing a common structure.
The needs and requirement analysis and the assessment of the feasibility served as theoretical background as well. Within the business plan and the organisational structure, theoretical options and possibilities for future business were to be presented.

RESULTS

Based on insights and findings from clinicians and researchers within the consortium, it became clear that the business plan was not going to focus on therapeutic aspects of using mesenchymal stem cells (MSCs) isolated from bone material during the project lifetime. However, the successful development of a possibility to isolate cells from material which would be wasted otherwise under current conditions, holds various business opportunities.
Within the business plan, potential stem cell products have been highlighted, considering the current conditions. These include nearly uncharacterised cells for research purposes, and the possibility of offering characterised cells "on demand". The results of researchers and clinicians, in addition to consultations with external companies



Representing the BONEBANK project at the BIO-Europe

and experts of the stem cell community, have shown that individual cells are of high interest for research. Moreover, as discussed in the literature, the use of exosomes could potentially be a strategy for the product portfolio, as exosomes from stem cells might also have a strong impact on novel therapy regimes.
These results served as a basis for the BONEBANK marketing strategy. The cluster agency Life Science Nord Management GmbH took charge of these marketing activities during national and international conferences. The business plan has been discussed with regional finance organisations. Moreover, possible products, a marketing strategy and the organisational model have been intensively discussed with the BONEBANK advisory board at the Executive Committee of ScanBalt, and during the Life Science Baltics conference. More than 19 meetings with 14 nations took place to discuss the strategy and portfolio, at the Bio-Europe fair in Copenhagen in September 2018.

CONCLUSIONS & OUTLOOK

The project's products, the concept and the organisational model, based on research findings, have met with great approval from external clinicians and companies. The business model will serve as a first step towards setting up an organisational structure, and will lay the groundwork for business discussions and marketing events.
The unique selling point of the BONEBANK is that human biological material is collected during mandatory routine surgeries. Usually, this material is discarded. Since the field of stem cell therapy is growing steadily, there will probably be a higher demand for MSCs in the future.

PROJECT FACTS

Duration: Sep. 2015 - Feb. 2019
Total budget: 2.4 million Euro, thereof 1.34 million Euro funding
Partners: 5 project partners, 2 network partners

BONEBANK extension phase:
Duration: Mar. 2019 - Aug. 2020
Total budget: 1.5 million Euro, thereof 870.000 Euro funding
Partners: 7 project partners, 3 network partners

Project management: DSN Connecting Knowledge, Kiel

More information: www.bonebank.eu

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THE PROJECT PARTNERS

The lead partner of the consortium is the **University Medical Center Schleswig-Holstein (UKSH).** The Clinic for Orthopaedics of the UKSH, Campus Lübeck, focus on injuries and disorders of the entire musculoskeletal system and has a large laboratory for biomechanics, biomechatronics, biomechatronics and sports medicine diagnostics as well as an established area for clinical studies. Further partners at UKSH are the Section for Transnational Surgical Oncology & Biobanking, Department of Surgery and the Interdisciplinary Center for Biobanking-Lübeck (ICB-L).

The **Odense University Hospital (OUH)** is a university hospital affiliated to the University of Syddansk and the largest clinic in Southern Denmark. The research group around Professor Moustapha Kassem is world-renowned for its studies on stem cell biology as relevant to applications within regenerative medicine and cell-based therapies.

Life Science Nord Management GmbH is a cluster management agency in Northern Germany. It brings together economy, research and politics in the north, activating expert knowledge from universities and research institutions as well as their close contacts with companies.

soventec GmbH is a Schleswig-Holstein-based company that offers software solutions and development services for industry, medicine and the life sciences. soventec has developed its own standard biobank and process documentation solution Lab OS®.

The **Stryker Trauma GmbH** is one of the world market leaders in bone fracture treatment. The company provides amongst others surgeons with state-of-the-art machines, accessories and other theatre equipment with high-quality components and maximum quality.

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