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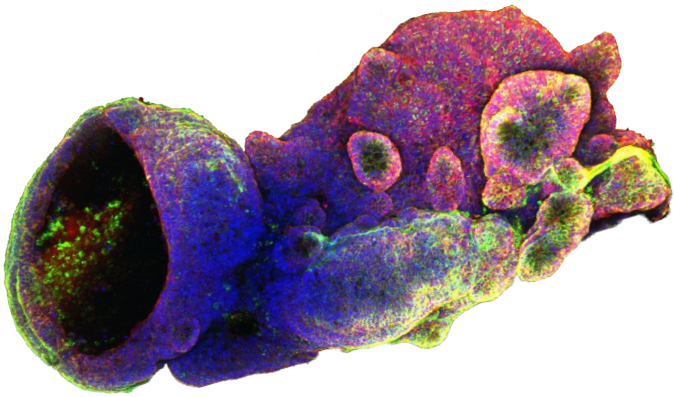
WHITE PAPER

ORGANOIDS: How Close are We to the Clinic?



Prospects for Organoids in Therapeutic Screening and Regenerative Medicine

The world of cell culture has undergone a paradigm shift in recent years, prompting a move away from traditional 2D cell lines in place of more detailed, multicellular 3D models. Rapid advances in cell culture and stem cell technology have given rise to **organoids**: *in vitro* multicellular structures derived from induced pluripotent stem cells (iPSCs) or adult stem cells (AdSCs), which imitate the precise cellular heterogeneity, assembly, and functionality of human organs.

Thanks to the development of human-derived organoids, it is now possible to generate remarkably accurate models of human organs and systems. Since organoids mimic their "real" human counterparts, carrying the same genetic information as their parent cells, organoids grown from patient-derived **stem cells** hold great promise for personalized medicine and therapeutic screening. In cancer treatment for example, patient-derived tumor organoids can be useful predictors of a patient's response to treatment.

Another possibility for organoids in the clinic, is their potential use for **regenerative medicine**. There is a clear and present need for effective alternatives to organ transplantation, which presents myriad complications from donor shortages to graft rejections. Today, researchers are hopeful that organoids could fulfil this need, and that regenerative organoid applications may soon make it into the clinic.

In this article, we will explore current insights into the clinical possibilities posed by organoids, and position the short and long-term prospects for organoids in therapeutic screening and personalized regenerative medicine.

The Extrapolation Problem

Traditional 2D cell lines have become universal in their application, and have been a powerful tool for *in vitro* biomedical research; improving our understanding of cell signaling pathways, drug mechanisms and diseases. In the drug discovery world, cell-based research has become a key first step before testing on animal model systems, and clinical trials in humans thereafter.

While traditional cell-based research has enabled our detailed understanding of human physiology and disease, an ever-present limiting factor has been the challenge of extrapolating results from cellular models to humans. Many important physiological features of the human body, from development to metabolism, simply cannot be accurately recreated with traditional cellular modelling[1], and this creates a significant bottleneck for drug discovery. So much so, that 8 out of 9 drug candidates that enter human trials fail[2].

The advent of 3D human cell culture techniques sparked great promise for overcoming the issues posed by traditional cell models. Organoids are unique among 3D cell culture systems because they are self-organizing, display distinct cellular heterogeneity, and are often histologically indistinguishable from natural human organs[3]. Generated from iPSCs or AdSCs, the natural process of organ development can now be replicated *in vitro*. As such, organoids have huge potential for developmental research, as well as for therapeutic screening and personalized medicine.

The Extrapolation Problem

Oncology Screening for Personalized Therapy

One of the first clinical applications to emerge from organoid technology has been in the screening of therapeutics as a predictor of a patient's response to treatment. In particular, organoid models have been widely implemented for modelling **cancer**[4]: During cancer treatment, various pharmaceuticals for chemotherapy, radiotherapy and immunotherapy, are administered previous to and after surgical removal of the tumor. Since individual patients display vastly different genetic patterns and tumor phenotypes, each patient may respond differently to a given drug.

Due to these vast differences between individuals, it is highly beneficial to test the efficacy and cytotoxicity of oncology drugs in a preclinical personalized model system. Patient-derived tumor organoids have fulfilled this need, demonstrating to be strongly predictive of an individual's response to treatment. Furthermore, patientderived "healthy" organoids provide a platform for drug toxicology testing. Together, the combination of tumorderived and "healthy" organoids creates an accurate and reliable model for tumor-specific treatment responses[1].

The success that organoids have brought to the field of oncology has provided proof of concept for organoids as a ubiquitous screening platform for personalized medicine. This has been built on further with the successful integration of organoids with microfluidic chips. So called **organoid-on-a-chip technology** yields a wealth of precise and relevant data readouts, and can integrate organoids of any type[5]. As personalized medicine continues to grow in popularity, we will surely see such technologies employed more and more for preclinical therapeutic screening.

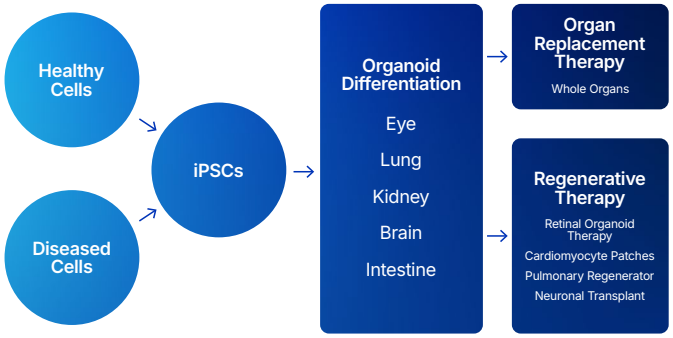
Inherited Diseases: the Kaladeco Success Story

Aside from cancer, the use of organoids for therapeutic screening is also a viable option for inherited diseases. One major success story in this field, has been the use of gut organoids for the screening of cystic fibrosis (CF) therapeutic Kalydeco. Kalydeco is highly effective at combatting CF, however the therapeutic doesn't work for every patient. CF is widely heterogenous, with over 2,000 genetic defects shown to play a role in the disease. If a patient's genetic profile isn't one that has been clinically tested against Kalydeco, the likelihood of success is considered too low to warrant prescription of the drug.

Rather than letting patients go untreated, Netherlands-based geneticist Hans Clevers devised a organoid-based screening platform. Following a rectal biopsy, patient-derived gut organoids could be grown, and used as a platform to test gut responses to Kalydeco. This pioneering work has enabled more CF patients to access the powerful drug Kalydeco, and helped to bring about regulatory change in the Netherlands[6].

Organoid Therapy

Organoids have benefitted researchers with enhanced cellular modelling and have already proved their worth in therapeutic screening applications. However, given their close physiology to human organs, the ultimate goal is to develop clinical applications in the regenerative medicine sphere. There are two main approaches towards this: Organoids are first cultured and differentiated from patient-derived stem cells. Following this, organoids could then be used to replace a failing organ. Instead, a small-scale organoid graft could be transplanted to repair or regenerate a failing organ (Figure 01).



// Figure 01 Map of organoid techniques for organ replacement therapy and regenerative medicine

Organoids for Replacement Therapy

Organ transplantation is an essential therapy for individuals with end-stage organ failure, and while surgical transplantation has progressed tremendously, there remain some unavoidable limitations. Foremost, is the lack of available organ donors versus the vast and growing number on transplantation waiting lists; a shortage that is felt worldwide[7]. Another all-too-common occurrence following transplantation is graft rejection. This occurs when the recipient's immune response attacks the donated organ, leading to is destruction.

Organoids have been put forward as the ultimate solution to this problem: The ability to grow human organoids *in vitro* theoretically represents an unlimited source of organs for transplantation, eliminating the need for donors altogether. Furthermore, if the transplanted organ were to be derived form a patient's own iPSCs, the cultured replacement organ would contain the individual's genetic information and immunologic phenotypes. As such, there would be zero chance of graft rejection.

Organoid transplantation has been evaluated by many studies using rodent models – with intestine, retina, kidney, liver, pancreas, lung, brain and heart organoids having been transplanted. Much of the preclinical evidence supports positive engraftment of organoids after transplantation in animal models, demonstrated by successful integration, maturation, vascularization, and the development of specific target tissue physiological functions[8].

Although a mass of research has reported success from *in vivo* animal models, organoid transplantation research remains very much in its infancy – and the jump to human transplantation is still some time away. The biggest obstacle to overcome here is size: At present, researchers have not found a way to culture organoids of an appropriate size to be suitable for human organ replacement.

Organoids in Regenerative Medicine

With human organoids for replacement therapy still in its early stages of development, researchers have been striving for alternative ways to utilize organoids for organ therapeutics. While organoids are limited by their small size, it is nonetheless possible for organoids to be grafted onto a dysfunctional organ in an attempt to improve its function. In this capacity, organoids have demonstrated high efficacy in a number of therapeutic areas. Some examples include:

- Following success in live animal studies, a group in Japan have developed a iPSC-derived retinal organoid therapy to target retinal ganglion cell diseases. This pioneering work has resulted in the first iPSC therapy to achieve clinical approval[9].
- iPSC-derived cardiomyocyte patches have been in development for transplantation following myocardial infarction, with the aim of restoring heart function. Early human trials show signs of successful grafting and toleration, demonstrated via wall motion recovery and the elimination of major adverse events[10].
- For many lung diseases, such as idiopathic pulmonary fibrosis, the only cure is lung transplantation. To combat this, transplantation of lung organoids (iPSC-derived autologous alveolar epithelial cells) has shown early promise in *ex vivo* models[11].
- Embryonic stem cell (ESC)-derived dopamine neurons have been transplanted into a small number of patients with an aim of providing a cell therapy for Parkinson's disease (PD)[12].

Challenges and Prospects for Organoids in the Clinic

The body of preliminary and proof of concept research is clear: organoids present an exciting opportunity for personalized and regenerative medicine. Before we witness human trials though, there are some fundamental issues yet to overcome:

Organoid size – most cultured organoids are very small (typically <1 mM in diameter) and generating larger structures will be crucial before organoids are suitable for organ replacement. Therefore, most current clinical trials focus on regenerative applications of organoids[7].

Cell maturation – organoid cells must be mature to ensure that the organoids will execute tissue-specific functions after engraftment. In some cases, differentiation protocols have been shown to yield cells more characteristic of fetal cells than adult cells, which might not be suitable for tissue replacement therapies[13].

Vascularization – Organoid vascularization is critical for organoid transplantation, since the absence of vasculature limits organoid growth and factor exchange, reducing nutrient distribution. Using endothelial cells as an organoid component may be an approach to overcome this[14].

Future Prospects for Organoids in the Clinic

Still in its infancy, organoid transplantation for the intestine, retina, kidney, liver, brain, heart, pancreas, and lung appears to be feasible and safe thanks to strong preclinical evidence showing engraftment and biocompatibility. Looking to the future, it is hoped that organoid replacement therapy could provide an alternative to the challenging transplantation of organs with a short period of viability outside the body such as the heart and lungs. Organoids may also become a key tool for regenerative treatments of organs that are at present, technically non-transplantable, such as the brain or spinal cord.

The positive outcomes of initial studies certainly encourage the further exploration of organoids for regenerative or replacement therapy, but there remain several key challenges to address before we see organoids in clinical use. To overcome these challenges, there is a real need for collaboration between stem cell biologists, bioengineers and transplant specialists.

How Close are We to Witnessing Organoid Applications in the Clinic?

In many ways organoids are already providing clinical support via their role in therapeutic screening and disease modelling, especially in oncology. When it comes to replacement/regeneration therapy however, there is work to be done. This creates an exciting opportunity for biomedical and clinical researchers to become pioneers in this emerging and rapidly evolving field of research.

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