

Aktivitetsplan 5 - Application for Strategic collaboration on joint development and implementation of service offerings between Bioneer A/S and Fraunhofer Institute for Biomedical Engineering

(Særskilt bevilling om Strategisk satsning på internationalt GTS-samarbejde)

1 Summary

The life science industry, including biotech, pharma and ingredients companies, is constantly seeking new strategies for optimising early steps in their development to reduce costs and improve their products. Such strategies often require specific know-how and facilities that the companies are unable to establish by in-house resources. The strategic collaboration between Bioneer A/S and Fraunhofer Institute for Biomedical Engineering will implement solutions covering needs for automated processing of living cells by jointly offering novel services to the life science industry. The joint service offerings addresses critical elements in early product development and are not currently offered in Denmark or Germany. The strategic collaboration will make automated living cell cryopreservation services and automated cell based screening services accessible to Danish companies, through jointly implementation and dissemination activities.

2 Needs of Danish companies

Bioneer has identified two major emerging unmet needs in the Danish life science industry, which is the main focus of this Strategic collaboration between Bioneer and Fraunhofer Institute for Biomedical Engineering (IBMT), Germany, regarding joint implementation of services. These needs are not yet addressed by any service provider in Denmark.

- Need for scalable and controlled storage of cellular samples

The Danish life science industry comprising approximately 100 pharmaceutical and biotechnological companies are using mammalian cells and microorganisms at a large scale in a highly diverse range of applications ranging from production of food ingredients, over industrial bioconversion processes and manufacturing of medical drugs to the use of mammalian cell lines for disease modelling, toxicity testing, and drug screening operations. Furthermore, a limited number of companies are developing therapies based upon human cells as novel, innovative treatment modalities in severe chronic diseases. The number of comparable companies in Germany is estimated to be at least five times more. Thus, live cellular materials represent a highly valuable biological resource making the storage and preservation of such biological materials critical to these companies.

Since mammalian cells and microorganisms represent increasingly valuable assets in production processes, screening procedures, therapy or re-documentation for regulatory bodies, the industry including smaller companies, and hospitals will need access to infrastructure and knowhow regarding banking, storage, and tracking of the growing number of such biological assets. Thus, major technical demands comprise

- improved technological solutions and methods for cryopreservation in order to preserve the biological quality and functionality of living material,
- access to scalable automation of cell banking processes,
- robust automated cell sample registration systems, and
- access to permanent or transient storage capacity e.g. in order to have duplicates of valuable cell banks.

- Needs for improved, scalable and automated laboratory test systems in early pharmaceutical development processes

Drug development costs have increased in recent years without delivering a correspondingly increased amount of marketed drugs. Therefore, it is a key strategy for the pharmaceutical industry to radically improve the earliest steps in the drug development chain by exploring novel types of

early decision tools by which companies can identify the candidate compounds with the highest probability of reaching the market and, conversely, terminate development of compounds with a low probability.

The early steps in drug development including the initial drug target analysis as well as early toxicological studies rely in part on laboratory-scale test systems based on various cell types. As the understanding of complex cellular interactions have been extensively improved alongside with recent developments in technical systems, new concepts of laboratory scale test systems are emerging. For example, liver cells (hepatocytes), which are central to general toxicity evaluation of pharmaceutical drug candidate compounds are usually used in a standard one cell-layer (2D) format. However, novel research has shown that hepatocytes growing in 3D-structures resemble their native counterparts better in terms of expression of key enzymes that increases their value in liver toxicity analysis considerably. We foresee that Danish pharmaceutical and biotech companies, and many foreign companies, will need access to such complex cultivation systems or knowhow regarding the building of such models systems expected to become the future industry standard. However, most companies, and in particular small and medium-sized companies, may not have the capacity to develop such cell-based systems nor the ability to scale such systems to the industrially relevant screening volumes. Major needs comprise access to:

- well-defined 3D tissue-like models, i.e. mm-sized organoids (e.g. of liver structures for toxicity)
- quality assessment of such 3D models prior to
- scaling such 3D models to a volume relevant for screening, i.e. growing medium to large numbers of organoids
- handling such numbers of organoids including fitting dispensing and analysis to industrial standard equipment
- securing high quality and homogeneous data read outs

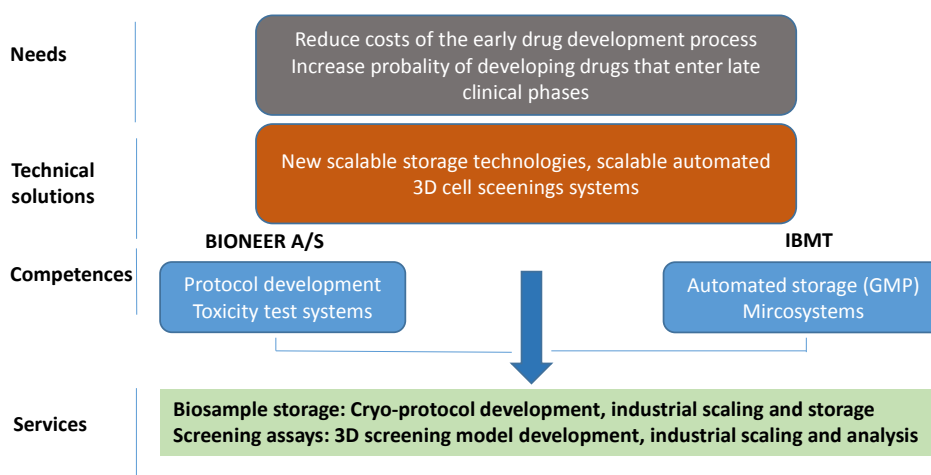


Figure 1. Rationale behind the Bioneer-IBMT collaboration. Bioneer has developed and delivered services in the area of development of disease and toxicity models based on living cells, including models based on induced pluripotent stem cells (iPS). IBMT is developing and has offered services in the area of cryopreservation technologies and industrial scale storage and assay processes. By offering combined knowhow and infrastructures both parties expect that companies (Danish, German, other countries) by accessing these services can cover a range of needs in industrial screening

3 Description of collaborating partners

Fraunhofer IBMT and Bioneer are both partners in the EBiSC project. EBiSC (European Bank for induced Pluripotent Stem Cells) is an Innovative Medicines Initiative funded project with the aim of banking induced patient-derived stem cells for toxicity tests, drug screening and stratified disease modelling, as the bank includes both healthy and diseased cell lines.

Fraunhofer Institute for Biomedical Engineering (IBMT) is specialized in the field of biomedicine and biotechnology, focusing on applications in medical diagnosis and therapy control, and with a fully automated cell-based production under GCLP regulations. IBMT has expertise and know how in cryotechnology (development of xeno-free cryomedia, sterile vitrification protocols and intelligent cryo-vial systems), bio-banking (operating the Global HIV Cryo repository financed by the Bill & Melinda Gates Foundation), stem cell research (coordinator of the FP7 projects Hyperlab and DropTech, for the establishment of automated embryo toxicity tests; work package leader for automation and cryopreservation within the IMI project EBiSC).

IBMT also offers a 20 years' long experience in the production of biomaterials, such as the high viscosity alginate microcarriers, used both for the expansion of induced stem cells in bioreactors and the encapsulation of therapeutically relevant cells (e.g. the Lagerhands islets for glucose concentration-dependent production of insulin). Pivotal keywords at IBMT are miniaturization, parallelisation and automation, for improved efficiency of the biological workflows under defined conditions.

Bioneer A/S is a biomedical service company fully owned by the Technical University of Denmark. Bioneer is approved as an Advanced Technological provider by The Danish Ministry of Science and Education. Bioneer provides research-based services to Danish and foreign biomedical, biotechnological, medico and ingredients companies. The service portfolio comprises protein manufacturing, pharmaceutical development, biomarker analysis and validation, body simulation tools as well as disease model development and mammalian cell technology including gene editing.

4 Novel Services

The services developed in this collaboration are based on existing capabilities and planned services at both Bioneer and IBMT. The combination of existing competences within 1) preservation and storage of biosamples and 2) development of improved laboratory test systems will result in integrated service offerings currently not offered in Denmark and Germany.

4.1 Biosample storage (cryopreservation)

In the field of biosample storage, IBMT and Bioneer have established core activities in the area of 1) scalable and automated biosample storage at GMP level (IBMT) and 2) small scale storage and protocol development (Bioneer). Services include:

- tailoring of technologies for cryopreservation of living material
- fully automated biobanking with an upscalable capacity to 60.000 samples that relies on cutting-edge technology and redundancy for maximum safety automation of registration systems, integrating chip and RFID labelling
- building logistics for permanent or transient storage capacity

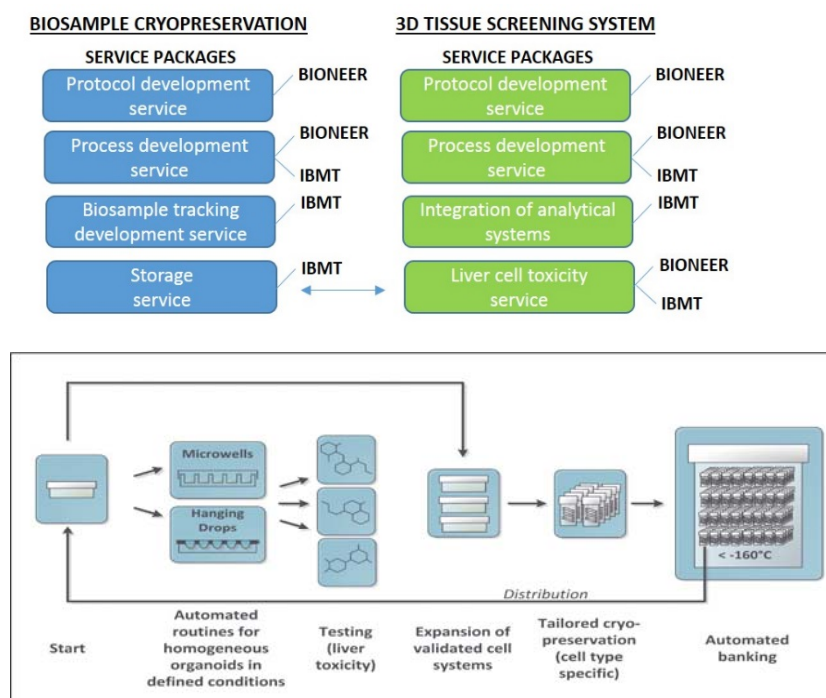


Figure 2: A) Bioneer/IBMT joint service program, B) Joint service program flow covering both Biosample Storage and 3D Tissue Screening Systems.

4.2 3D tissue screening systems

In the field of optimized laboratory test systems IBMT and Bioneer have established core activities in the area of 1) Automated microsystems for cellular test systems, 2) test systems for toxicity, especially liver toxicity. Services include:

- knowhow on and development of customized 3D organoid assays using microfluidic technology and robotic technologies for generating micro tissues for early product development
- quality assessment and validation of such assays, securing high quality data read outs
- knowhow on and scaling of organoid assays to fit industrial needs
- micro tissue system for liver toxicity testing

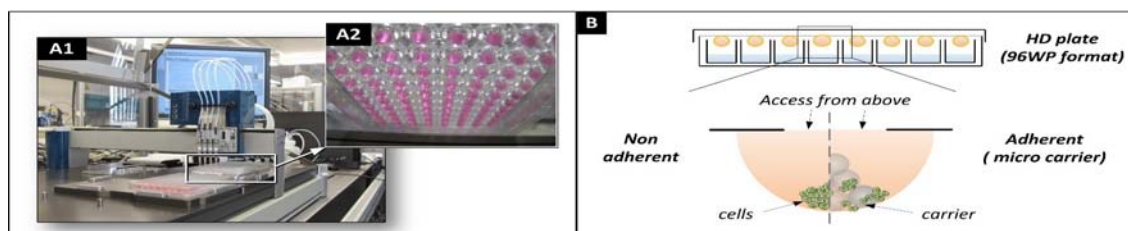


Figure 3. Four-channel pipet robot capable of running automated cell culture routines like the handling of cells in hanging drops (A1). View from below of a hanging drop plate (HD plate) operated by a pipet robot (A2). Schematic of a hanging drop system for culturing cells either as adherent (left) or non-adherent (right) (B).

5 Effects of service offerings to Danish companies and German companies

Bioneer and IBMT will strive to handle the service offerings in the context of “a one stop shop” where companies experience that services are smoothly handled.

5.1 Biosample storage.

In the field of biosample storage, Bioneer and IBMT have activities in the area of 1) cryo storage protocol development (Bioneer), and 2) industrial scale biosample storage technologies including at GMP level if requested (IBMT). Customers to these services are companies working in the fields of cell banking or cell therapy, companies handling cells for screening and production in their

research and development or production. Furthermore, the services will be critical for hospitals working with cell therapy. The effects for customers include that they:

- can increase the quality, functionality, and usability of their biological materials, thus securing reproducibility of long term redundant industrial processes such as screening and biomanufacturing.
- can build logistics for permanent or transient storage capacity
- have easy access to securely stored biomaterial.
- have the option of accurate traceability of biosamples through integrated software platforms

5.1 Laboratory test systems

In the field of optimized scalable laboratory test systems IBMT and Bioneer have established core activities in the area of 1) Microsystems for miniaturized scalable cellular tests, 2) Test systems for toxicity, especially liver toxicity. The service offerings will make it possible for companies to develop novel laboratory test systems for early pharmaceutical development.

- These systems will be based on the combined IBMT-Bioneer competences in making customized micro tissue constructs (organoids) and further establish automated scalable production and cryopreservation of such complex biological systems.
- A specific service offering will be focused on scalable micro assay systems for improved liver toxicity analysis. IBMT-Bioneer will in the field of liver toxicity offer companies liver micro systems for their internal use or as a complete toxicity service. This is an important opportunity for especially the pharmaceutical industry where improved test systems are essential for a more efficient and cost-effective development.

Customers to these services are companies with drug development activities; either small SMEs with limited research and development resources or large pharmaceutical companies without in-house expertise in developing and up-scaling 3D micro tissue test systems or ordinary test systems. The effects of these services for especially Danish SME customers include that they:

- can build or access novel and more *in vivo* like assay systems thus providing a better foundation for decisions on selecting good candidate compounds.
- can get their assays scaled to fit the planned screening programs
- have access to store and preserve microtissues (organoids) for other rounds of screening

6 Accessibility of services

The collaborative project is designed to make the new services available to the Danish life science industry and to document this through relevant demonstrator projects. The collaboration project will implement logistic processes, work flows and communication channels between Bioneer and IBMT to secure Danish customers access to fast and efficient services in the fields of biosample storage and 3D tissue screening systems. The goal is to secure a transparent, fast and consistent entry process for Danish life science companies as well as an effective feedback to their specific requests. Bioneer and IBMT will ensure this by completing demonstrator projects for each of the new service offering as outlined later and by developing a joint web-based portal that allow companies to quickly access the combined service offerings.

7 Strategic implication of the collaboration for the parties

The collaboration fits the intention of Bioneer to cover an increasing range of services in the preclinical part of the drug development chain. A partnership with IBMT secures that Bioneer has access to a technology provider who is an expert in industrial scale operations regarding cryopreservation and cellular screening operations. It would be impossible for Bioneer to build the infrastructures and develop the technology competences similar to those available at IBMT. Thus, it

is much more cost-effective for Danish companies and the Danish society that Bioneer offers Danish companies, hospitals, and research institutions access to the facilities and competencies through a partnership with IBMT. On the other hand, IBMT will also gain value from Bioneer's knowhow on disease models and stem cell-based technologies as well as Bioneer's ability to build complex cell models and assay systems. Thus, IBMT will be able to offer German companies access to Bioneer's capabilities in this and related areas. Furthermore, it may well be that other complementary service possibilities in fields outside the suggested project will emerge when the partnership is running.

7.1 Formal aspects regarding collaboration

The attached “Letter of Intent” between Bioneer and IBMT will form the basis for a complete Collaboration Agreement describing the terms and obligations for both Bioneer and IBMT in the development and implementation of the joint service offerings described in this project proposal.

7.2 Access to facilities

During the project employees of Bioneer and IBMT will have access the individual facilities of the parties as an integral part of the project.

7.3 Sharing of competences

Bioneer and IBMT will share competences related to the fields of the joint service offerings during and after the project. Sharing of competences will be a key element as implementation of the service offerings depends upon knowhow contributed by both parties. As the fields of both biosample storage and improved test systems are constantly evolving, a continual close interaction between Bioneer and IBMT will be required. Competences related to understanding customer needs and market information will similarly be essential for the joint service offerings. The sharing of competences technologically and business wise, respectively are ensured by:

1. Technology-focused service-specific meetings (3-4 times per year) between relevant personnel representing Bioneer and IBMT.
2. Establishment of a virtual data-sharing platform that captures data and emerging technologies relevant for the service offerings.
3. Business-focused meetings (2 times per year) between relevant personnel representing Bioneer and IBMT.

7.4 International service offering aspects

Bioneer and IBMT anticipate that their combined and/or individual service offerings in the field may be appealing to companies in other countries than Denmark and Germany. When the first services are near to maturation and ready for the Danish and German markets, respectively the parties will disseminate these services through a range of selected marketing channels. Based on the success of the service programs in the market IBMT and Bioneer may choose to disseminate elements of or the full the service programs in other selected European countries as well.

8 Central activities

Work package 1 - DEMONSTRATION of joint cryopreservation service offering.

Prior to offering combined services IBMT and Bioneer will jointly identify two different industrial relevant cell types/organoids that will serve as *demonstrator cases* for the cryopreservation part.

The following steps will be part of the demonstration project;

1. Cell production for storage protocol development (Bioneer)
2. Set-up of logistical steps including registration systems for transferring cells and associated data from Bioneer to IBMT.
3. Establishment of quality control systems at Bioneer and IBMT
4. Software integration into biosample transfer

D1: The deliverable from this WP will be a defined process and logistical set-up offering customers both small scale storage development and automated, large scale storage of biosamples.

Work package 2 - DEMONSTRATION of joint micro tissue system development service offering

In this work package biological evaluation of novel micro tissue organoid technologies will be performed, followed by transfer of identified micro tissue technology for scale up and automation. As demonstrator case, neuronal organoids developed and created in another Bioneer performance contract 2016 - 2018 activity will be used (Activity 4: Patient specific models in drug development, sub activity 4.3 Maturation of neurodegenerative models).

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The following steps will be part of the demonstration project;

1. Test of different technologies for micro tissue fabrication, generation of data to validate the performance of neuronal micro tissue and generation of handling protocols (Bioneer)
2. Tech transfer from Bioneer to IBMT (IBMT/Bioneer)
3. Scaled micro tissue manufacturing to small, medium and large quantities (IBMT)
4. Parallel micro tissue handling/dispensing setup for large screening experiments (IBMT)
5. Validation of micro tissue performance relative to scale of screening experiments, i.e. can the same qualitative data be generated irrespective of scale of experiments (IBMT/Bioneer)

D2: The deliverable from this WP will be optimized technologies for development and production of micro tissue test systems in general, as demonstrated by creating functional neuronal micro tissues.

Work package 3 - DEVELOPMENT of liver cell culture set-up in micro tissue system format

This work package is specifically focused on liver-specific micro tissue systems. The collaborators will develop specific systems by combining tools and knowhow already present at Bioneer and IBMT. This will also include implementation of liver specific analytical methods into micro tissue systems. The analytical methods are already implemented at Bioneer and the task of this work package will be focused on integrating the methods present at both parties into the jointly developed liver culture set-up. The following steps will be part of the joint development;

1. Selection of optimal fabrication technology for liver cells (Bioneer/IBMT)
2. Experimental set-ups to follow liver tissue development in micro tissue system (Bioneer/IBMT)
3. Integration of liver specific functional analysis, e.g. CYP enzymatic activity analysis, (Bioneer/IBMT)
4. Implementation of high-through put read out from liver micro tissue systems (IBMT).

D3: The deliverable from this work package will be a specific micro tissue system for testing pharmaceutical compounds for liver cell toxicity.

Work Package 4 (DEMONSTRATION of liver micro tissue system for toxicity)

The following steps will be part of the joint demonstration;

1. Translation of laborious manual routines to automated procedures using microfluidic and robotic platforms in small scale bioreactors (Bioneer/IBMT).
2. Tech-transfer from Bioneer to IBMT (Bioneer/IBMT).
3. Demonstrator process including small scale test with reference compounds and further scale-up to automated systems (Bioneer/IBMT).

D4: the deliverable from this WP is completion of a full demonstrator process demonstrating the proper functionality and proper work processes between Bioneer and IBMT. Furthermore the official launch of the joint liver micro tissue service offering on the public web-portal.

Work Package 5 (DISSIMINATION of joint service offerings)

This work package covers dissemination activities as outlined below. The work package ensures that Bioneer and IBMT complete a series of dissemination activities together;

1. One joint workshop in Denmark with participation of relevant companies and institutions. Agenda: The strategical partnership and planned joint services.
2. General biosample storage service offering presented to at least 20 companies in Denmark and at least 30 companies in Germany through B:B meetings.
3. Micro tissue system service offering presented for at least 20 companies in Denmark and at least 20 companies in Germany.
4. Liver micro tissue system presented for 40 companies in Denmark and 50 companies in Germany.
5. Public web-portal fully implemented at both Bioneer and IBMT.

D5: The overall deliverable from the dissemination work package is a fully implemented service offering portfolio at Bioneer and IBMT, that have been presented at both B:B meetings and through several jointly organized workshops, ensuring the awareness of the relevant customer segments.

	2016		2017		2018	
	Q1-Q2	Q3-Q4	Q1-Q2	Q3-Q4	Q1-Q2	Q3-Q4
WP 1: DEMONSTRATION of joint cryopreservation service offering		D1				
WP 2: DEMONSTRATION of joint micro tissue system development service offering			D2			
WP 3: DEVELOPMENT of liver cell culture set-up in micro tissue system format					D3	
WP 4: DEMONSTRATION of liver micro tissue system for toxicity						D4
WP 5: DISSIMINATION of joint service offerings						D5

Figure 4: Gantt chart illustrating WPs and key deliverables for the whole project period. The dissemination WP will be active throughout the whole period – see below.

9 Dissemination of research activities

Bioneer and IBMT expect to complete several meetings and workshops in Denmark where the new opportunities are presented to Danish companies. Workshops focusing on the jointly performed activities related to building the services will be arranged during the entire project period to capture specific needs and establish awareness of the strategic collaboration. Bioneer and IBMT expect to publish research activities, both in general life science magazines, in scientific journals and through presentations at scientific conferences. Furthermore, Bioneer and IBMT will use the EBiSC project as a channel to communicate research activities to a broader group of companies and research groups in both Denmark and the EU.

10 Dissemination of services

Bioneer and IBMT will establish an easily accessible web-portal containing basic information on the collaboration and use this portal to inform potential customers on the joint services that will be accessible during and after the project period. The launch of the services will be performed by Bioneer and IBMT by exploiting channels such as newsletters, webpages, B:B meetings, confined technical conferences or business conferences. Additionally, Bioneer will regularly contact all potential Danish customers to the services.

In addition, workshops during 2017 and 2018 in both Germany and Denmark will specifically inform Danish and German companies on the jointly established service offerings.

11 Milestones

Milestones 2016	M1.1: Joint information system and logistics have been set up between IBMT and Bioneer, including public web-portal (Competence) M1.2: Biosample transfer and process transfer between IBMT and Bioneer demonstrated. (Competence) M1.3: QC analysis panel identified and demonstrated (Competence) M2.1: At least 3 different micro tissue fabrication technologies tested (Service) M5.1: One workshop in Denmark completed with participation from relevant companies and institutions. (Knowledge dissemination)
Milestones 2017	M2.2: Micro tissue fabrication technologies tested and implemented at both Bioneer and IBMT. M3.1: Fabrication methods for liver micro tissue system identified (Service) M4.1: Manual procedures of cultivation to be automated identified (Competence) M5.2: General biosample storage service offering presented to 20 companies in Denmark and 30 companies in Germany. (Knowledge dissemination) M5.3: Micro tissue system service offering presented for 20 companies in Denmark and 20 companies in Germany. (Knowledge dissemination)
Milestones 2018	M3.2: Implementation of at least two high-through put analytical systems into the liver micro tissue system. (Service) M4.2: Full demonstration of the liver cell microtissue system completed, including testing with at least three different regulatory approved reference compounds.(Service) M5.4: Liver micro tissue system presented for 40 companies in Denmark and 50 companies in Germany. (Knowledge dissemination) M5.5: Public web-portal fully implemented at both Bioneer and IBMT.