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 Check for updates

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Organoids are innovative three-dimensional and self-organizing cell cultures of various lineages that can be used to study diverse tissues and organs. Human organoids have dramatically increased our understanding of developmental and disease biology. They provide a patient-specific model to study known diseases, with advantages over animal models, and can also provide insights into emerging and future health threats related to climate change, zoonotic infections, environmental pollutants or even microgravity during space exploration. Furthermore, organoids show potential for regenerative cell therapies and organ transplantation. Still, several challenges for broad clinical application remain, including inefficiencies in initiation and expansion, increasing model complexity and difficulties with upscaling clinical-grade cultures and developing more organ-specific human tissue microenvironments. To achieve the full potential of organoid technology, interdisciplinary efforts are needed, integrating advances from biology, bioengineering, computational science, ethics and clinical research. In this Review, we showcase pivotal achievements in epithelial organoid research and technologies and provide an outlook for the future of organoids in advancing human health and medicine.

Over the past couple of decades, the establishment of three-dimensional (3D) epithelial organoids has initiated a new era in biomedical research and dramatically changed the fields of regenerative medicine and stem cell biology. The concept of growing organoids from human stem cells was first reported by Eiraku et al.¹, who demonstrated the generation of cortical neuroepithelia from self-organizing cultures of embryonic stem cells. These 3D aggregates self-organized and polarized in culture, traits that later defined organoids². In 2009, Sato et al.³ successfully

cultivated tissue-derived adult stem cells into complex 3D intestinal ‘organ-like’ structures. Two years later, it was shown that intestinal organoids can also be derived from human induced pluripotent stem (iPS) cells⁴.

Adult stem cell-based organoids are often derived from a single-germ layer (endodermal) cell lineage of tissue-resident stem cells or progenitor cells, while iPS cell organoids can generate both epithelial organoids and multi-lineage organoids, which contain a variety

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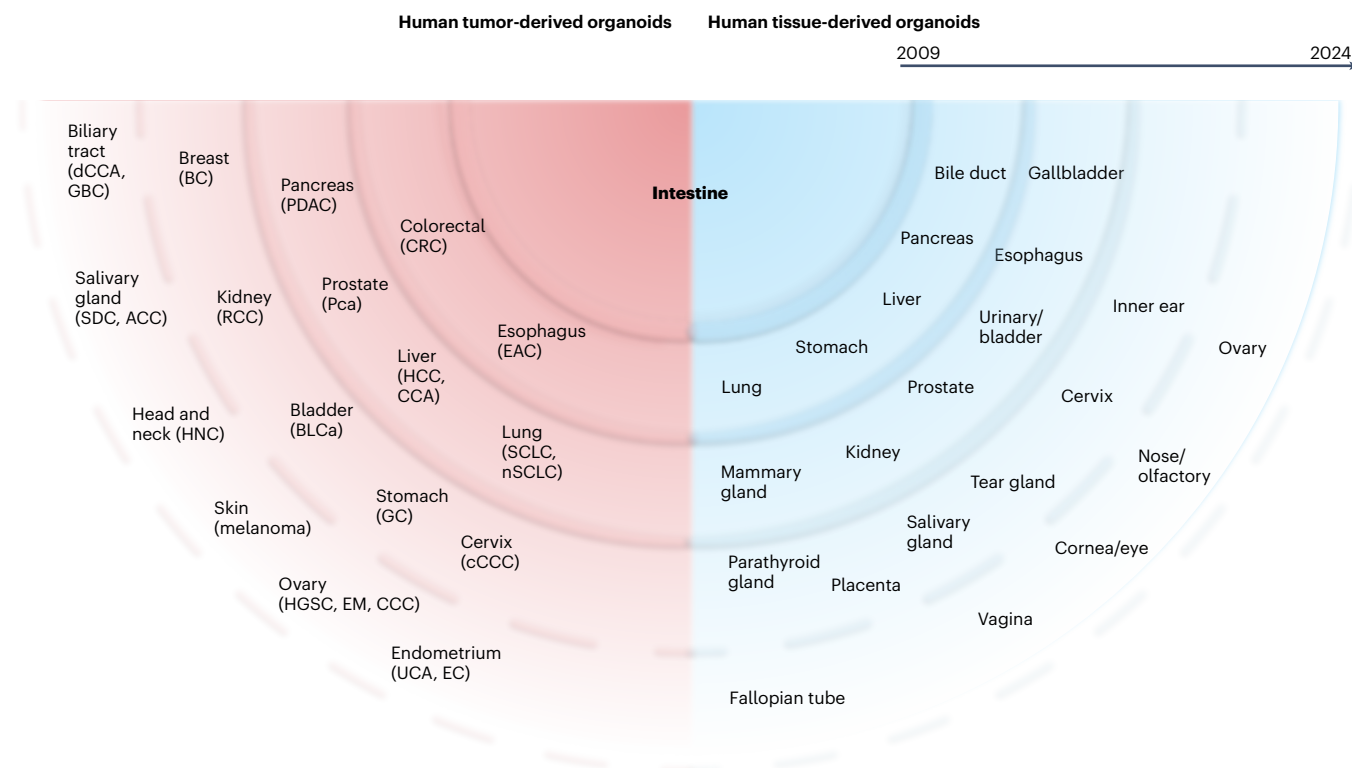


Fig. 1 | The ripple effect of the epithelial organoid discovery. Since the development of adult stem cell-derived epithelial organoid cultures by Sato et al.³, organoids have been initiated from many tissue types using similar work-up and culture conditions. These include organoids from healthy and diseased tissue (in blue), including tumors (in red). This is an ongoing process, and even more tissue types will be used in the coming years. ACC, adenoid cystic carcinoma; BC, breast cancer; BLCa, bladder cancer; CCA, cholangiocarcinoma; CCC,

clear cell carcinoma; CRC, colorectal cancer; EAC, esophageal cancer; EM/EC, endometrial cancer; GBC, gallbladder cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HGSC, high grade serous carcinoma; HNC, head and neck cancer; nSCLC, non-small cell lung cancer; PDAC, pancreatic duct adenocarcinoma; Pca, prostate cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SDC, salivary duct cancer; UCA, uterine carcinoma; carcinoma.

of cell types, including non-epithelial cells². Although iPSC cell-derived organoids share the same potency as adult stem cell-derived organoids, the latter represent the most widely studied organoid type, with the literature containing over ten thousand publications describing the generation and/or use of epithelial organoids, illustrating the huge ripple effect of this technology (Fig. 1).

The field of organoid technology has rapidly evolved since its inception, revolutionizing the study of human biology and disease. Innovative technical advances include augmenting organoids with multiple cell types^{5–7} and the development of organ-specific extracellular matrix to increase complexity and better mimic various healthy or diseased tissues^{8,9}. In parallel, organ-on-chip and advanced 3D bioprinting technologies have accelerated the use of organoids for regenerative medicine and (pre)clinical applications^{10,11}, while genetic engineering using CRISPR–Cas9 systems makes organoids valuable tools for studying genetic diseases and testing targeted therapies^{12,13}. Looking ahead, the integration of organoid technology with other cutting-edge techniques such as microfluidics and bioprinting holds great promise. These interdisciplinary approaches could further enhance the physiological relevance of organoids, although their full clinical potential has yet to be realized.

Most applications using organoids remain in the fundamental or preclinical research phase, being extensively used in disease modeling (including for personalized medicine) and drug screening. With that, the field stands at a crucial point in translating or extending these findings toward clinical application. Some organoid-based applications, for instance, in donor organ repair during machine perfusion¹⁴, are on the cusp of clinical use, while others are currently being evaluated

in early clinical trials. In the fields of toxicology and pharmacology, adult stem cell-derived or iPSC cell-derived organoids are increasingly used to predict human responses to drugs and chemicals, potentially reducing reliance on animal testing. Regulatory agencies are beginning to recognize the value of these animal-free models in preclinical safety assessments, which could accelerate their adoption in drug development pipelines^{15,16}. At the same time, these developments also raise ethical issues that should be navigated responsibly.

In this Review, we outline the technological advances that are propelling organoid research forward and we highlight promising translational and clinical applications of organoids. We focus primarily on adult stem cell-derived epithelial organoids, as these have been more widely studied and are therefore closer to clinical translation than those from other primary tissue types (connective tissue, muscle tissue and nervous tissue, reviewed elsewhere^{17–20}). We accentuate the most relevant findings in the clinical context and discuss advancing first-in-human applications.

Technological advances in organoid research

Technological advances have important implications for both upstream and downstream organoid research. While some of this potential has already been exploited, there are many underused opportunities at the intersection of biomedical technology and organoid research. Supplementing 3D epithelial organoids with other cell types such as immune cells²¹, fibroblasts^{22,23} or neural cells and adding vasculature²⁴ and extracellular matrix components²⁵ increase the complexity, providing better mimicking of tissue and disease models (Fig. 2a). The identification of isolated biological processes driving disease development and

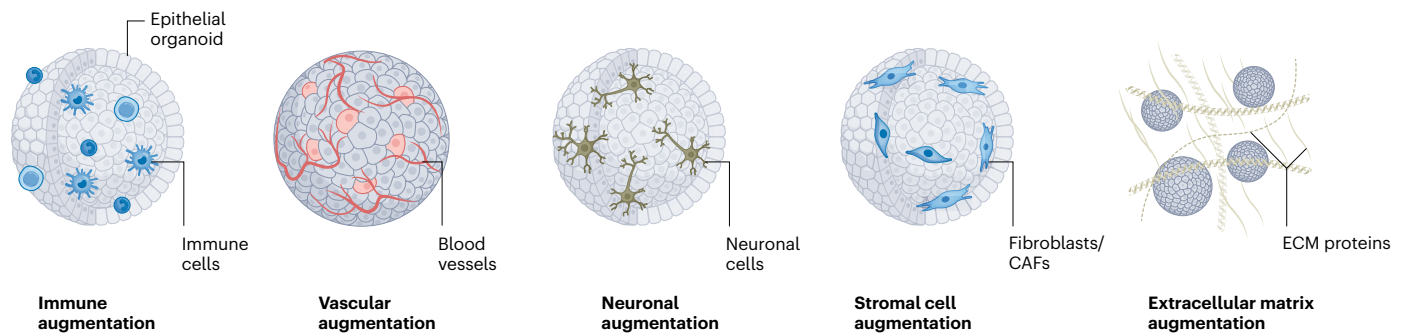
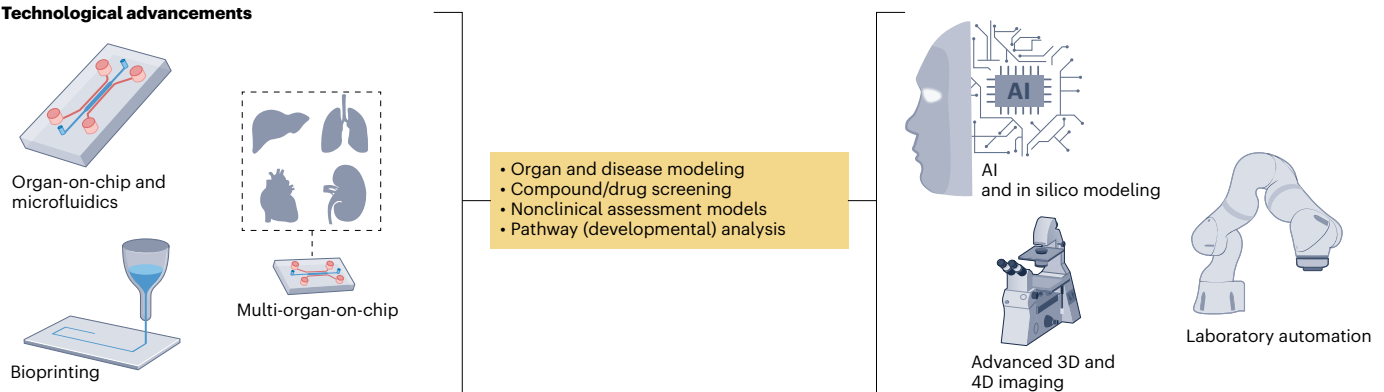
a Multicell type organoid systems**b Technological advancements**

Fig. 2 | Technological advances with organoids. **a**, By augmenting organoids with other (single) cell types such as immune cells and fibroblasts, adding vascular and neuronal networks and inclusion of organ-specific extracellular matrix (ECM), the complexity and, with that, the deployability of organoids can be leveraged. **b**, Technical advancements such as organ-on-chip using microfluidics to provide a continuous medium flow and 3D bioprinting of

organoids enhance the physical and physiological surrounding of epithelial cells, especially when combined with multiple organs in one system. Automation and robotics will become more available in the future and will help to initiate or passage and assess cultures uniformly and accurately. Moreover, highly developed computational resources, such as machine learning and AI, aid in improving organoids, disease characterization and drug assessment.

progression has been greatly facilitated by the application of CRISPR–Cas9 technology to generate genetically engineered organoids^{12,13}. For example, CRISPR-engineered human hepatocyte organoids were designed to model different mutations responsible for fibrolamellar carcinoma, revealing a role for combined loss of BAP1 and PRKAR2A in the pathogenesis of this rare and lethal liver cancer²⁶.

Augmenting conventional organoid cultures with 3D bioprinting has proven to be a powerful strategy for scaling up the size and complexity of organoids, including 3D printing of multicellular constructs. Three-dimensional bioprinting allows for arbitrarily complex spatial distribution of different cell types and cell densities within the construct while also enabling the same kind of complex distributions for mechanical (stiffness), biological (growth factors) and geometrical (curvature) cues. Moreover, (multimaterial) 3D printing allows for the incorporation of channels that could be used to supply the organoid constructs with nutrients and oxygen while also temporally controlling the concentration of other types of molecules, for example, to stimulate angiogenesis, to modulate the immune response within the construct or to control the differentiation pathways of various cell types. The precise and automated nature of bioprinting increases the throughput of organoid generation²⁷ and has been applied in modeling liver²⁸ and kidney²⁷ tissue. More sophisticated disease models, including those replicating tumor microenvironments²⁹, are developed at the nexus of bioprinting and organoid research, which can also be applied to drug screening³⁰. Overall, the self-organization behavior achieved by combining bioprinting with organoid-forming cells takes

the (microscale) complexity of the modeled tissues to levels not usually attainable by traditional, manual approaches³¹.

A major challenge addressed using recent technological developments is the need for changing specific dimensions over time, as the organoid develops and grows, including the properties of the biomaterial or the concentration of specific physical or biological cues. While novel solutions such as hydrogel-in-hydrogel live bioprinting³² have been proposed for such time-dependent dynamic control of the tissue microenvironment, four-dimensional printing³³ can provide a more general solution to address such challenges. 4D bioprinting³⁴ is an extension of 3D bioprinting in which the shape and/or properties of the bioprinted construct change with time, upon application of a specific stimulus. 4D bioprinting can elevate the sophistication of technological approaches involving organoids and has, for example, been used for drug screening using glioblastoma organoid models³⁵. This is in addition to the other dynamic behaviors usually achieved in microfluidic and organ-on-chip systems³⁶.

Organoids could also have a major role in enabling the application of artificial intelligence (AI) in biomedical research (Fig. 2b). The application of AI-based techniques to multiple areas of biomedical research, including regenerative medicine, drug screening and toxicology, is often hampered by the lack of sufficiently large databases that could be used to train AI models with high predictive power. At the heart of this challenge lies the representation accuracy–scale dichotomy, in which high-throughput data that can be collected at scale are generally not precise enough to represent the exact test conditions, while accurately

representative data cannot be collected at scale. Organoid-based models present a way out of this dichotomy by making it possible to create high-throughput yet representative models that can be used to collect the large datasets needed for training AI models. This opportunity is not yet fully exploited but is expected to gain more traction as more applications of AI in biomedicine emerge, leading to more advanced in vitro models³⁷. Conversely, AI models could accelerate the development and application of organoid-based healthcare solutions, which may include the construction of new types of organoid systems, multiscale image analysis and high-throughput analysis of multiomics data^{38,39}.

Organoid-guided diagnostics and precision medicine

One of the hallmarks of tissue-derived adult stem cell organoids is that they recapitulate characteristics such as genetic mutations of the tissue they are initiated from. In addition, these adult stem cell organoids exhibit self-renewal capabilities and the potential to produce fully differentiated, self-organizing mature epithelial cells⁴⁰. These characteristics make organoid cultures an excellent model to study patient-specific diseases and therapeutic responses (Fig. 3).

The culture of patient-derived organoids can be initiated by obtaining viable cells from a small biopsy of an organ or tissue that is dissociated by enzymatic digestion steps. Alternatively, organoids can also be initiated directly from body fluids such as urine^{41,42}, bile^{43,44} or amniotic fluid⁴⁵. Either by initiating organoids from individual patients or by engineering organoids to model diseases or single pathways leading to disease, organoids reflect disease characteristics in both histological and mutational aspects. With this, a medium-to-high-throughput analysis can be performed to screen organoids for their response to different drugs or drug combinations. Organoids can thus provide a personalized model to both develop and assess novel or repurposed drugs, achieving what was previously not feasible with two-dimensionally grown (primary) cell lines or animal models. Correspondingly, patient-derived organoids provide a promising tool to facilitate treatment decisions. This will have a major impact on treatment stratification and medical decision making, which is beneficial for the quality of life of patients and may yield benefits in terms of healthcare costs. As there are many applications of organoids with regard to diagnosis and precision or personalized medicine, the subsections below highlight particularly promising clinical–translational advancements.

Advanced cancer modeling

Organoids established from patient tumor tissues exhibit high histological and functional similarity to tumors in vivo. Organoids have been established for various types of cancer including colorectal cancer^{46,47}, prostate cancer⁴⁸, pancreatic cancer⁴⁹, gastric cancer^{50,51}, liver cancer⁵², biliary tract cancer⁵³, breast cancer⁵⁴ and neuroendocrine tumors⁵⁵. Drug screening using these patient-derived organoids is underway, making tumor organoids powerful research tools for advancing drug discovery and personalized medicine^{56–58}. A search in the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database as of October 2024 revealed 36 trials using organoids for personalized medicine in various types of cancer (Table 1 lists the 20 trials that have been completed, are active or are recruiting). At present, organoid-based personalized cancer medicine has not been approved,

Fig. 3 | Organoid-based precision medicine and clinical decision making.

a, Organoids initiated from patient tissues can be used for disease modeling and testing of drug responses at the individual level. **b**, It is important that the organoids reflect the patient's disease characteristics in both histological and mutational profiles. **c**, Organoids can be screened for their response to different (combinations of) drugs and with that provide a personalized model to assess which treatment gives the best results. **d**, With this, patient-derived organoids can be an excellent tool to facilitate treatment decisions.

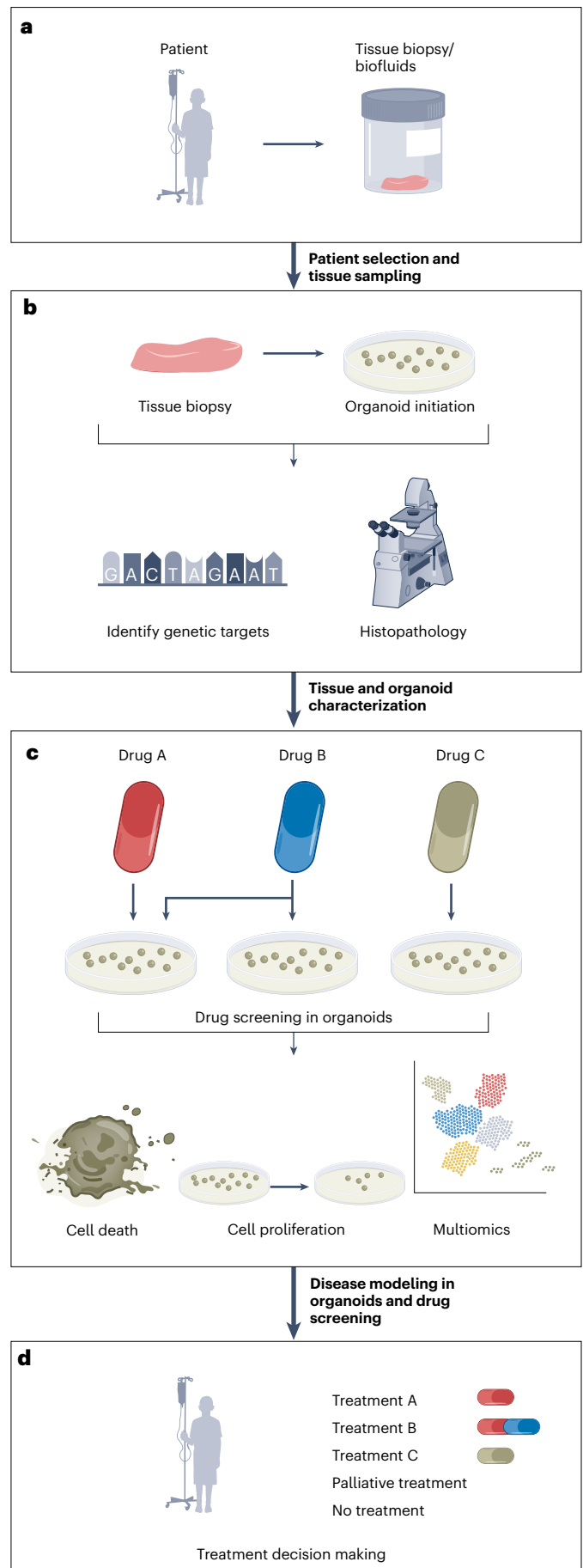


Table 1 | Ongoing clinical trials using organoids for personalized medicine

NCT number	Study title	Status	Condition	Phase	Enrolled	Type (int/obs)	Location	Posted
NCT06315868	Breast cancer subtype characterization through patient's derived organoids	Recruiting	Breast cancer		306	Obs	Italy	March 2024
NCT06102824	Organoid-based functional precision therapy for advanced breast cancer	Recruiting	Breast cancer (HER2 ⁺ /advanced)	2	252	Int	China	October 2023
NCT04450706	Functional precision oncology for metastatic breast cancer	Recruiting	Breast cancer (HER2 ⁺)	N/A	15	Int	United States	June 2020
NCT06268652	Patient derived organoid-guided personalized treatment versus treatment of physician's choice in breast cancer	Recruiting	Breast cancer/refractory breast carcinoma	3	302	Int	China	February 2024
NCT05304741	The culture of advanced/recurrent/metastatic colorectal cancer organoids and drug screening	Recruiting	Colorectal cancer		30	Obs	China	March 2022
NCT05725200	Study to investigate outcome of individualized treatment in patients with metastatic colorectal cancer	Recruiting	Colorectal cancer (metastatic)	2	40	Int	Norway	February 2023
NCT05401318	Tailoring treatment in colorectal cancer	Recruiting	Colorectal neoplasms		40	Obs	Norway	June 2022
NCT02732860	Personalized patient derived xenograft (pPDX) modeling to test drug response in matching host	Recruiting	Colorectal/breast/ovarian (neoplasms/cancer)		120	Obs	Canada	April 2016
NCT06332716	Research on the correlation between organoid drug sensitivity testing and precise treatment of gastrointestinal tumors	Recruiting	Gastrointestinal tumors	3	68	Int	China	March 2024
NCT03890614	Novel 3D hematological malignancy organoid to study disease biology and chemosensitivity	Recruiting	Hematologic malignancy		70	Obs	United States	March 2019
NCT05913141	PDO/PDO-TIL/PDOTS for drug screen	Recruiting	Liver cancer/metastatic liver cancer		30	Obs	China	June 2023
NCT05669586	Organoids predict therapeutic response in patients with multi-line drug-resistant lung cancer	Recruiting	Lung cancer	2	50	Int	China	January 2023
NCT06406608	Patient-derived organoid drug sensitivity guided treatment for drug-resistant recurrent non-small cell lung cancer	Recruiting	Lung cancer (nSCLC)	N/A	20	Int	China	May 2024
NCT06406660	Patient-derived organoid drug sensitivity guided treatment for recurrent small cell lung cancer	Recruiting	Lung cancer (SCLC)	N/A	20	Int	China	May 2024
NCT04768270	The culture of ovarian cancer organoids and drug screening	Recruiting	Ovarian cancer		30	Obs	China	February 2021
NCT06482086	Efficacy of organoid-based drug screening to guide treatment for locally advanced thyroid cancer	Recruiting	Thyroid gland carcinoma (locally advanced)	2	75	Int	China	July 2024
NCT05267912	Prospective multicenter study evaluating feasibility and efficacy of tumor organoid-based precision medicine in patients with advanced refractory cancers	Not recruiting/active	Advanced, pretreated solid tumors	N/A	61	Int	France	March 2022
NCT04561453	Feasibility study of multi-platform profiling of resected biliary tract cancer	Not recruiting/active	Biliary tract cancer		14	Obs	United States	September 2020
NCT05196334	Pharmacotyping of pancreatic patient-derived organoids	Not recruiting/active	Pancreatic cancer		88	Obs	Denmark	January 2022
NCT04342286	To establish a reproducible organoid culture model with human kidney cancer	Completed	Kidney cancer		20	Obs	Hong Kong	April 2020

Source: October 2024, [ClinicalTrials.gov](https://clinicaltrials.gov) database. Int, interventional; obs, observational; NCT, National Clinical Trial; N/A, not available; PDO, patient-derived organoids; PDO-TIL, patient-derived organoids-tumor-infiltrating lymphocyte coculture system; PDOTS, patient-derived organotypic tissue spheroids.

but two trials are in phase 3 (Table 1); therefore, it is possible that such applications will be approved and applied clinically in the future.

Despite the advancement of organoid-based precision medicine strategies into clinical trials, the complexity of tumors poses an ongoing challenge (one not exclusive to organoid approaches). Tumors contain many nontumor cell types including stromal cells, such as cancer-associated fibroblasts (CAFs) and immune cells, that

collectively regulate inflammation responses and immunity. These stromal cells have crucial roles in tumor growth, malignant cell invasion, metastasis, angiogenesis and drug resistance. Studies using pancreatic tumor organoids have reported that CAFs secrete growth factors such as WNT, maintaining stem cell phenotypes, and that pancreatic cancer growth becomes independent of WNT during disease progression⁵⁹. In cancer immunotherapy, immune checkpoint

inhibitors that block the binding of the immune checkpoint molecules PD-1 or CTLA-4 and their ligands demonstrate potent anti-tumor effects in some cancers through activation of cancer antigen-specific cytotoxic T cells^{60–63}. Furthermore, the extracellular matrix, within or surrounding the tumor, is often altered and has a critical role in cancer development and progression⁶⁴. Current organoid culture protocols remove all stromal components such as fibroblasts, immune cells and the extracellular matrix during the organoid initiation process, culturing only epithelial cancer cells. Therefore, it is difficult to truly recapitulate the effects of therapeutic drugs (particularly immunotherapy) and the interactions between cancer cells and CAFs, immune cells and the extracellular matrix.

To address these issues, it is crucial to further evolve conventional organoid culture techniques and establish next-generation organoids by co-culturing or augmenting cancer organoids with CAFs, peripheral blood mononuclear cells, tumor-infiltrating lymphocytes and other immune cells and the extracellular matrix to mimic the tumor microenvironment (Fig. 2a). This is an area of active research. Recent studies have shown that co-culturing cancer organoids with immune cells can be used to assess the efficacy of T cell-mediated tumor killing^{6,21,65,66}. In the case of bile duct cancer, the use of isolated tumor extracellular matrix has proven superior to the standard basement membrane extracts that are commonly used in organoid culture⁹. Of note, biliary tumor organoids start remodeling their environment in culture and show remarkable differences depending on the matrix they are grown in, again proving that it is important to include a representative tissue microenvironment when modeling disease and evaluating the effectiveness of cancer therapy^{9,67,68}. Next-generation organoids, which recapitulate stromal and noncellular components of the microenvironment, are expected to be powerful preclinical models for personalized medicine against refractory cancers, hopefully leading to improvements in treatment outcomes for patients with cancer.

These patient-derived cancer organoids can be used to predict the efficacy of various therapeutic drugs including molecular targeted drugs and immune checkpoint inhibitors in advance^{69,70}. Organoids can also be used to study the mutagenic effects of bacteria and viruses. Rosendahl and colleagues developed a fast and robust detection method to identify genotoxin colibactin-induced mutations in colorectal cancer. For this, they used co-cultures of *Escherichia coli* strains and intestinal organoids in which specific mutational motifs could be identified⁷¹.

Reproductive system and prenatal screening of birth defects

In the context of reproductive health, the past 15 years of epithelial organoid research have provided huge breakthroughs in modeling the reproductive system. Epithelial organoids have been established to model the different regions of the female reproductive tract such as the ovaries^{72,73}, fallopian tubes^{74,75}, endometrial tissue^{76–78}, the cervix^{79–81} and placental trophoblasts^{82,83}. As reviewed elsewhere, these organoids have been used to study a broad range of diseases affecting female reproductive tissues, including cervical cancer and endometrial carcinoma, endometriosis, infertility and preeclampsia⁸⁴. Although organoids have been more broadly applied to female reproductive organs, organoid cultures have also been established from the testis and the prostate to study male reproductive tissue biology^{85,86}. The latter have already been harnessed for biobanks and used to predict therapeutic efficacy and, with that, guide treatment and inform clinical trial designs⁸⁷.

Beyond studying the adult reproductive system, there is great interest in using epithelial organoids in the context of fetal development and congenital diseases and potentially screening and monitoring of these conditions. Fetal epithelial organoids have been successfully derived from a number of fetal tissues after pregnancy termination⁸⁸, but collecting fetal biopsies during continuing

pregnancy is not considered desirable. Interestingly, however, a recent study showed that primary fetal small intestine, kidney and lung epithelial organoids can be safely initiated from amniotic fluid sampled during pregnancy⁴⁵. These organoids were derived during pregnancies with healthy children and those with congenital diseases, starting from 16 weeks of gestation and provide a promising avenue to assess developmental progression of an organ in a developing fetus. Currently, the study of birth defects and congenital genetic disorders relies on imaging, genetic testing and biochemical analyses⁸⁹, none of which can assess the developmental progression of fetal organs. One in 30 fetuses develops some form of congenital malformation as a result of structural or chromosomal abnormalities or single-gene disorders⁹⁰, and, as fetal interventions become available for some of these conditions, early diagnosis and patient selection present a substantial challenge.

For example, in congenital diaphragmatic hernia (CDH), the fetoscopic endoluminal tracheal occlusion procedure can reversibly block the trachea of the fetus with a latex balloon and promote lung development during gestation^{91,92}. However, appropriate patient selection is important because CDH is associated with 30% mortality, but intervening also poses a risk to both the mother and the fetus. Fetal organoids could potentially be used to monitor lung development, identify the most accurate treatment pathway and provide an *in vitro* system to test innovative therapies. Indeed, when organoids were derived from amniotic fluids of CDH pregnancies, substantial gene expression and functional differences were detected in comparison to non-CDH organoids. Additionally, these differences were consistently observed in CDH organoids generated from samples before fetoscopic endoluminal tracheal occlusion compared to the ones generated after treatment, suggesting for the first time that organoids could provide a good model to assess treatment efficacy⁴⁵. Overall, fetal fluid-derived organoids could support advanced functional diagnosis of birth defects and offer a personalized approach to fetal therapies⁹³.

Organoids to study emerging public health challenges

Unraveling the impact of environmental risk factors

Epithelial tissues represent the initial layer of tissue affected by any external perturbation, particularly in extreme environments such as microgravity and in the case of solar or other types of radiation. Epithelial organoids have emerged as a potent tool for *in vitro* assessment of environmental pollutant toxicity, genotoxicity and drug toxicity. Organoids have been used to evaluate the health risks posed by various toxins including the pneumotoxicity of polystyrene microplastic fibers and particulate matter (PM_{2.5}) in airway organoids^{94,95}, the cardiotoxicity of polystyrene microplastics in cardiac organoids⁹⁶, the hepatotoxicity of polystyrene microparticles in liver-derived organoids⁹⁷, the nephrotoxicity of hydroxylated generation 5 PAMAM dendrimer nanoparticles in kidney organoids⁹⁸, breast toxicity in mammary organoids after exposure to bisphenol A, mono-*n*-butyl phthalate and polychlorinated biphenyl 153 (ref. 99) and the gastrointestinal toxicity of benzo[*a*]pyrene-loaded aged polystyrene microplastics in colon organoids¹⁰⁰. Furthermore, organoids have been used to assess genotoxicity; a recent study used healthy intestine-derived organoids to mimic chemoradiotherapy-induced DNA damage *in vitro*, highlighting flumazenil as a promising chemoradioprotective agent¹⁰¹.

Microplastics are emerging as an important (and understudied) component of the human exposome, and organoids are being used to study their health impacts^{102,103}. Microplastics are also of concern in the context of viral transmission, as they (and other environmental pollutants) might carry pathogens that can be transferred through inhalation or ingestion¹⁰⁴. Future research should therefore expand the applications of organoids to assess the impact of such combined environmental exposures (Fig. 4).

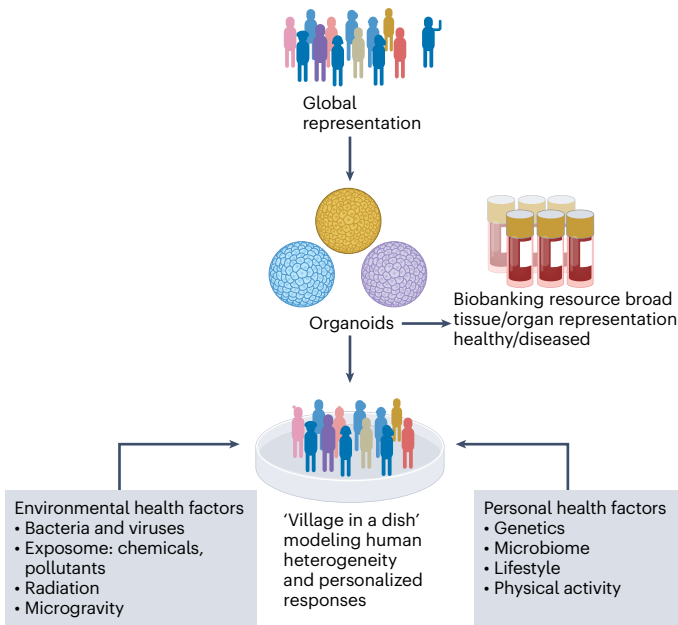


Fig. 4 | Organoid-based assessment of the exposome and environmental risk factors. Aside from different genetic makeup (internal personal health factors), individuals are continuously exposed to factors both by their own choice (external personal factors such as smoking, diet, use of chemicals) and through environmental exposure (emissions, radiation, microplastics and pests). All these factors could be studied in organoids at the individual level but also at the societal level in a ‘village in a dish’¹⁶⁶. Subjecting organoid banks to these factors (solely or en masse) allows us to study how the exposome affects genetics and (group) immunity and how infectious diseases might be restricted and provides clues to facilitate healthy aging.

Pandemic preparedness and response

Over the past 100 years, major epidemics and pandemics, caused by (mainly viral) infectious diseases, have occurred, each taking over one million recorded lives¹⁰⁵. These unpredictable outbreaks are facilitated by the ability of viruses to frequently (re)emerge in humans from natural reservoirs such as wild and domesticated animals. A powerful showcase of the utility of organoid technology in studying viral infection came from the demonstration that intestinal organoids can support productive infection of human noroviruses¹⁰⁶. Following more than four decades of efforts to culture human noroviruses, this was the first demonstration of robust, reproducible *ex vivo* cultivation. Over the past decade, organoids have been used to understand cellular tropisms and pathogenic mechanisms of a range of viruses, often during active outbreaks.

During the 2015–2016 Zika epidemic in the Americas, microcephaly was increasingly reported. Brain organoids were widely used to understand the causality between Zika virus and malformations in fetal brains¹⁰⁷. The use of trophoblast organoids helped researchers to understand transplacental infection of Zika virus (implicated in vertical transmission) and the resulting congenital malformations in infants^{108,109}. The applications of organoid technology in pandemic response were fully explored during the recent COVID-19 pandemic. In addition to the use of human airway organoids to model the primary infection of SARS-CoV-2¹¹⁰, kidney¹¹¹, liver¹¹² and intestinal¹¹³ organoids were used to recapitulate the broad tropism of this virus and understand the associated systemic manifestations. During the ongoing global mpox outbreak, human skin organoids have been shown to effectively support mpox virus infection, recapitulating the primary infection in patient skin¹¹⁴. However, mpox can also cause a broad spectrum of systemic manifestations often associated with poor outcomes, frequently related to acute kidney injury. Indeed, human kidney

organoids are susceptible to mpox infection, and, interestingly, mpox preferentially damages the glomerular and proximal tubular structures but not the distal tubular structures of the organoids¹¹⁵.

Overall, these current applications primarily focus on the use of organoids to model the viral life cycle. However, in infected patients, many viruses (particularly those with pandemic potential), cause severe pathogenesis that is often accompanied by hyperinflammation¹¹⁶, which cannot be recapitulated in virus-exposed organoids. Another essential application of organoids in pandemic response lies in drug discovery and testing. Current efforts are mainly restricted to evaluating individual antiviral agents to prevent infection^{114,117}, while small-scale antiviral drug screening has been demonstrated to be feasible in virus-infected organoids^{118,119}. Improving large-scale organoid production with ensured quality control would facilitate medium-to-large-scale drug screening. Furthermore, epithelial organoids augmented with the relevant immune cells would enable the development of more advanced treatment strategies such as simultaneously targeting the virus and pathological inflammation. Integration of epithelial organoids with immune cells may also enable assessment of vaccine responses and efficacy following pathogen challenge. Indeed, the recent development of immune organoids from lymphoid tissues (specifically tonsils) allowed testing of immune responses to rabies and SARS-CoV-2 vaccines¹²⁰.

To strengthen pandemic preparedness, it is vital to assess the zoonotic potential of pathogens circulating in animals in a timely manner. Given that bats are natural reservoirs for many coronaviruses, Zhou et al.¹²¹ demonstrated that both bat and human intestinal organoids are susceptible to SARS-CoV-2 infection. Mirroring this retrospective approach, we postulate that building an integrated platform of human- and animal-derived organoids would enable prospective assessment and help to understand the zoonotic potential of emerging pathogens, contributing to prevention measures or early response to future pandemics.

Challenges of aging populations

Over the past two centuries, human life expectancy has doubled in most developed countries¹²². An aging population will have societal consequences impacting the economy, social structures and health-care systems. Aging is characterized by the accumulation of cellular and chromosomal damage, disrupted homeostasis and a decline in the regenerative capacity of organs¹²³, processes that are well suited to analysis in organoid models. By sequencing clonal organoids derived from the small intestine, colon and liver, genome-wide mutation patterns were shown to accumulate steadily over time. Interestingly, different cell types showed different mutation spectra, which seemed to be linked to cell division rate and other intrinsic processes that can initiate tumorigenesis¹²⁴. Other organoid studies showed that these mutational differences are likely due to different DNA repair mechanisms employed in different organs and are affected by underlying diseases^{125,126}. Moreover, intestinal organoids have been used to identify the regulatory role of defects in intestinal stem cells and their niches in the aging intestinal epithelium¹²⁷. Similarly, alveolar organoids also serve as *in vitro* injury repair models and revealed that persistent cell senescence could diminish alveolar regeneration, leading to pulmonary fibrosis¹²⁸.

It is important to mention that senescence represents a cellular state that, as well as being associated with human aging, also negatively affects the efficiency of organoid formation and stem cell self-renewal potential. Studies show a decline in the frequency of human organoid formation from aged intestinal epithelium compared to intestinal epithelium from younger research participants¹²⁹. Moreover, cold preservation during liver transplantation triggered cholangiocyte senescence and reduced the efficiency of cholangiocyte organoid formation and functionality, which was shown to be ameliorated by senolytic treatment¹³⁰. Epithelial organoids therefore have great

Table 2 | Ongoing clinical trials using organoids in cell-based therapies

Number	Study title	Status	Condition	Phase	Enrolled	Type (int/obs)	Location	Posted
UMIN000030117 ^a	Mucosal regeneration therapy by autologous intestinal stem cell transplantation to inflammatory bowel disease patients	Recruiting	Ulcerative colitis	Safety	8	Int	Japan	April 2018
NCT04593589	Submandibular gland stem cell transplantation (RESTART)	Recruiting	Head and neck cancer	1	18	Int	The Netherlands	October 2022
NCT06415643	The use of islet organoids in the treatment of pancreatic surgery-related diabetes	Recruiting	Diabetes (T3c)	N/A	5	Int	China	August 2024

Source: ^aUMIN registration, Japanese registry (<https://www.umin.ac.jp/ctr/>) and the [ClinicalTrials.gov](https://clinicaltrials.gov) database, October 2024. T3c, pancreatogenic.

potential for aging research. In the future, they could help unravel tissue- and organ-specific differences in aging mechanisms and create a platform to study preventive and therapeutic strategies to counteract aging-associated diseases.

Health insights from space research

Radiation and microgravity adversely impact human health at the cellular and tissue levels, including alterations in gene expression, cellular function and tissue morphology^{131,132}. Organoid experiments performed in space could help address these by analyzing how microgravity affects organoid development and differentiation, offering insights into tissue adaptation during space travel and revealing new targets for therapeutic interventions. By subjecting epithelial organoids, derived from the gastrointestinal tract, kidneys or lungs, to simulated microgravity on Earth or conducting experiments aboard space stations, the underlying mechanisms of space-induced alterations can be addressed^{133–135}. These insights may help to mitigate adverse health effects on astronauts and future space travel.

While the initial aim of using organoids in biological space research was to study how microgravity and radiation affect the astronauts' tissues, organoid models are also being used to study the mechanisms of accelerated aging in space environments, contributing to (anti-)aging research, which is relevant to both space travelers and populations on Earth. Studies such as the Twin Project¹³² illustrate how insights gained from space research can enhance our understanding of human health and disease, including aging processes. Organoids are particularly deployable when investigating the effects of extreme conditions, such as those encountered in space but also in war zones or remote locations with harsh environmental circumstances. They offer distinct advantages in terms of scalability and allow for a high number of replicates, which is crucial in size-restricted laboratory environments such as those in space stations. Despite their advantages, the use of organoids in space research is not without challenges, mostly concerning the technical limitations in culturing and maintaining organoids in a microgravity environment, which necessitate creative experimental setups and technological innovations. Although progress has been made, particularly on the International Space Station (<https://www.nasa.gov/international-space-station/>), optimizing organoid culture systems in space remains a priority. This involves establishing biobanks of primary (stem) cells, robotic process automation for medium changes and sampling, handling of extracellular matrix, formulating growth factor cocktails and integrating advanced imaging and omic technologies to comprehensively characterize cellular responses.

Cost is an important factor in this context, which must be balanced against potential clinical benefits at the population level. Multidisciplinary efforts involving space agencies, academic institutions and biotechnology companies are essential for addressing these challenges and fostering advancements in space medicine with applications for terrestrial health. The establishment of a complete cell or tissue culture environment within future space stations (after the International Space Station era) will be imperative for meeting all

requirements and providing the necessary controlled conditions for successful research.

Organoids in regenerative medicine

The growing preclinical evidence that organoids are a good model to study disease or patient-specific characteristics has paved the way for clinical trials. Patient-derived organoids enable the use of (autologous) cells for regenerative applications and cell-based therapies of histocompatible organoids without risk of alloreactivity or rejection.

Cell therapy applications

So far, only three phase 1–2 clinical trials that involve organoids for transplantation or cell-based therapies have been registered (Table 2). These include treatment of ulcerative colitis using intestinal organoids (clinical trial [UMIN000030117](#), Japanese Registry), diabetes with islet organoids (clinical trial [NCT06415643](#)) and radiation-induced xerostomia using salivary gland organoids (clinical trial [NCT04593589](#)).

A particularly successful example involves the use of salivary gland organoids to treat patients with head and neck cancer treatment-induced xerostomia (dry mouth syndrome). During radiotherapy of head and neck cancer, the salivary glands are often inevitably irradiated, resulting in severe adverse effects such as xerostomia in about 40% of patients. Hyposalivation can dramatically impact quality of life, causing altered taste, a dry and painful mouth, continuous thirst and difficulty eating (while increasing the risk of infection and dental problems) and is extremely difficult to manage¹³⁶. Although multiple factors have a role in the tissue's response to irradiation, the ability (or inability) of stem cells to produce a new population of functional cells determines the onset and severity of radiation-induced side effects¹³⁷, prompting the development of stem cell therapy to treat this condition. First, salivary gland stem cells were localized using targeted high-precision proton irradiation combined with functional analyses¹³⁸. Subsequent organoid cultures were established from mouse¹³⁹ and human¹⁴⁰ salivary glands and used for transplantation in locally irradiated submandibular glands. Both in mice and humans, this led to successful regeneration of the glands, which showed improved morphology and secretory function. The 80% function recovery found in mouse-to-mouse transplantations indicates the huge potential of such therapy¹³⁹. In clinical trials, it is important to prepare a clinical-grade organoid culture complying with set acceptance and stability criteria. In this case, the manufactured salivary gland-derived cells were assessed to be self-renewing, differentiating and functional¹⁴¹. With these data and sufficient safety studies, ethical approval was obtained for a phase 1–2 trial from the Dutch Central Committee on Research Involving Human Subjects (CCMO). In December 2022, the first patient was transplanted with autologous salivary gland organoid-derived cells cultured from a biopsy taken before the radiotherapy. This is the first in-human clinical phase 1–2 trial to use patient-derived organoids to prevent radiation-induced side effects (clinical trial [NCT04593589](#)). More clinical trials are on the verge of being initiated, supporting the initial

concept that organoids can be broadly employed from fundamental research to clinical medicine.

Emerging applications in organ transplantation

Organ transplantation is the only curative treatment option for patients with end-stage organ failure. Despite the current success of organ transplantation, there is a tremendous gap between the number of patients in need of a donor organ and the number of available transplantable grafts. To bridge this gap, 'extended criteria donor' organs (organs from any donor over the age of 60 years or a donor over the age of 50 years) are used, but this is associated with graft injury and post-operative complications¹⁴². Machine perfusion recently emerged as a dynamic method for graft preservation and opened up new avenues for repair and regeneration of damaged organs, which could include organoid applications¹⁴³. For instance, in the context of liver transplantation, machine preservation offers opportunities for organoid-based repair of damaged bile ducts before transplantation, with the ultimate goal of reducing post-transplant complications^{14,144}. In a proof-of-concept study, Sampaziotis et al.¹⁴ were the first to demonstrate the regenerative potential of organoids in human liver grafts. Here, cells derived from cholangiocyte organoids were infused directly into the peripheral branches of liver bile ducts while the organs were undergoing ex vivo normothermic perfusion, where they increased bile production and biliary pH, restoring bile duct function. As these repaired grafts were not actually transplanted into humans, it remains to be seen whether organoids prevent biliary complications after transplantation. To avoid potential alloimmune response against organoids, autologous cells of the recipient should ideally be used, and organoids could be initiated at the time of enlistment for organ transplantation. Safe, minimally invasive methods to obtain autologous cells for organoid initiation include fine-needle aspiration biopsies or sampling from bile^{43,44}. To reach the high numbers of organoid cells needed for such treatment in a short time, more efficient culturing methods are being developed. Biobanking of organoids, for instance, from patients on a transplant waiting list, could make them readily available for regenerative purposes at the time when a donor organ is available for transplantation. In the future, these strategies could be applied for transplantation of organoid-enhanced kidneys, hearts and lungs.

Challenges to clinical organoid applications

Technical considerations

Initiation of organoid cultures from either tissue biopsies or fluids such as bile^{43,44}, pancreatic juice¹⁴⁵ or urine¹⁴⁶ is feasible but not always efficient. For example, the efficiency of initiating tumor organoids from primary liver tumors is little over 30%, meaning that, from every 100 tumors, only 30 will be grown in organoids that have proven to be an actual tumor⁵⁸. The challenge here, and most probably in all tumor-related personalized medicine applications, is to reduce or eliminate the growth of nonmalignant cells that, in the current expansion protocol^{52,53}, have a proliferative advantage at the expense of tumor cell growth. To address these challenges, culture conditions need to be reconsidered and optimized. Moreover, it is essential to determine the tumorigenicity of every organoid line after its establishment, as this is not always recapitulated in the culture.

For some applications, such as organoid-derived cell infusion to treat xerostomia, only low numbers of cells are needed. By contrast, certain other cell therapy applications demand many organoids. Repairing damaged bile ducts, for instance, to regenerate otherwise discarded donor livers, requires millions of cells¹⁴ to be effective. Producing these large numbers, especially in a clinical-grade fashion, is labor intensive and expensive and requires a lot of disposable plastics, creating environmental concerns. Scaling of 3D organoid cultures therefore requires innovative protocols. Recent advances in cell expansion technologies include purpose-designed spinner flasks that enhance the expansion of liver-derived organoids¹⁴⁷. However, these still require the use of mouse

tumor-derived basement membrane extracts (or Matrigel), which are not well defined, have batch-to-batch variability and might not be easily approved by regulatory authorities¹⁴⁸. Alternative hydrogels, either synthetic^{149–151} and/or organ derived^{152–155}, are not yet available in large quantities of constant quality, nor is it known how long these alternative hydrogels can support organoid expansion in culture.

Currently, adult stem cell-derived organoids contain only epithelial cells, lack relevant stromal cells and have only limited matrix interactions. Although iPS cells might be more broadly applicable in that sense, differentiation of all types of stromal cells from iPS cells is even a bigger challenge. Therefore, the current general vision is to design more complex models by augmenting epithelial organoids with other cell types such as immune cells, fibroblasts, neuronal cells and extracellular matrix (Fig. 2). This is a considerable challenge and requires well-established (animal product-free) culture medium that supports all cell types. Additionally, the optimal cell ratios and keeping immune cells and fibroblasts in the acquired activation state are issues yet to be addressed. Future directions for research include deciphering cell–cell and cell–matrix communication in co-culture systems to better study disease progression or tissue regeneration.

Ethical considerations

The development and use of organoids raise ethical issues^{156–158}, which may differ according to organoid type and application. Brain organoids¹⁵⁹ and embryo models in particular come with distinct ethical challenges, reviewed elsewhere¹⁶⁰. To responsibly guide organoid development and use, it is important to proactively identify and evaluate the ethical implication of their use¹⁶¹; some key ethical considerations are noted below.

An important ethical consideration of organoid research is its potential contribution to reducing and replacing animal testing; therefore, evaluating whether and under which conditions organoids can and should replace animal research should be a priority¹⁶². In terms of commercial use, organoids may advance innovation and translation, but this also raises concerns about the just distribution of related (non) monetary benefits between commercial parties, researchers, patients and donors. Benefit-sharing measures that can foster justice include returning clinically relevant results to individual patients or donors, ensuring that patients have access to innovative therapies, reinvesting profits in sustainable organoid infrastructures and embracing open-science principles and ethical licensing practices^{156,163}. Related to this is the prominent ethical discussion about how to obtain consent for organoid research¹⁵⁸. The traditional 'consent or anonymize' paradigm is somewhat challenged as the organoid contains genetic material of the donor. Anonymization may also not be desirable, as patient identification is necessary for organoid-guided precision medicine and anonymization would make it impossible for donors to impact how their samples are used^{156,163,164}. Moreover, the appropriate level of donor engagement in biobanking governance is an important topic of ethical discussion. It is argued that active donor involvement is particularly important for biobank research studies given the unknowns related to future research at the time of consent, the involvement of commercial parties and the blurring boundaries between research and care (in the context of personalized medicine applications) in organoid research¹⁶⁴.

Finally, clinical research, such as transplanting organoids into patients, invokes ethical questions related to potential risks and uncertainties^{156–158,165}. The move to first-in-human trials must involve careful ethical analysis, which should not only involve detailed analysis of risks but also choosing the appropriate study population, study design and outcomes and comparators^{156,165}.

Conclusion

In the short time since their discovery less than two decades ago, organoids have revolutionized stem cell biology and disease modeling. We look forward to the future in which we anticipate technological

innovations that expand their use with precision and scale, enabling broad clinical application as well as determining the effects of emerging infectious diseases and environmental exposures on human health.

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Competing interests

The authors declare no competing interests.

Additional information

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