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2020 April

Special Topic Edition:

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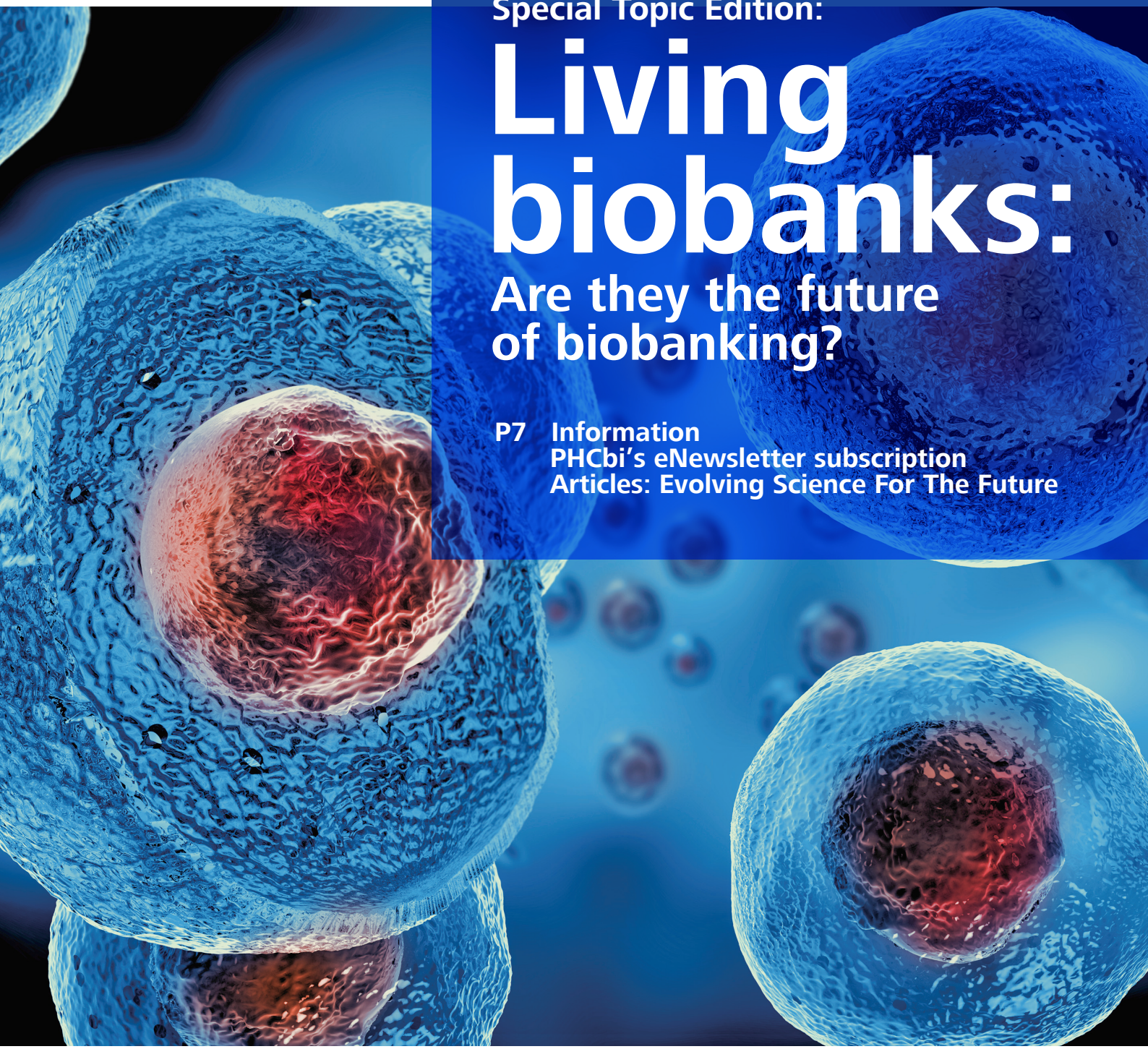
Are they the future of biobanking?



PHC Corporation, Biomedical Division

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Special Report

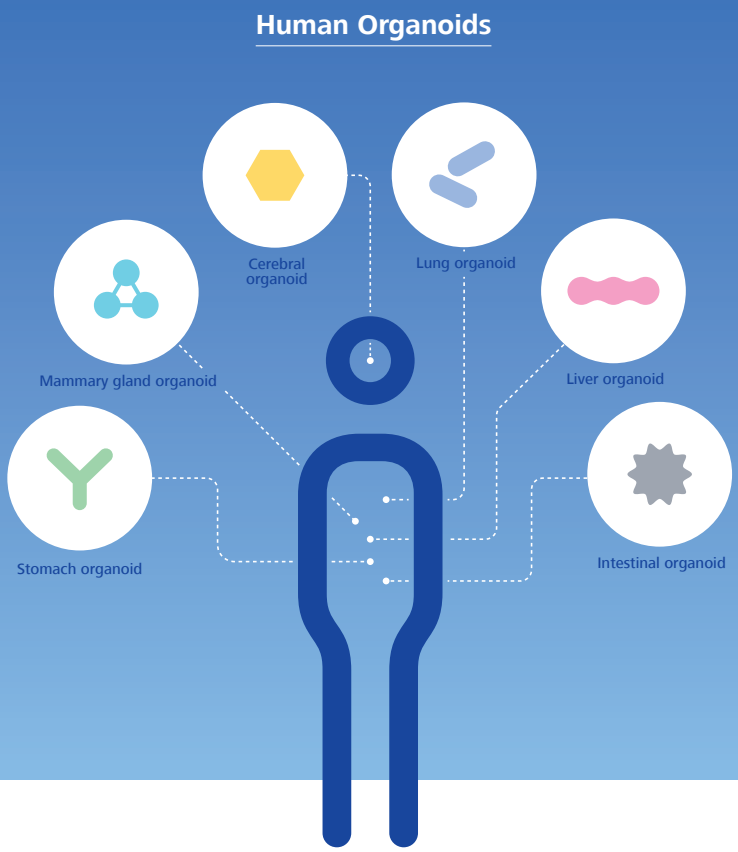
Roshini Beenukumar

Living biobanks: Are they the future of biobanking?

Traditional tissue biobanks containing formalin-fixed paraffin-embedded (FFPE) or fresh frozen tissues are key sources of starting material for translational studies. However, such samples are usually non-viable with limited potential for use in functional studies. This limits their applicability in target discovery and precision medicine.

Living biobanks, an upcoming concept in the biobanking sector, aim to overcome many of the limitations of such traditional biobanks. In contrast to traditional biobanks that store non-viable specimens, living biobanks store viable and functional tissue samples such as patient-derived xenograft models, organoids, conditionally reprogrammed cells or induced pluripotent cells. Living biobanks have the potential to bring precision treatment for multiple diseases from bench to bedside. [1,2]

In the following sections, we explore in detail the concept of living biobanks, case studies describing established living biobanks as well as some of the key applications of this promising biobanking concept.



Patient-derived disease models and living biobanks

A number of recent approaches have enabled the establishment of patient-derived disease models, which form the basis of living biobanks. Here we discuss some of these technologies and examples of biobanks that utilize these technologies from around the world.

Induced pluripotent stem cells (iPSCs):

Human iPSC banks offer researchers an inexhaustible source of both healthy and disease-specific pluripotent stem cells for disease modeling and regenerative medicine.

iPSCs can be generated from multiple cell types – such as fibroblasts from skin biopsies and peripheral blood mononuclear cells (PBMCs) from the blood. The first iPSCs were generated by Dr.Yamanaka and colleagues from mouse fibroblasts using a cocktail of transcription factors – the Yamanaka factors comprising of Oct4, Sox2, Klf4, and c-Myc. Nowadays, PBMCs are the preferred starting material as they can be easily obtained from a small amount of blood. Cellular reprogramming to iPSCs was initially carried out using retrovirus and lentivirus. These days, the Sendai virus, an RNA virus that does not enter the nucleus, is the preferred reprogramming method for many iPSC banks due to its reliability and high efficiency. Most iPSC banks follow certain common characterization methods as per the suggestions laid out by the International Stem Cell Banking Initiative **(Figure 1)**. Besides, iPSC banks follow strict quality assurance protocols to ensure the pluripotency and quality of cells and the quality of banked iPSC vials.[3] Dr. Glyn Stacey of the National Institute for Biological Standards and Control, United Kingdom emphasizes the importance of quality control of iPSCs – "Not all laboratories will have the same level of expertise in cell culture or familiarity with vital quality control procedures. These will be essential to avoid the circulation of iPSC lines that have become contaminated or switched with other cell lines. Such events can lead to fundamental flaws in the published literature and are a waste of precious research resources."[4]

Figure 1: Common characterization methods of iPSC biobanks

California Institute of Regenerative Medicine's (CIRM) iPSC repository – an iPSC cell bank

Jonathan Thomas, Ph.D., J.D., CIRM Chairman

CIRM's The Human Pluripotent Stem Cell (hPSC) Repository is currently the world's largest biobank of high-quality, disease-specific iPSCs for non-profit and for-profit uses.

"The CIRM iPSC bank is proving to be an important resource for researchers, both in academic universities and the biotechnology industry, to study diseases in a dish and identify new treatments for them. The collection draws from samples obtained from thousands of individuals representing many common diseases afflicting Californians and people worldwide. The breadth of individuals that the bank represents and consistency among the cell lines is making live disease modeling feasible across populations in ways not possible before."

Conditionally reprogrammed cells (CRCs):

Conditional reprogramming is a cell culture method capable of rapidly and reversibly converting cells (both normal and tumor) to a 'stem-like', highly proliferative state while maintaining their original karyotypes. Target cells are co-cultured with fibroblast feeder cells in the presence of a Rho kinase inhibitor (Y-27632). The capacity for differentiation can be restored by simply removing these conditions.

Like iPSCs, conditional reprogramming can be applied to create living biobanks. Starting material for CRC generation is obtained from multiple sources including tissue and liquid biopsies and brushed cells. These specimens are then cryopreserved and stored together with the patient's omics and clinical data. Conditional reprogramming technique is applied to these samples to generate inexhaustible cell cultures for living biobanks which can be used for drug discovery, disease modeling, or regenerative medicine. **(Figure 2)** In addition, conditionally reprogrammed cells can be used to generate organoid and patient-derived xenograft biobanks.[1]

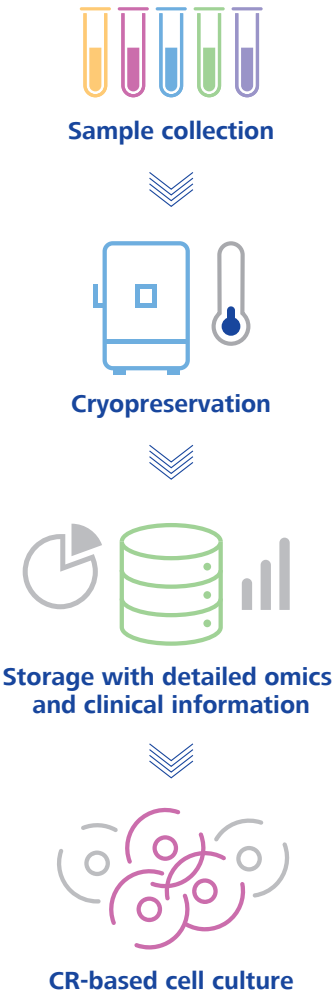
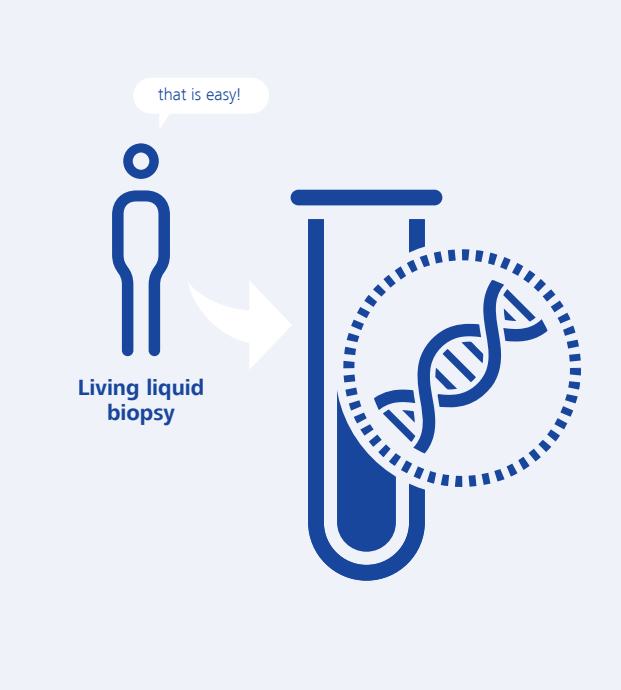


Figure 2: Typical workflow of conditional reprogramming-based living biobanks



Patient-derived bladder cancer model combines ease of liquid biopsy with conditional reprogramming

A personalized noninvasive diagnostic technique for bladder cancer applied conditional reprogramming to urine-derived tumor cells.

"This is the first study to show, using patient samples, that a 'living liquid biopsy' from urine can help determine treatment. This work also suggests that we might be able to grow and test cancer cells for treatment from other 'living biomarkers' found in blood and saliva. We are just at the beginning of this new diagnostic innovation."

"The analysis of the mutation ratio for both patient tissue and corresponding conditional reprogramming cultures confirmed that both single nucleotide variants and DNA insertions and deletions were retained during the culturing. We also identified some mutations not identified in the original tumor biopsies, suggesting that the urine cell cultures better reflect overall tumor diversity than a single biopsy. The conditional reprogramming culture technique may also expand our understanding of how low-frequency mutations help lead to bladder cancer development and progression. Overall, conditional reprogramming cultures may identify new actionable drug targets and help explain why this cancer is so often resistant to treatment." – Xuefeng Liu, MD, Professor of Pathology and Oncology and member of the Center for Cell Reprogramming at Georgetown University and Georgetown Lombardi Comprehensive Cancer Center.[5]

Patient-derived xenograft (PDX) models:

Patient-derived xenograft (PDX) models are established by implanting patient-derived tumors into immunocompromised mice for more precise disease modeling and precision medicine. Unlike traditional cell lines, PDX models better preserve the original characteristics of the primary tumor in terms of histology, transcriptome, and genome.

Establishing biobanks of PDX models is a complex and costly procedure involving multi-disciplinary teams. Patients are selected as per the correct Institutional Review Board (IRB) protocol. Next, samples are collected and examined by surgery and pathology personnel and transported to the research lab in a timely manner. The research labs process and implant the tumor samples in mice or store them for later analysis. Resulting xenograft mice models are molecularly and histologically characterized and maintained by the facility[6].

Organoids:

Organoids are 3D cell culture models derived from primary tissue or pluripotent stem cells that functionally resemble a targeted organ. Unlike traditional 2D cell cultures, organoids are derived from stem cells cultured in a three-dimensional extracellular matrix to reflect the in vivo cellular heterogeneity.[7]

Patient-derived tumor models for next-generation biobanking

A research team at the Department of Pathology and Molecular Pathology at the University Hospital Zurich established a next-generation biobanking platform using patient-derived 3D cell-culture models.

"We are using 3D cell culture to generate pathophysiologically relevant cell models that can be used to study tumor biology and rationally design precision treatment strategies for patients. To do this, we have developed a next-generation comprehensive biobanking platform that includes the generation of patient-derived in vitro cell models alongside the diagnostic workflow at the department of pathology. This is not only done for kidney cancers but also for a variety of other tumor types such a colorectal, pancreatic and lung cancer. As part of our biobanking strategy, we aim to generate 3D cell models that are representative of their respective cancers and can subsequently provide toolkits for many research projects addressing various questions in basic, translational and clinical research." – Dr. Hella Bolck, senior research fellow in the Department of Pathology and Molecular Pathology at the University Hospital Zurich.[8]

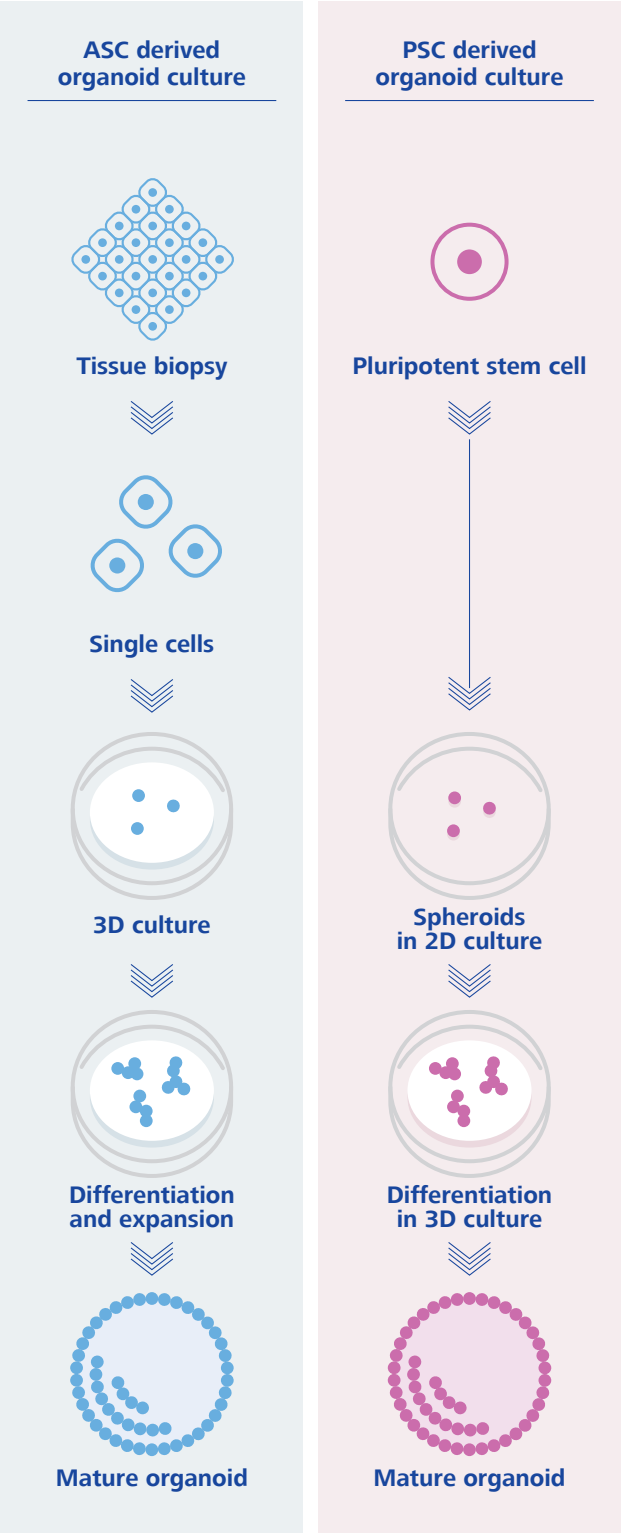


Figure 3: Organoids-derived from adult and pluripotent stem cells. Primary sources of organoids include embryonic or induced pluripotent stem cells (iPSC) or adult stem cells (ASC's) retrieved from organs. In the case of PSC organoids, 2D cell cultures of stem cells are grown into spheroids before 3D culturing and differentiation into the tissue type or organoid. ASCs are derived from organs and converted to cell suspensions and then embedded in an extracellular matrix containing tissue-specific growth factors. Due to the intrinsic capacity of stem cells for self-renewal and differentiation, organoids can be cryopreserved as biobanks and expanded indefinitely. Organoids derived from tumor tissue biopsies are powerful tools for disease modeling and precision medicine.[7]

Living biobanks – applications in precision medicine, regenerative medicine, and drug discovery

Living biobanks for precision oncology:

Cancer is a disease notorious for its heterogeneity. A therapy highly successful in some patients may not work in others with a similar disease. Current pre-clinical targets are identified and anti-cancer drugs are screened in immortalized cell lines, which does not allow precision medicine for the multitude of cancer types and subtypes, resulting in low treatment response rates.

Current precision oncology approaches provide tailored treatment based on the patient's genetic profile. Living biobanks with patient-derived models of cancer (PDMCs) such as PDXs, CRCs, organoids, and iPSCs take this approach one step further. These approaches enable High-throughput drug-screening to identify the right drug or treatment strategy for heterogeneous cancers.[1]

Living biobanks for regenerative medicine:

Current advances in organoid technology such as the discovery of factors that help differentiate pluripotent stem cells to any mammalian cell type and the development for functional 3D organoids of the intestinal epithelium offers great promise in its use in regenerative medicine. Large patient-derived iPSC, CRC, and organoid biobanks could solve many of the current challenges in regenerative medicine.[1]

Establishment of a living biobank for precision oncology

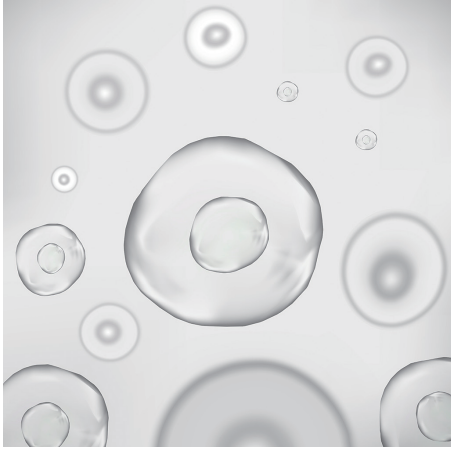
56 in vitro tumor organoids

19 in vivo xenografts

Pauli, C. et. al in the journal Cancer Discovery describes the establishment for a living biobank to aid precision oncology. "Over a period of two years, we established 56 in vitro tumor organoids and 19 in vivo xenografts from 18 different solid tumor types. Tumor morphology and molecular profiles show good concordance between the in vitro and in vivo models compared to their native tumor. High-throughput drug screening (up to 160 drugs) has been tested on eight tumor organoid lines. Seven of them underwent an additional combination drug screen. We nominated several targeted small molecules and novel combinations that have been validated in corresponding xenograft models. This precision medicine approach outlines the integration of genomic data with drug screening from personalized preclinical cancer models to guide precision cancer care. It also fuels next-generation research and has been implemented for clinical trial development."[9]

Conditional reprogramming for airway reconstruction and lung transplantation

Conditionally reprogrammed cells have the unique ability to differentiate when CR conditions are removed and differentiation conditions are applied. Several studies explored the use of conditional reprogramming-based regenerative medicine for respiratory conditions. Esophageal epithelial cells were isolated and expanded from eosinophilic esophagitis patient biopsies for potential use in the regeneration of the esophagus. A 3D tracheosphere culture scaffold, which was biocompatible when engrafted into decellularized rabbit trachea, was made from CR airway cells and lung fibroblasts.[10]



Living biobanks for drug discovery:

Most current drug discovery protocols use immortalized cell lines which often fail to reproduce the tumor environment. Novel cell culture and organoid models are more pathophysiologically relevant than traditional cell culture models to study tumor biology and develop precision treatment strategies. Next-generation living biobanks such as tumor organoid or iPSC banks take this precision medicine initiative to the next level as they often contain comprehensive information regarding the banked samples such as clinical, genomic, and transcriptomic information.[1]

PreCanMed – an EU-funded project for personalized cancer medicine

PreCanMed is a strategic project funded by the European Union which uses patient-derived organoid technology for targeted drug development for cancer patients.

'PreCanMed' project partners implemented protocols for i) the generation and cryo-conservation of 3D tumor-organoid models from primary tumor tissues ii) the genomics analysis of these models for the identification of genetically driven tumor dependencies and vulnerabilities, iii) the testing of the efficacy of different therapeutic approaches on tumor organoids. Along with this, they generated shared resources of biological material and data for precision cancer medicine.

One of the goals of the project is the creation of a tumor organoid living biobank. The biobank collects all relevant clinical information as well as genomic and gene expression data of the patient-derived organoids.[11]

"The biobank that we are going to create will represent a unique, invaluable resource for cancer research and for the development of precision anti-cancer treatments, not only for the Italian and Austrian partners of the project. Just because of its importance, and aiming at extending the future outreach of our efforts, the biobank will be made accessible, under collaborative agreements with PreCanMed, to other regional, national and international researchers" Stefan Schoeftner, Project coordinator and researcher at the Italian Consorzio Interuniversitario per le Biotecnologie – Laboratorio Nazionale in Trieste, the Lead Partner of PreCanMed.[12]

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