WHITEPAPER

# Trends in Precision Medicine: Cancer

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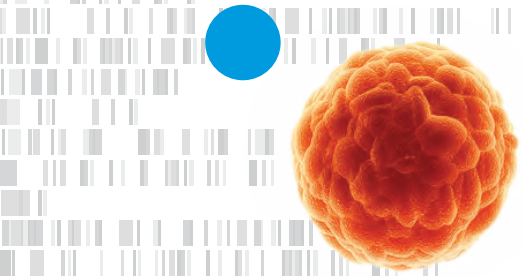
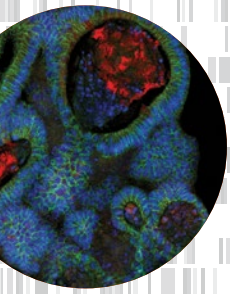
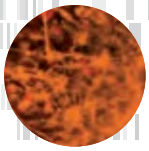






Precision medicine uses information about an individual's genes, proteins, and environment to prevent, diagnose, and treat diseases, including cancer. The first iteration of the human genome project was completed in 2001 and was quickly followed by the integration of transcriptomics and proteomics into biomedical research. Differences in DNA, RNA, and protein can be identified in individual tissue samples, and even in individual cells. The massive data sets generated from this research have driven advances in data science and are used to inform additional studies and clinical practice. Standard treatment for some cancers now include genotyping or molecular imaging in living patients.

Basic research and clinical studies have revealed the constant genetic changes that occur within tumors as they respond to changes in their environment. Until recently, there was no convenient way to analyze the behavior of living cells within 3D printed organs under different conditions, which is essential to fully understanding disease progression and developing effective therapeutics. For decades, biomedical research has relied heavily on immortalized cancer cell lines, which grow as 2D monolayers that lack tissue architecture and complexity. Genetically engineered mouse models and patient-derived tumor xenografts are more clinically relevant, but they take at least six months to develop and are an expensive option.

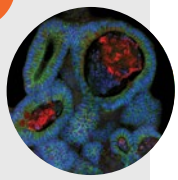
The enormous gap between laboratory research and clinical research has undoubtedly contributed to the failure of many drugs in clinical trials, as well as decisions to remove potential drugs from consideration because of high costs and possible risks. This slows medical progress which can impact lives.

# 3D Cultures: Spheroids and Organoids

Spheroids are simple, multicellular 3D models that form due to the tendency of adherent cells (including many tumor cells) to aggregate under certain cell culture conditions. They offer a more physiologically relevant model compared to 2D cell culture and can be conveniently handled in **spheroid microplates**. Furthermore, patient-derived tumor spheroids can be generated and evaluated for their response to specific treatments within just one to two weeks.[1]

Organoids, or "mini organs," are an extension of stem cell research. Cells are grown in a defined *in vitro* environment, where they form mini-clusters of cells that self-organize and differentiate into functional cell types, recapitulating the structure and function of an organ *in vivo*. Organoids can be produced from embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), adult stem cells (ASCs) from organ epithelia, or cancer stem cells. Organoids can be generated from healthy or pathological tissue, and from cells that have been subjected to gene editing. They're made of stem cells or progenitor cells and self-assemble when given a scaffolding extracellular environment. When that happens, they grow into microscopic versions of parent organs viable for 3D study. Spheroids can't self-assemble or regenerate, and thus aren't as advanced as organoids.

The first 3D organoid culture was reported in 2009.[2] It was derived from a single adult intestinal stem cell and grown in **Corning® Matrigel® matrix**. The technique has since been adapted to generate organoids for liver, pancreas, lung, kidney, thyroid, intestine, prostate, retina, and different regions of the brain. Researchers are working to identify the proper growth conditions for a wide variety of other organ systems.



# Organoids in Cancer Research

Patient-derived tumor organoids (PDTOs) have been used to create cellular models of many different cancer types, including colon, breast, brain, pancreatic, liver, lung, endometrial, prostate, and bladder. Multiple studies have shown that PDTOs can faithfully recapitulate the phenotypic and genomic features of the primary tumors, and their response to pharmaceuticals, chemotherapy, and chemoradiation.

Organoids have been so useful in cancer research that Larson, et al. published a pan-cancer organoid platform for precision medicine in 2021.[3] One goal was to provide a consistent protocol that could be used to generate organoids from many different tumor types and would be easily scalable for high throughput screening. As with many previous studies, the researchers used Corning® Matrigel® matrix. Starting with samples from over 1,000 cancer patients, they created a biobank of organoids for common tumor types. To simplify data analysis, they developed a neural-network-based computer model to analyze microscope images of organoids grown in 384-well microplates. The computer model used artificial intelligence and deep data to predict fluorescence microscopy phenotypes accurately from simple light microscopy. This eliminated the need for expensive fluorescent dyes and decreased the time required for microscopy. The utility and reliability of artificial intelligence will increase as more data become available.

**"Using an organoid approach could provide a quick turn-around for determining a patient's sensitivity to multiple therapeutic options, as well as how that relates to the clinical responses seen in other patients."**

Dr. Benjamin Hopkins, assistant professor at the Icahn School of Medicine at Mount Sinai, New York

By bridging the gap between laboratory research and clinical research, organoids have contributed to cancer research and precision medicine. It's now possible to test a wide variety of potential treatments on a library of patient samples, enabling identification of therapeutic strategies that work well, but only for a fraction of patient samples. Established methods in genomics, transcriptomics, and proteomics can then be used to determine why some patient samples respond well and others don't, so that future beneficiaries can be identified.

Data science can assist in finding relevant differences within huge data sets. Gene editing provides an additional layer of experimental possibilities, for example by producing matched pairs of cancerous and non-cancerous organoids, which can be used to increase treatment specificity and decrease toxicity. Gene editing of patient-derived tumor organoids can also reveal how changes in signaling pathways or tumor suppressors can contribute to tumor progression.

In clinical practice, organoids derived from the tumor of an individual patient can be used to test a variety of different treatments quickly and guide treatment for that patient.

# Tumor Microenvironment

While 3D organoids provide many advantages over 2D cell lines and labor-intensive mouse models, they do not fully mimic the environment of tumors *in vivo*. The tumor microenvironment (TME) in living organisms includes blood vessels, stromal cells, growth factors, metabolites, fibroblasts, endothelial cells, immune cells (including lymphocytes, macrophages, myeloid-derived suppressor cells, dendritic cells, and natural killer cells), and the extracellular matrix (ECM). These factors play a vital role in determining how the tumor behaves, and are potential targets for cancer treatment.

In recent years, monoclonal antibodies that target immune checkpoints (specifically PD-1 and PD-L1) have been used to enhance antitumor T-cell responses and have dramatically increased cancer survival in some patients. As of June 2020, there were 7 FDA-approved checkpoint inhibitors,[4] but approximately 80% of treated patients experienced no benefit. Nonetheless, immunotherapy is a relatively new treatment, and most trial participants have been at advanced stages of disease. A reasonable hypothesis is that introducing immunotherapy earlier in the course of disease may further improve survival.

Another option is adoptive cell therapy (ACT), in which immune cells harvested from the patient's body are expanded *in vitro* and then reinfused into the patient. The immune cells may also be reprogrammed to recognize tumor-specific antigens. The different types of ACT include tumor-infiltrating lymphocyte (TIL) therapy, chimeric antigen receptor (CAR) T-cell therapy, engineered T-cell receptor (TCR) therapy, and natural killer (NK) cell therapy.

A third option is personalized vaccines. As tumors accumulate somatic mutations, they may express new, cancer-specific epitopes. T-cells may identify these new epitopes as foreign bodies, making them ideal vaccine targets. A small number of these cancer-specific epitopes are shared between cancers, which raises the possibility of ready-to-use vaccines for patients who share the same epitope. Alternatively, it should soon be possible to identify cancer-specific epitopes through sequence analysis and produce personalized vaccines on demand.

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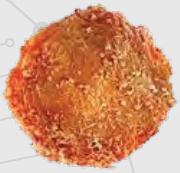
# Organ-on-a-Chip and Body-on-a-Chip

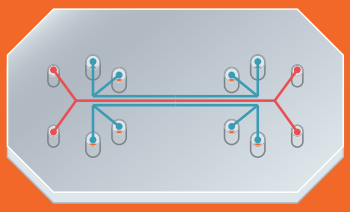
To overcome the limitations of organoid culture, recent studies have combined organoids with microfluidics to model physiological conditions *in vitro* more precisely. This has led to the development of organ-on-a-chip platforms, which allow for the precise control of nutrients, shear stress, and geometry in organoid culture. Furthermore, chambers containing different organoids can be connected by fluid flow, modeling how tissues and organs in the body are connected by a common blood supply. These organoid chambers might be large enough to fit into a 24-well plate, or so small that several chambers can be laser-cut into a piece of acrylic the size of a microscope slide.

Achberger, et al. (2019) detailed the development of a retina-on-a-chip, which included at least seven essential retinal cell types derived from human induced pluripotent stem cells (hiPSCs).[5] The system was able to model physiological interactions between mature photoreceptors and retinal pigment epithelium (RPE), which is essential to retinal function and to understanding retinal diseases. The system used micro flow control technology to provide vasculature-like perfusion.

In 2020, Skardal, et al. reported an integrated multi-organoid body-on-a-chip system connected through a recirculating perfusion system.[6] The system can support seven human organoid types (liver, cardiac, vascular, lung, testis, colon, or brain) for at least 28 days. The system was developed as a more physiologically relevant tool for preclinical drug screening. As an initial test, ten drugs that were recalled by the FDA for adverse effects were tested on heart organoids and liver organoids. The organoids were found to be better than 2D cultures at modeling the clinically observed adverse effects.

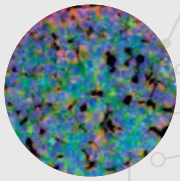
Complications with the liver or heart account for roughly 90% of all drug failures and recalls. Furthermore, the liver is the most important organ in terms of drug metabolism. Skardal, et al. tested their multi-organoid body-on-a-chip system with two drugs that are known to require liver metabolism to be effective: capecitabine (used to treat breast and colorectal cancer) and cyclo-phosphamide (used to treat leukemia and lymphomas). When liver organoids were present in the system, cytotoxicity was observed in the cardiac organoids and lung organoids. When liver organoids were removed, no cytotoxicity was observed.





**"Patient chips provide the additional advantage of multiplexing and can obtain readouts from multiple cell types and organ systems at the same time, from the same stimulus, in the same experiment."**

Dr. Kacey Ronaldson-Bouchard



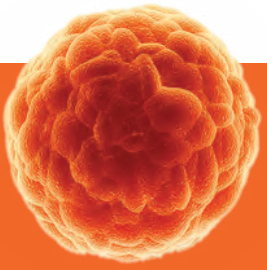

These multi-organoid microfluidic devices were constructed by layering adhesive films with acrylic plates that were laser-cut with chambers, channels, and ports. Organoids were incorporated by immobilization in hydrogels within each chamber. Semi-porous membranes enabled inclusion of vascular and lung modules. Fluid flow was provided by a micro-peristaltic pump and media reservoir.

While there is still a long way to go before a true “body-on-a-chip” is developed, the recently developed technology significantly expands the toolkit for biomedical research and has the potential to greatly improve pre-clinical drug screening.

# 3D Bioprinting

At present, organoids grown in 3D culture are no more than a few cubic millimeters in size. While this may be sufficient for preliminary drug testing and fundamental research in genetics and cell biology, it is six orders of magnitude smaller than a fully functional organ.

**3D bioprinting** is being used to accelerate the process of constructing larger organoids. There is particular interest in incorporating vascular structures and immune cells, which are essential to the tumor microenvironment and how a tumor behaves in response to treatment. Creating organoids of a more realistic size will help, as will achieving a more precise architecture in space. To accomplish these goals, researchers are experimenting with different ways of using bioinks, including hydrogels such as Collagen and Corning® Matrigel® matrix with the **Corning Matribot® bioprinter**, and different ways of applying cells at different stages of differentiation.




# The Future

This is an extraordinarily exciting time to be involved in precision medicine for cancer. But there's still more to be done, including:

- Using existing organoid models to understand cancer progression and treatment better.
- Developing a wider array of organoid types for healthy and diseased states.
- Developing more physiologically relevant organoid systems that include different organ types, as well as blood vessels and immune cells.
- Working to ensure that preclinical models (e.g., organoid biobanks) and clinical trials reflect the diversity of the patient population.
- Working to ensure that all patients receive adequate and early care.
- Developing a better understanding of the tumor microenvironment and how the immune system can be used to defeat cancer.

Luckily, there are many individuals who are determined to discover new and effective ways precision medicine can prevent, diagnose, and treat diseases such as cancer.

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