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Global Meta-Analysis of Organoid and Organ-on-Chip Research

*Jun-ya Shoji, Richard P. Davis, Christine L. Mummery, and Stefan Krauss**

Organoids and cells in organ-on-chip platforms replicate higher-level anatomical, physiological, or pathological states of tissues and organs. These technologies are widely regarded by academia, the pharmacological industry and regulators as key biomedical developments. To map advances in this emerging field, a meta-analysis based on a quality-controlled text-mining algorithm is performed. The analysis covers titles, keywords, and abstracts of categorized academic publications in the literature and preprint databases published after 2010. The algorithm identifies and tracks 149 and 107 organs or organ substructures modeled as organoids and organ-on-chip, respectively, stem cell sources, as well as 130 diseases, and 16 groups of organisms other than human and mouse in which organoid/organ-on-chip technology is applied. The meta-analysis illustrates changing diversity and focus in organoid/organ-on-chip research and captures its geographical distribution. The downloadable dataset provided is a robust framework for researchers to interrogate with their own questions.

1. Introduction

Organoids are self-organizing, 3D tissue cultures, typically grown from stem cells, that model aspects of organ development, composition, and function. Organ-on-chip (OoC) by contrast is microfabricated devices that support cell culture and often include microfluidic flow, thus closely resembling in vivo microenvironments. Over the past decade, organoids and OoC have emerged as physiologically relevant model systems that are complementary, and sometimes superior, to 2D tissue cultures and animal models. Accordingly, they are increasingly used to model organ physiology and disease conditions. Moreover, they are recognized as valuable models for drug development and personalized medicine, as evidenced by the "FDA" Modernization Act 2.0" bill[1] recently approved by the US Senate that specifically mentioned these models as being acceptable in drug filing for market approval.

The term "organoid" dates from the mid-1940s when it was used to describe a cystic teratoma,[2] a type of benign testicular tumor. It was later sporadically used to describe other tumor types or abnormal cellular growth,[3,4] or to refer to 3D cell cultures originating from small tissue fragments taken from organs.[5,6] In 2009, the term organoid was reintroduced in a paper reporting the first intestinal organoids generated from stem cells that self-organized into 3D structures recapitulating aspects of the native tissue architecture and function.[7] This is now the generally accepted definition of the term,[8] with organoid technology in a broader sense also increasingly being used to study organogenesis and early embryogenesis.

An important foundation of organoid research in the modern sense was laid in the 1950s when cells from testicular teratocarcinomas were shown to form organized aggregates of different cell types after injection into mice.[9] Growth of these aggregates, termed embryoid bodies (EBs), was later demonstrated in vitro.[10] In parallel, methods for long-term culture of primary human cells were established in the 1970s,[11] leading, for example, to the generation of confluent sheets of skin epidermis for treating patients with severe burns,[12] or corneal sheets to treat corneal blindness.[13,14] Likewise, propagating and differentiating human adult stem cells (ASCs) from the mammary gland in 3D led to structures referred to as mammospheres that recapitulated features of primary mammary tissue.[15] An important enabling technology for organoid research was the isolation, or recombinant synthesis, of extracellular matrix (ECM), structural proteins essential for supporting cell viability and growth.[16–18] The market introduction of Matrigel, an ECM isolated from connective tissue cancers in mice,[19] facilitated the broader use

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of ECM-based culture methods. Cells from many organisms and tissues underwent striking morphological and secretory changes reminiscent of their tissue of origin when cultured on, or in, Matrigel.[20] Another milestone was the derivation of the first mouse embryonic stem cells (mESCs) from mouse blastocyst-stage embryos[21,22] that can differentiate to cell types from all three germ layers (ectoderm, endoderm, and mesoderm), recapitulating aspects of early mammalian development including some extraembryonic lineages.[23–25] These studies provided the basis for deriving human (h)ESCs from blastocysts,[26] and later human induced pluripotent stem cells (hiPSC). hiPSCs are derived by reprogramming somatic cells (e.g., skin) to a pluripotent state using transcription factors expressed in ESCs.[27] In parallel, developmental biologists identified signals and mechanisms that direct cell fate.[28] Timed activation or repression of these signals, combined with control of the extracellular environment have become the guiding principle for directing stem cells to differentiate to organ-specific cell lineages.

Together, these developments enabled research leading to seminal publications in the field. First in 2008, with the generation of cerebral cortex organoids in 3D from mESCs in the Sasai laboratory ,[29] and in 2009 with intestinal organoids from mouse ASCs by Clevers' group.[7] These papers heralded the age of stem cell-based organoid research. Since then, a plethora of tissue types have been generated as organoids. These include organoids from different regions of the gut, as well as from other endodermal organs such as liver and pancreas, mesodermal organs including the kidney and endometrium, and ectodermal-derived tissues, for example, areas of the brain and the retina, among others. Organoids have not only been developed from mouse and human, but also from domestic animals, reptiles, and fish to study species differences, disease mechanisms as well as forming a basis for bioproduction. Recently, attention has also focused on stem cell-based embryo models (e.g., gastruloids, blastoids, embryoids), in which aspects of germ layer formation and subsequent embryo development are replicated.[30–32] This work was further advanced by the recently reported development of human post-implantation embryo models from PSCs.[33–35] Indeed, in vitro embryo models were described as one of the seven technologies to watch in 2023 by the journal Nature.[36] Taken together, the field has established that i) ASCs and pluripotent stem cells (PSCs) can differentiate in culture to many different cell types in 3D in response to chemical-, macromolecular-, cellular- and mechanical signals, ii) 3D cell culture often mimics in vivo tissues more closely than 2D in the spectrum of cell types formed and their interactions and hence can serve as preclinical models for drug testing and iii) organoid technology can be an enabling tool for clinical transplantation.

While organoid technology largely relies on 3D self-organization of stem cells, OoC was initially pioneered by biomaterial scientists and engineers with the primary goal of developing simple, high-throughput platforms that mimic tissue micro-architecture and physiological functions in a format suitable for drug screening and testing.[37] OoC technology started with cell culture applications in the early 2000s using perfused liver cultures in microfluidic devices.[38] Later, more complex lung-on-chip models were developed in Don Ingber's laboratory by co-cultivating primary lung alveolar and capillary cells on two sides of a porous mechanically stretchable membrane in a microfluidic device.[39] Following this breakthrough, other OoC models evolved, including those with organ functionalities of the liver, heart, and intestine, as well as barrier functions such as the blood-brain barrier (BBB) and in the kidney. Of note, much like organoids, most OoC systems mimic only some aspects of organ function and do not necessarily recapitulate in vivo histology. For example, the original lung-on-chip design featured two cell types, while a human lung has at least 58.[40,41] Nevertheless, in 2020, OoC technology took a major step towards preclinical practice with the US Food and Drug Administration signing collaborative agreements with Emulate Inc. and CN Bio to evaluate lung-on-chip devices.[42,43] A further boost for microphysiological systems collectively, including organoids and OoC, is projected as a result of the FDA Modernization Act, mentioned above. The bill gives drug sponsors the option to use scientifically rigorous, proven non-animal test methods including human-relevant methods such as cell-based assays, microphysiological systems, bio-printing or computer models. These may be acceptable as evidence in drug filing.

Here, we provide a meta-analysis of the global organoid and OoC research from 2011 onwards, when the first human organoid paper was published.[44] We retrieved more than 16 000 papers and analyzed them using an in-house purpose-built algorithm, along with manual data inspection to ensure that key research topics were included. Within the resulting publicly available dataset, we first systematized modeled organs and substructures in a hierarchical tree. Cell source, organoid types, research organisms, disease models, and preclinical/clinical translation were subsequently extracted, analyzed, and organized in comprehensive graphical representations. In addition, we examined the geographical distribution of research internationally, expressed as per capita output. Based on publications from the last three years, we depict current research trends and foci. Our principal findings were as follows: i) in the past decade, organoid and OoC literature has undergone extraordinarily strong annual growth of 41% and 50%, respectively, with 149 and 107 organs/substructures modeled as organoids and OoC, respectively; ii) Pioneering research in multiple sub-areas has led to preclinical applications modeling over 130 diseases that we categorized into 13 groups; iii) Human brain, intestine, and lung organoids were quickly implemented to study COVID-19 infection early in the pandemic, followed by airway and cardiovascular models, highlighting the versatility of organoids and their high "technology readiness level" for rapid use when needed; iv) While most early organoid research (2011-2014) used mouse cells, human organoids have rapidly superseded this cell source, now accounting for over 70% of research articles. Organoid and OoC models are increasingly also reported from organisms such as snakes, pets, and farm animals; v) The USA contributes the largest number of academic papers on organoids and OoC, with the European Research Area in second. After adjusting publication numbers to population, the Netherlands, Luxembourg, Switzerland, and Singapore are academically the most productive countries, while China and South Korea are rapidly expanding in terms of publication volume.

These are some of the insights our analysis has provided. The full data and code of the analysis made available here allow readers to investigate further research topics of interest.

2. Results

2.1. Overview of Academic Publications

Academic publications on organoids and OoC from 2011 onwards were collected from four major academic publication databases (EMBASE, PubMed, Scopus, Web of Science). In addition, preprint publications were collected from the bioRxiv database. Each academic publication was assigned to either "organoid," "tumor organoid," "OoC." or "ToC (representing tumor-on-chip)" corpora (Figure S1, Supporting Information). The "organoid" and "OoC" corpora were used for downstream analysis in this meta-analysis, while the "tumor organoid" and "ToC" corpora form the basis of a complementary analysis (Shoji et al., in preparation). We use the term "research articles" to refer to non-review publications, and "academic publications" to collectively refer to both non-review and review publications. The "review" and "non-review" classifications were made in the publishers/literature databases before retrieval, such that "research articles" in our corpora still include opinion articles. While our approach is based on computationally reading titles, keywords, and abstracts of academic publications, manual adjustments were performed as needed. For example, computational classifications were manually checked and corrected for infrequently studied organ models and organisms.

A major expansion in organoid and OoC publications occurred between 2011and 2022, with average annual increases of 41% and 50% respectively (Figure S1, Supporting Information). By comparison, publications on tumor research only increased by 5.3% annually in the same period (see supplementary data in the GitHub repository: https://www.github.com/jyshoji/text_analysis_organoids; https://doi.org/10.5281/zenodo.8138389). Preprint publications on organoids and OoC first emerged in 2014 and 2017, respectively, and have since grown annually by 158% and 126%. Among the research articles where a computational classification was made, 75% (30 research articles) of organoid models were mouse-derived in 2012, with the remaining (25%) human-based (Figure S2A, Supporting Information). By 2022, this had reversed with 22% (288 articles) and 74% (957 articles) being on mouse and humans respectively. In the same period, 1–5% of articles described organoids derived from other organisms (see below). In contrast, OoC has always predominantly used human cells (85–95% except for 2011; Figure S2A, Supporting Information). For organoids, publications mentioning iPSCs (hiPSCs) in the title or abstract increased steadily from 0% in 2012 to 35% in 2022, while the use of ESCs apparently remained stable during this period (4–9% after 2012) (Figure S2B, Supporting Information), although not all abstracts distinguished whether hiPSCs or ESCs were used. By contrast, the use of stem cells in OoC was first mentioned in 2013, reaching ≈10% of all research articles after 2017 (not shown), with hiPSCs now the most frequently used (Figure S2B, Supporting Information).

2.2. Models of Organs and Substructures

Following the nomenclature used by authors, we identified 149 and 107 organs/substructures modeled as organoids and OoC, respectively. These were classified into hierarchical categories (Figures S3–S5 and Tables S1 and S2, Supporting Information) following anatomical structures and substructures in the body, with adaptations to accommodate previously published organoid classifications.[8,45] Although retinal organoids are often referred to as neural organoids,[46] we classified them under ocular organoids as this facilitated our later analysis of disease models. **Figure 1** (organoids) and **Figure 2** (OoC) depict the first and second levels of the hierarchical organ/substructure categories that were identified by the classification, including an extra level for neural and gastrointestinal organs.

2.2.1. Organoid Models

Gastrointestinal organoids are the research subarea with the highest publication count (Figure 1). This includes the second-level categories of intestine, stomach, esophagus, and gastroesophageal junction, with the intestine further sub-categorized into large and small intestine. Although intestinal organoids were among the first and most abundantly reported,[7] the publication count showed only a moderate increase in the past three years suggesting that the subarea is reaching maturity while transitioning from being mainly focused on research development to use as a tool in translational applications. Nevertheless, new subareas continue to emerge (Figure S3, Supporting Information), such as human and mouse duodenal organoids[47,48] and caecum organoids in mouse[49] and rabbits.[50,51]

Neural organoids account for the second largest publication volume and show considerable upward trends in the past three years, particularly regarding brain organoids. This increase is driven largely by the establishment of forebrain organoids, followed by diversification into other human brain substructures such as the cerebellum,[52–54] midbrain,[55] striatum,[56] hypothalamus,[57,58] and thalamus.[59] Neural organoids also include trending models such as the BBB,[60] choroid plexus,[61] dorsal root ganglia,[62,63] neuromuscular junctions,[64] neurovascular units,[65] the neuroimmune system,[66] and spinal cord.[67] In addition to addressing an obvious need for modeling the most complex organ of the human body, the convergence of several technologies and disease states have contributed to the expansion of neural organoid studies: i) the development of cerebral cortical organoids;[29] ii) availability of commercial kits for differentiating hPSCs into neural cells; iii) robust protocols for generating cerebral organoids from hiPSC,[68] enabling the use of patient-derived material, and iv) the Zika virus outbreak between 2015 and 2016 in the Americas that prompted brain organoid use to model viral infection and study microcephaly in babies of mothers infected in pregnancy (reviewed in[69,70]). Neural organoids were also used to model SARS-CoV-2 infections, accounting for a similar number of articles as that modeling Alzheimer's disease (≈4%) in 2020. The recent report showing circuit integration of human neural organoids transplanted in rat brains will likely further enhance interest in the field.[71]

Hepatic, pancreatic, and biliary (HPB) organoids are the third most studied subarea, with pancreatic and biliary organoids showing recent increases in publication counts (Figure S3, Supporting Information), driven by research on human models of islets and bile duct (see recent reviews[72,73]). Respiratory organoid publications have, not unsurprisingly, increased in the

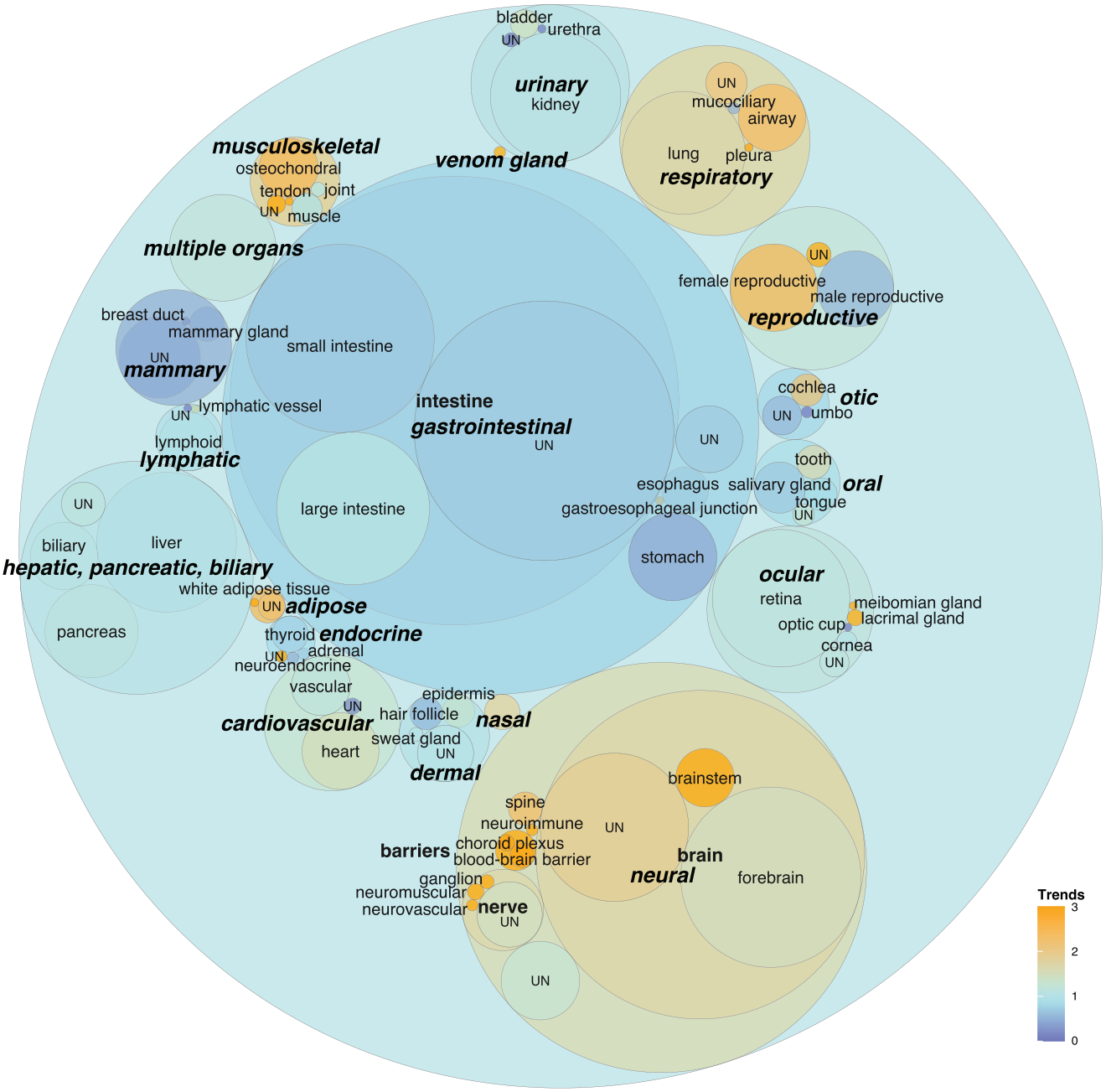


Figure 1. Publication trends of organs and substructures modeled by organoids. Circular packing graph showing two-level hierarchical classifications of organs and substructures modeled by organoids. Only research articles in which organoids were computationally determined were included in the plot (5714 research articles out of 12 375 academic publications). Gastrointestinal and neural organ models include an extra level of categories. Sphere size reflects the number of research articles on the corresponding organ model. The color shows publication trends as calculated by relative increases in the number of research articles in recent years (from *2020* onwards) compared to the earlier period (2011–2019 inclusive) for each organ/substructure, and then adjusted for the relative increase in the entire corpus. "UN" (i.e., unspecified) as a category represents papers classified as studying the corresponding upper-level organoid category without computer-recognizable description of the specific lower-level categories. Note that spheres representing neural and gastrointestinal categories are relatively enlarged due to housing an extra level of lower categories.

past three years, spurred by the need for human models for SARS-CoV-2 infection[74] (Figure 1, see also Figure S10, Supporting Information). Another subarea with notable recent activity is that of ocular organoids, where human models of corneal limbus,[75] lacrimal glands,[76] and meibomian glands[77] have been reported. Research on musculoskeletal organoids has also shown an upward publication trend, with key new developments including reports on cartilage organoids in human[78] and farm animals,[79,80] human tendon organoids,[81] as well as human synovial organoids[82] and synovial organoid-on-chip[83]

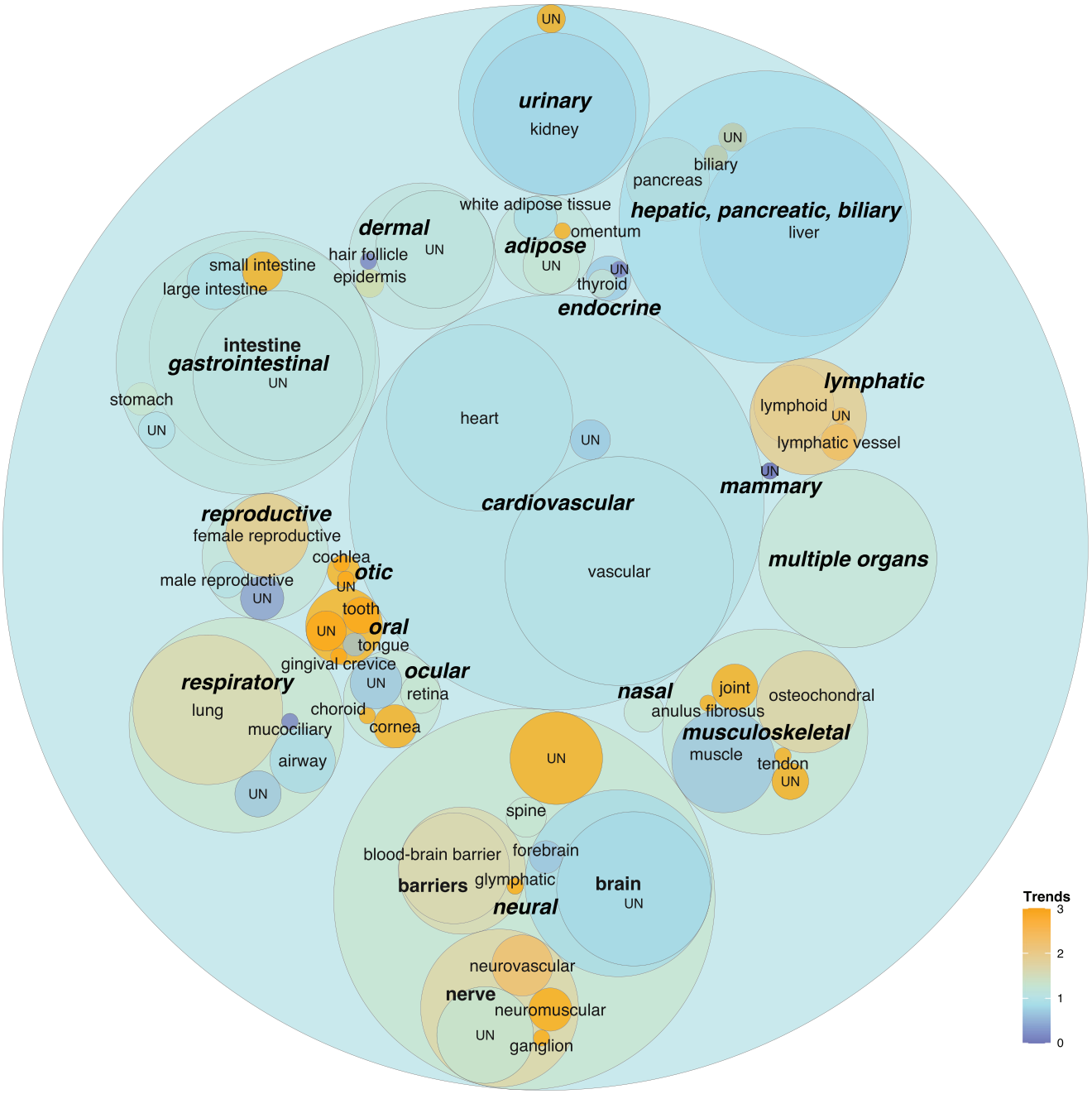


Figure 2. Publication trends of organs and substructures modeled by OoC. Circular packing graph showing two-level hierarchical classifications of organs and substructures modeled by OoC. Only research articles (i.e., excluding reviews) in which researched OoC models were computationally determined were included in the plot (1515 research articles out of *3818* academic publications). Colors reflecting publication trends were calculated as described in Figure 1.

(Figure S3, Supporting Information). The upward publication trend of organoids modeling the female reproductive system is mostly due to reports on human endometrial organoids, and new human cervical organoid models (reviewed in[84]) (Figure S3, Supporting Information). Human organoids of the reproductive system reflect the importance of reproductive organoids for drug development, modeling disease, and detecting reproductive toxicity due to the intrinsic differences between human and animal reproductive systems and difficulty in accessing human primary tissue.[85,86] However, animal reproductive models are also being developed, e.g., mouse vaginal organoids.[87]

The analysis of 1018 preprints reporting organoid models of organs and substructures shows that a preprint publication strategy has been broadly adopted (Figure S6, Supporting Information). As observed with peer-reviewed publications, research subareas with marked recent increases in preprint publication

counts are respiratory and neural organoids. Noteworthy research subareas include lymphatic (lymphoid), nasal, nervous, cardiovascular, respiratory, endocrine (thyroid), otic (cochlea), oral (tongue and tooth), hair follicle, and esophageal organoids.

2.2.2. OoC Models

OoC platforms, which nearly always contain human cells, differ from organoid research not only in the predominant organs and substructures modeled (Figure 2, Figure S4, Supporting Information), but also that including microfluidics allows the study of cell barrier functions, cell interfaces, perfusion, and mechanical properties of tissues as well as aspects of the immune/tissue interface. The recent scope of OoC technology for human disease modeling, drug testing, and toxicology thus includes subareas with: i) complex physiological structures (e.g., tooth/periodontium, osteochondral/joints, epidermis, female reproductive system including endometrium and placenta, cochlea); ii) liquid-producing/transporting structures (e.g., blood vessels, lymphatic vessels, biliary ducts); iii) barrier structures (in particular the BBB) and iv) structures with emerging clinical applications (e.g., cornea, retina).

Cardiovascular OoC is the research subarea with the highest overall publication count, reflecting their potential to model cardiovascular disease phenotypes and their value in detecting cardiotoxicity. OoC not only offers technical options for studying heart muscle and support cells (e.g., fibroblasts), but also the endothelial lining of cardiac vessels, the perivascular niche[88,89] and the dorsal aorta[90] in cardiovascular disease and drug responses (Figure S4, Supporting Information). Analogous to the organoid corpus, OoC models in the categories "neural" and "HPB" are the second and third most studied groups. Neural OoC offer several benefits, including: i) control over cell self-assembly, size, and connectivity in neural circuits;[91] ii) the possibility to integrate electrodes to stimulate and measure neural circuits;[92] and iii) a layout for modeling barrier functions. Hence, neurovascular OoC models to investigate the BBB, comprising a highly selective layer of endothelial cells protecting neurons from potentially harmful substances circulating in blood, is a trending neural subarea. Other emerging subareas include cortico-hippocampal networks to study neuropsychiatric diseases,[93] as well as models of the glymphatic waste clearance pathway,[94] neuromuscular junctions to study muscle denervation[95] and the spinal cord for therapeutics.[96]

Likewise, the high research output in HPB OoC models reflects the liver's key role in (drug) metabolism, and the crucial roles of both pancreatic islets and liver in energy metabolism, along with a high clinical interest in diseases such as liver failure and diabetes. Although liver OoC does not have the physiological and metabolic complexity of a liver, they are extensively used and have been validated as key platforms for disease modeling, drug development, and toxicity assays.[97,98] Notably, bile duct OoC with tubular architecture and barrier functionality were recently reported and are expected to benefit disease modeling.[99] Interestingly, gastrointestinal OoC models contribute to just 6% of publications (cf. 27% in organoids), likely because organoid models have proven sufficiently predictive, in particular for screening applications. However (small) intestine, duodenum, and colon OoC were recently described for studying central/intestinal barrier function, host–microbe interactions and assessing drug metabolism.[100,101] Despite lung-on-chip being among the first OoC reported, respiratory OoC models do not predominate in publications. However, they do simulate key aspects of in vivo lung microenvironment and function, with cyclic mechanical stimulation representing stretch forces in the lung alveoli; they are showing promising advances in testing drug safety and effectiveness.[102] As in organoid research, recent interest in respiratory OoC was also driven by the need for human models for SARS-CoV-2 infection.[103] Kidney OoC in the urinary subgroup model the basic structure and function of the kidney and promise to deliver high-fidelity methods for drug toxicity screening.[104] Musculoskeletal OoC encompassing bone and cartilage models show increases in publication counts, in addition to emerging synovium OoC,[83] annulus fibrosus OoC to model intervertebral disc degeneration,[105] and an anterior cruciate ligament model which is under development.[106] OoC technology is also used to study multiple aspects of the (human) female reproductive system such as modeling ovarian follicle development, the menstrual cycle, decidualization, implantation and placentation, maternal-fetal crosstalk, infertility, and reproductive diseases.[107–110] In addition, testicular OoC have been generated from mouse,[111] human,[112] and a non-human primate[113] to study spermatogenesis.

2.2.3. Models of Early Development

An organoid subarea recently showing increased activity is modeling early mouse and human embryogenesis as blastoids, embryoids, and gastruloids (Figure S5, Supporting Information). These stem cell-based embryo models recapitulate aspects of pre-implantation (blastoids) and post-implantation (gastruloids, embryoids) development up to the early stages of organ formation. Blastoids are PSC-derived blastocyst-like structures that exhibit features of pre-implantation embryos: the inner cell mass, blastocoelic cavity, and trophectoderm.[114] They were first derived from mESCs[115] but work producing human blastoids soon followed.[116] More recently, prolonged (15 d) culture of cynomolgus monkey blastoids derived from naïve ESCs resulted in the development of the embryonic disk stage with yolk sac elements and a primitive streak apparently evident. When these blastoids were transplanted into surrogate mothers, they implanted in the uterine wall and, for a limited period, released pregnancy hormones progesterone and chorionic gonadotropin, both signs of pregnancy.[117] Mouse embryoids show even more advanced developmental features: mouse embryoids for example complete gastrulation and develop beyond neurulation to the equivalent of embryonic day 8.5 post-fertilization.[31,32] Extension of this work to naïve human PSCs showed embryoid development including the formation of extraembryonic and yolk sac-like cells when certain genes were overexpressed.[35] While further work is needed to understand, reproduce and explore the potential and risks of ESC-derived embryo models, governance and regulatory frameworks will need to keep pace.[118]

Gastruloids are also PSC-derived structures that represent aspects of post-implantation development.[32,119–122] Gastruloids are sometimes referred to as "non-intact embryos" since, unlike

blastoids,[123,124] they appear unable to form cells of extraembryonic tissues that give rise to the placenta, so cannot become a complete conceptus. Gastruloid development can be tailored, with various reports describing: i) somitogenesis,[125–127] ii) heart field formation[121] and iii) neurulation.[32] In parallel to these studies on embryo models, extraembryonic components have been also engineered such as human placenta-like organoids,[128] as well as human extraembryonic cells including yolk sac-like cells[129] and trophectoderm lineages.[130,131] A noteworthy development in this area is a spatial multiomics analysis of post-implantation trophoblast differentiation at the maternal-fetal interface, which was based on in vivo samples and in vitro models including primary trophoblast organoids.[132] While most of the above studies focus on forming embryonic and extraembryonic structures, gastruloid utility in toxicology was recently described.[133] Of note, gastruloid-like structures (pescoids) have also been described in zebrafish,[134] and in the cave fish *Astyanax mexicanus*, the latter to study how early embryogenesis affects the emergence of sighted and blind eco-morphotypes.[135]

Figure S5A,B (Supporting Information) summarizes research on models for early development using human- or mouse PSCs. Currently, there are more publications in this subarea using human rather than mouse cells, although mouse models remain well represented in the literature. Pre- and peri-implantation structures have mostly been modeled as self-organizing organoids, although OoC is now contributing to this research subarea (Figure S5C, Supporting Information). For example, OoC models of the placental barrier between maternal and fetal cells have been reported for studying bacterial infection,[136,137] trophoblast invasion,[138] pre-eclampsia,[139] and for (reproductive) toxicology[140–142] including nanoparticle risk assessment.[143,144]

2.3. Multiorgan Models

In the organoid and the OoC corpora, 4% and 7% of research articles, respectively, were computationally classified as "multiorgan," i.e., containing multiple organ models (**Figure 3**, Figure S7 and Table S3, Supporting Information). The paper reporting the highest combination of organ models was from Skardal et al., where an OoC platform containing liver, heart, lung, vascular, testis, colon, and brain tissues was described and tested for net drug responses.[145] Gastrointestinal and HPB organoid models were already widely used prior to 2020, but more recently organoid and OoC models with combinations of cardiovascular, neural, and respiratory tissues have been described.

2.3.1. Multiorgan Organoid Models and Assembloids

The most frequently reported combinations of organ models to date are colon and small intestine (Figure S7, Supporting Information). Other common combinations of organoid terms include bile duct-liver-pancreas, intestine-liver, intestine-lung, and liver-lung. However, in most cases, they are collectively used to study non-organ-specific processes (e.g., new technology testing[146] or viral tropism[147]), rather than addressing the functional interplay between organs (e.g., the gut-liver axis). An important development was the creation of organoids comprised of multiple distinctly patterned organoids or the inclusion of additional cell types, collectively referred to as "assembloids." These composite organoids were initially made by assembling regionalized brain organoids. Examples of neural assembloids include cortico-striatal and cortico-spinal-motor combinations.[148] Other noteworthy examples include human endometrium, assembling gland-like organoids and primary stromal cells,[149] a model for human hepato-biliary-pancreatic organogenesis by combining anterior and posterior gut spheroids,[150] liver assembloids containing human endothelial cells and mouse liver organoids,[151] human tooth organoids created as mesenchymal-epithelial composites,[152] and human bladder organoids with a connective tissue layer made of fibroblasts and endothelial cells.[153] A particularly noteworthy example of assembloid potential is recent studies using assembloid technology to develop mouse or human stem cell-derived integrated embryo models, containing both embryonic and extra-embryonic structures.[30–32,35]

2.3.2. Multiorgan OoC Models

In OoC research, the most frequently combined models are the intestine and liver (Figure 3). Research articles using this combination addressed the functional interplay between the two organs, such as the gut-liver axis,[154] or gut absorption and hepatic metabolism of drugs/metabolites.[155] Other common combinations include heart-liver to address the effects of hepatic drug metabolism on the heart,[156,157] kidney-liver to mimic renal excretion and hepatic metabolism,[158] and lung-liver to mimic the effects of aerosol inhalation on the liver.[159] Overall, the functional interplay among organs is more commonly studied with OoC than organoid models since microfluidic channels allow the exchange of chemical compounds and other signals between tissues. Many of these OoC platforms, however, remain simple mimics of organs and typically contain single rather than multiple cell types as in an organoid.

2.4. Organoids-on-Chip

One approach to enhance physiological complexity and potential biological relevance of OoC is to include organoids rather than single cell types (organoid-on-chip). Another is to use organoids to expand cells and/or induce differentiation to specific cell fates (e.g., organoid-derived epithelium) for use in OoC.[160] Organoids and OoC have been discussed collectively in more than 200 primary research articles with most organoid-on-chip reports dating from the past few years (Figure S8, Supporting Information).

The distribution of tissues described as organoids-on-chip (including OoC models with cells isolated from organoids) largely mirrors that of organoid models, with intestinal and brain organoids-on-chip being the most common. An important recent development was the establishment of anaerobic human intestine-on-chip using organoid-derived epithelial cells as this enables studying gut–microbiota interactions at physiologically relevant levels of microbial diversity, including obligate anaerobic bacteria.[161,162] In addition, human intestinal organoid-on-chip models are used to study complex (patho)physiological processes, such as SARS-CoV-2 infections,[163] effects of human

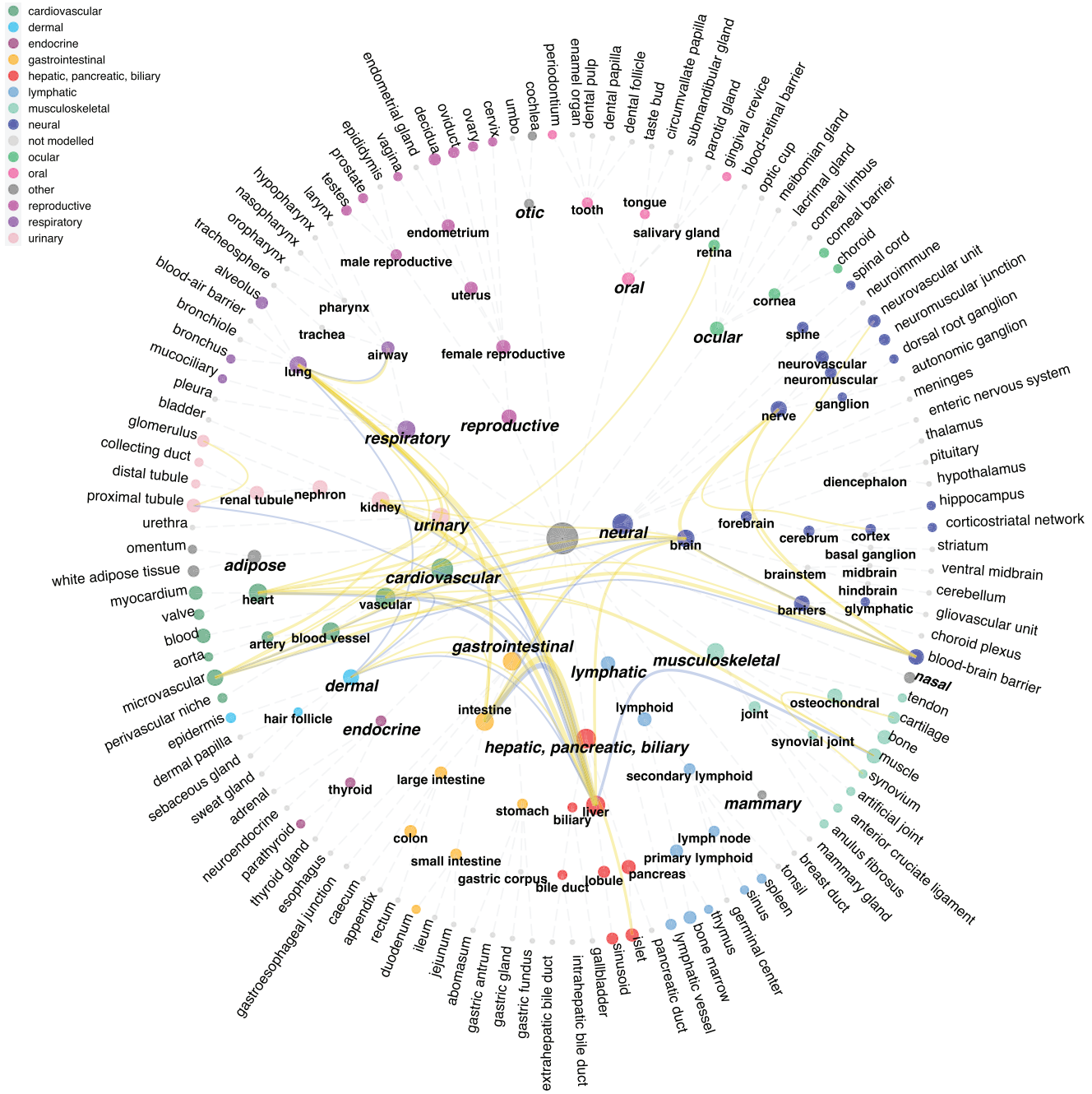


Figure 3. Organs and substructures collectively researched by OoC. The dendrogram shows hierarchically categorized organs and substructures that are modeled by OoC, with edge bundling to show collectively researched organs/substructures. Spheres representing organs/substructures are sized according to publication counts and color-coded according to level 1 organ categories. Spheres corresponding to substructures that are only modeled by organoids but not by OoC are colored in light grey. Curved lines connect organs/substructures that are mentioned in combination in OoC in research articles, and are only drawn for organ/substructure combinations that appear in 2 or more articles. The colors of the curved lines indicate publication year (blue: 2010–2019; orange: 2020 onwards), with their width reflecting publication counts. The widest line (intestine–liver in orange) corresponds to 13 research articles.

milk oligosaccharides on gut microbiota and intestinal barrier function,[164] transcriptional and phenotypic changes to intestinal cells in inflammatory bowel disease[165] and environmental enteric dysfunction.[166] Brain organoid-on-chip models have been used to study multiple conditions including the effects of breast cancer-derived exosomes on human neurodevelopment,[167] and neuroinflammation in humans upon exposure to an opioid receptor agonist.[168] Human brain organoids-on-chip have also been explored as a low-cost platform to facilitate long-term in situ live-cell imaging.[169] Other noteworthy studies include human

kidney organoid-on-chip that showed improved maturation[170] and human retinal organoid-on-chip to test viral vectors.[171]

In addition, some articles have reported multiple-organoids-on-chip platforms. Besides those mentioned above,[145] human organoids-on-chip including liver, heart, lung, endothelium, brain, and testes have been developed to mimic the activation of a chemotherapeutic prodrug by the liver and subsequent flow through the microfluidic channels allowed the effects of the active form of the drug to be studied in other (downstream) organs.[172] Similarly, a human liver-heart organoids-on-chip model was used to examine the effects of liver metabolism on an antidepressant prodrug on the heart,[157] and human thyroid-liver organoids-on-chip were developed to model homeostasis and chemically induced perturbation of thyroid hormones.[173] In addition, a liver-islet organoids-on-chip was used to study insulin secretion and glucose utilization in context of diabetes,[174] and a kidney-liver platform to explore the therapeutic potential of mesenchymal stromal cell-derived extracellular vesicles.[175] Moreover, an assembloid-on-chip platform was recently developed, whereby hiPSC-derived cortical, hippocampal, and thalamic organoids were assembled on a microfluidic device in a controlled, flexible, and high-throughput manner, with the aim of facilitating brain disease modeling.[176]

2.5. Comparing Commonly Used Models for Different Organs and Disease Groups

Both organoids and OoC are used for disease modeling. Overall, in the gastrointestinal, mammary, neural, ocular and oral subareas, diseases are mostly modeled as organoids, whereas cardiovascular, lymphatic and musculoskeletal diseases are frequently studied as OoC (**Figure 4**, Figure S9 and Table S4, Supporting Information). The choice of model obviously depends on the disease group being studied and on the specific research question. For example, OoC is frequently chosen for drug development/testing, pharmacokinetics/dynamics, and toxicology. Model preference in categorized disease groups is discussed below.

2.5.1. Main Disease Groups

To identify platform preference for disease modeling, we first selected the main disease categories identified in the analyzed publications, and subsequently created disease-specific subgroups. This allowed a stratified overview of model choice in a particular disease group. Neurological, neurodegenerative, and mental disorders are predominantly modeled using neural organoids (Figure 4 and Figure S9, Supporting Information), although a number of OoC for specific neural disease conditions are emerging.[177] Studying neurological diseases, including neurodevelopmental disorders, is a challenging task due to brain complexity and limited accessibility. hiPSC-derived brain organoids provide a new tool for investigating the intricate pathogenesis of developmental abnormalities not otherwise accessible, as these models exhibit similar structural organization features and cell type diversity as the developing human brain.[178,179] Neurodevelopmental disorders being studied include autism spectrum disorder,[180,181] as well as genetic disorders autosomal recessive primary microcephaly,[68] Rett[182] and Down's[183,184] syndromes (see the "genetic disorder" group in the figure), and others.[179] Microcephaly research shows a slow increase in publication count, but it nevertheless served to pioneer exploratory studies using brain organoids to mimic the developing human fetal brain and understand the cellular origin of (maternal) Zika-induced microcephaly during the epidemic.[70,185,186] As protocols to generate human cerebral organoids from hiPSC emerged,[68] models of Alzheimer's disease have been developed (reviewed in[187]), while generating human midbrain organoids (Figure S3, Supporting Information) enhanced in vitro studies of Parkinson's disease. Other neurodegenerative diseases modeled with organoids include frontotemporal dementia,[188] and Huntington´s disease.[189] Notably, numerous research articles use non-neural organoids to study the effects of neurological and mental disorders on other organs. Examples include gastrointestinal dysfunction as an early indicator of Parkinson's disease,[190] and studying the link between zinc deficiency, gut microbiota, and autism spectrum disorder using (porcine) gastrointestinal organoids.[191]

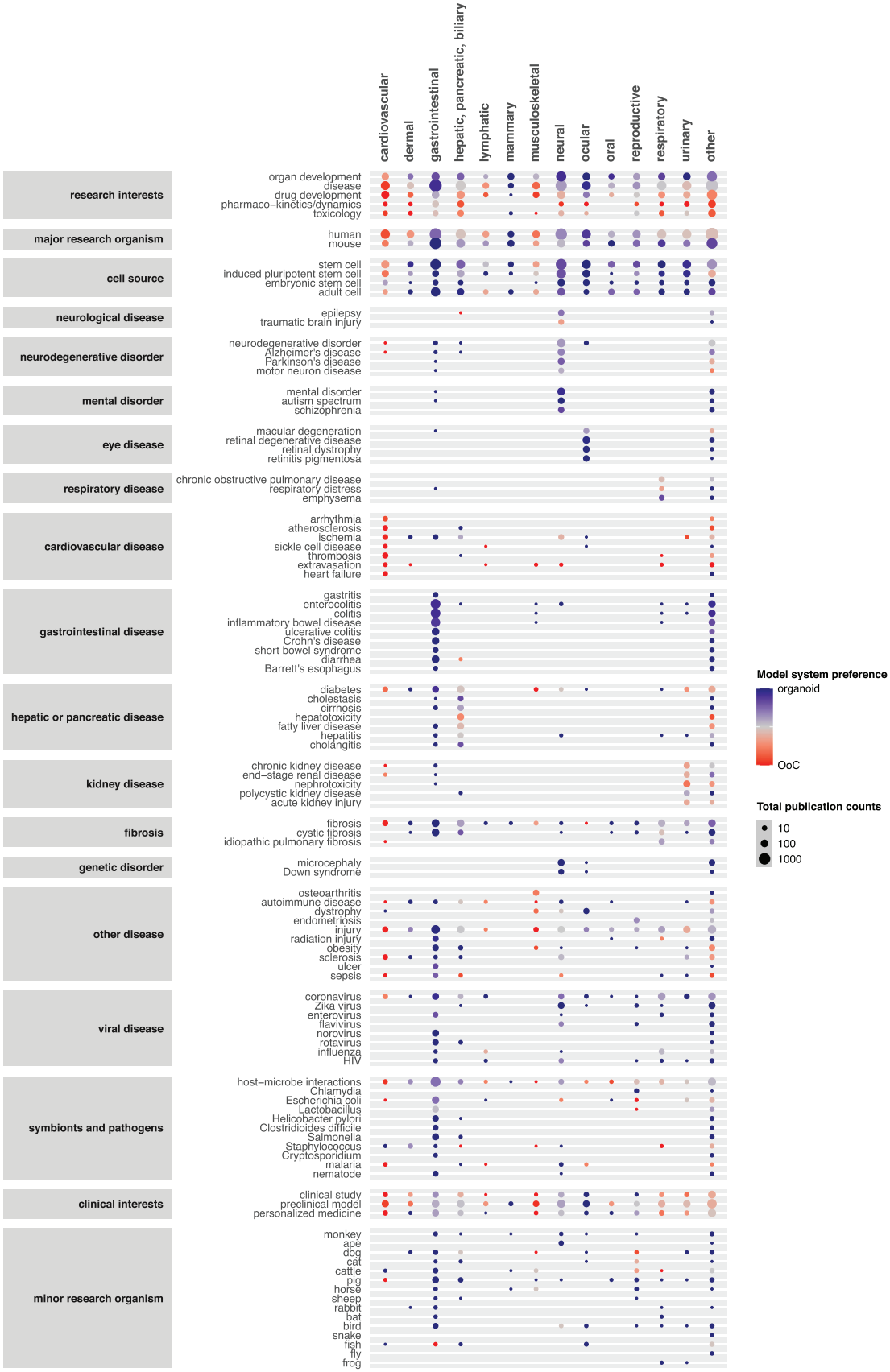
OoC for specific brain regions and the BBB have been used to model both normal and pathophysiological conditions (reviewed in[177]). Microfluidics-based models[192] have shown that active fluid flow is necessary to develop a proper endothelial barrier as in the BBB. Likewise, dynamic flow is necessary for efficient barrier function and the highly dynamic in vivo microenvironment in the neural vascular unit.[177] While BBB OoC models predominantly are used to test permeability to different drugs and toxins,[193] there is increasing interest in modeling various neurological diseases[192] such as Alzheimer's[194] and Parkinson's diseases[195] as well as amyotrophic lateral sclerosis.[196] Traumatic brain injury has been investigated using both organoids[197] and neural OoC, with the latter incorporating microelectrodes into the chip to measure the electrical action potential patterns of the neuronal networks.[198,199]

Eye diseases, including macular degeneration and retinal dystrophy, are predominantly modeled as ocular organoids; this reflects to some extent clinical interest in using them to replace dysfunctional retinal cells. Ocular OoC are used to study eye diseases, especially for replicating the outer blood-retinal barrier where functional impairment contributes to vision loss in age-related macular degeneration.[200]

Respiratory diseases are studied using both organoids and OoC (Figure 4 and Figure S9, Supporting Information). Organoids are for example used to investigate chronic obstructive pulmonary disease (COPD).[201] Examples for OoC models include COPD,[202] pulmonary edema,[203] and lung inflammation.[204]

Cardiovascular diseases are predominantly studied on OoC platforms, with upward publication trends in arrhythmia, atherosclerosis, heart failure, and ischemia. Organoid (or cardioid) models on the other hand, tend to be used to study congenital heart defects, ischemia, non-ischemic cardiomyopathy, and fibrosis.[205] These studies are all based on hPSCs since the adult mammalian heart is not believed to contain an endogenous stem cell population.[206]

Gastrointestinal organoids have transformed research on gastric and intestinal physiology during homeostasis and



disease.[207] Gastrointestinal diseases now represent the most extensively studied disease groups using organoid models, with notably rapid increases in publication counts on inflammatory bowel diseases (i.e., Crohn's disease and ulcerative colitis) (Figure S9, Supporting Information). Necrotizing enterocolitis is studied using mouse liver[208] and brain[209] organoids since it affects both organs. OoC models are used less frequently but the number of publications is increasing, in part because they are a convenient platform to study host-microbe interactions[101,161,162] and inflammatory bowel disease.[165]

Although organoid and OoC models for the liver are technically advancing, key challenges remain in recapitulating the structural and functional complexity of the liver, most notably identifying formats that reflect the complex interplay among the main liver cell types,[210] including liver "zonation" which is key to its metabolic activity and for several diseases.[211] Among conditions listed under the "hepatic or pancreatic disease" group, liver organoids are used to study impaired liver function, with upward trends in publication counts for cirrhosis, hepatotoxicity (including drug-induced liver injury), steatosis (fatty liver disease), and hepatitis. A notable recent study used human CRISPR/Cas9-engineered fetal liver organoids representing three different triggers for liver steatosis to screen for drug candidates and identify steatosis mediators.[212] Hepatotoxicity[213] and steatosis[214] are also studied in liver OoC, while diabetes is studied using multiple organoid and OoC models, reflecting the broad effects of the disease on the body.[215] The main application of pancreatic islet organoids in diabetes research is to develop insulin-producing beta-cells for physiological studies and for future transplantation in regenerative medicine.[216] In contrast, pancreatic/islet OoC is primarily used for modeling preclinical diabetes-related conditions, in drug development, for studying islet- or stem cell-derived islet-like structure function[217] and for investigating metabolic crosstalk.[174,218] In addition, OoC models for the glomerulus and vasculature are used to study diabetic nephropathy[219] and blood flow in diabetic patients,[220] respectively. Intestinal organoids are also frequently used for diabetes research where, for example, the role of the intestine in glucose metabolism is being investigated as a route to promote insulin secretion.[221] OoC is convenient platforms for studying dialogue between organs, such as the gut-liver axis,[154] and pancreas-muscle-[222] or liver-adipose tissue[223] interactions in diabetes.

The kidney is crucial for controlling the volume and electrolyte concentrations of body fluids and clearing metabolic waste through the glomerular filtration barrier. Thus, kidney models benefit from including microfluidics that allow the integration of fluid flow and filter structures. In addition, red blood cell deformability during end-stage kidney disease has been modeled in OoC.[224] The last three years have seen a considerable increase in the number of research articles using organoids to address kidney conditions, including chronic kidney disease, end-stage renal disease, polycystic kidney disease, and acute kidney injury.[225–227]

Organoids are broadly used to study mechanisms of fibrosis, reflecting the paucity of predictive preclinical animal models for this condition in humans.[228] For example, human gastrointestinal organoids are the predominant model for investigating cystic fibrosis (CF), and have become established as a prognostic tool for identifying which patients will respond to CF modulators in particular the recently approved Trikafta.[229] This model has now been complemented by organoids from the human nasal epithelial stem cells.[230] Recent increases in publication counts for studies on CF using pancreatic/biliary organoids reflect the functional impairment of these organs in this disease,[231,232] and in fibrosis.

Among the disease groups listed under "other diseases," osteoarthritis is increasingly studied using both organoids[233] and OoC (Figure S9, Supporting Information), as OoC models permit to incorporate finely controlled mechanical actuators which are important for in vitro disease modeling of osteoarthritis.[234] For example, an OoC model of the knee joint was recently established, in which human bone-marrow-derived mesenchymal stromal cells were used to create an osteochondral complex and synovial-like fibrous tissue, with the aim of test potential treatments for osteoarthritis.[235]

Notably, OoC platforms are also used to co-culture several cell types to mimic the interplay between organs and tissues in physiological and pathological conditions. Examples include nerve-vasculature-bone to model innervated, vascularized bone,[236] synovium-cartilage separated by a synovial fluid channel to model monocyte extravasation to the synovium,[237] osteochondral complex-synovial-like fibrous tissue-adipose for disease modeling and drug testing,[238] and macrophage-mesenchymal stromal cells under osteogenic differentiation conditions to model immunocompetent bone.[239] Another rapidly developing research subarea is endometriosis with reproductive organoids. These studies are developing a holistic view of the endometriosis microenvironment in both affected and unaffected individuals, with the aim to contribute to the development of future treatments and diagnoses.[240,241]

2.5.2. Viral Infections

Aside from using human brain organoids to mimic Zika-induced microcephaly as previously discussed, another particularly noteworthy development was the rapid mobilization of organoid technology in 2020 in response to the COVID-19 pandemic,[74] caused by the SARS-CoV-2 virus (Figure S10, Supporting Information). Even before the pandemic, gastrointestinal organoids were used to study coronaviruses such as porcine epidemic diarrhea virus[242,243] and Middle East respiratory syndrome coronavirus.[244] After the COVID-19 outbreak, over 30 research

Figure 4. Model system preference for organ models and research topics. The matrix shows correlation between organ model groups (in X-axis) and selected research topics (in Y-axis), along with model system preference for research topics. Sphere size reflects the number of research articles in the organ model groups that mention the respective research topics. Sphere color reflects whether the combinations of research topics and organ models are more frequently investigated with organoid or OoC models. Specifically, the color was determined by the ratio of the proportion of research articles for each combination between the two corpora.

articles were published in 2020 using gastrointestinal, HPB, brain, and lung organoids. The second year of the pandemic (2021) saw a further increase in published research articles (>80) with increases in studies using gastrointestinal and lung models, along with cardiovascular, ocular, airway, and kidney organoids. The rapid implementation of human organoids was in part because of structural differences and poor affinity of the mouse ACE2 receptor to SARS-CoV-2 virus and thus inefficient infection in mice. Transgenic mice expressing human ACE2 at the time of the COVID-19 outbreak were not readily available and SARS-CoV-2 susceptible animal models such as hamsters (*Mesocricetus auratus*) and ferrets (*Mustela furo*) as well as nonhuman primates housed in BSL-3 facilities were limited. Hence, the exploration of human organoids as a possible alternative was rapidly initiated. Although OoC is less frequently used to study SARS-CoV-2 infections, they have been used to investigate crosstalk between different lung regions using a multi-compartment platform mimicking the nasal passage, the mid-bronchial airway region, and the deep acinar region.[245] Of note, OoC is also used to study strain-dependent virulence, cytokine production, and the recruitment of circulating immune cells.[246] The number of research articles using respiratory organoids to study influenza also showed a marked increase in 2022 (seven articles, compared to two in 2020 and one in 2021), possibly reflecting technical advances in generating these organoids following the COVID-19 pandemic.

Last, another infectious virus increasingly studied with organoids is norovirus (Figure S9, Supporting Information), a major cause of foodborne gastroenteritis. Human gastrointestinal organoids have enabled study of norovirus replication and susceptibility, and to address questions on innate immunity to human norovirus.[247]

2.5.3. Symbionts and Pathogens

Organoids and OoC are increasingly used to investigate "symbionts and pathogens," which include a range of mutualistic or antagonistic host-microbe interactions. The research on "host-microbe interactions" as a whole centers on gastrointestinal models where intestinal bacteria, including *Escherichia coli* and *Lactobacillus* species, are increasingly studied, reflecting the central role that microbiota plays in gut physiology, as well as in other organs through metabolites originating from the interactions.[248] A particularly noteworthy infectious disease area in gastrointestinal organoid research is nematodes. These parasitic worms have colonized a quarter of the world's human population and most grazing livestock. The reductionist nature of organoids allows the dissection of individual effects of these parasites on the gastrointestinal epithelium and modeling the life cycle of nematodes as well as the host response.[207,249]

Other models for host–microbe interactions include human and mouse reproductive organoids to study *Chlamydia* infections,[250] as well as human neural organoids[251] and vascular OoC to study malaria.[252] An emerging research topic on host-microbe interactions using neural organoids is the gut-microbiota-brain axis,[253–255] which refers to the network of connections that allow bidirectional communication between gut microbiota and the brain that can affect neural development and may contribute to brain disorders.[256]

2.5.4. Toward Clinical Trials

The term "clinical study" in publication abstracts is increasingly mentioned in neural and gastrointestinal organoid research (Figure S9, Supporting Information). This predominantly refers to using organoids from patient biopsies or exploring organoids carrying specific mutations for personalized drug testing (e.g., CF). Of the 62 nontherapeutic and 19 therapeutic clinical trials using hPSCs globally,[257] there are four PSC-derived 3D cellular structures entering clinical trials to date. These are: i) hESC-derived beta cell organoids using two different cell lines and approaches,[258–261] ii) hiPSC-derived retinal pigment epithelium sheets for age-related macular degeneration,[262] iii) hiPSC-derived corneal sheets to recover vision in stem cell-deficient human eyes[263,264] and iv) hiPSC-derived cardiomyocyte spheroids for patients with advanced heart failure.[265] Additionally, there are two clinical trials transplanting organoids generated from patient-derived (adult) stem cells, namely the transplantation of autologous stem cells derived from salivary gland organoids after radiation therapy of head-and-neck cancer,[266] and the transplantation of autologous intestinal organoids from the colonic mucosa in patients with ulcerative colitis.[267] Hence, with a few notable exceptions, the clinical use of organoid and OoC technology is still largely limited to exploring i) the potential for studying diseases preclinically, ii) the potential for exploring and personalizing (stratified) treatment, and iii) developing technological tool kits for future transplantations.

2.5.5. Other Research Organisms

OoC and, in particular, organoid models have been generated from a range of organisms other than human and mouse (Figure 4 and **Table 1**). For these, five major research interests can be identified: i) animal alternatives as specific benchmark research models such as for drug testing where animal data can be directly correlated to data obtained from organoids/OoC, ii) models to map physiological differences among species, iii) models for environmental toxicity testing, iv) disease modeling for the welfare of pet animals, and v) health and productivity of farm animals. Overall, gastrointestinal organoids have been derived from the widest range of organisms (Figure 4), followed by HPB organoids where liver organoids for example are being used for toxicology tests in fish[268,269] and disease modeling in pet animals.[270,271] Particularly noteworthy studies are ape/monkey brain organoids to understand the evolutionary development of the human brain. For example, Benito-Kwiecinski et al.[272] used cerebral organoids derived from human, gorilla, and chimpanzee cells to study developmental mechanisms driving evolutionary brain expansion. Bats are another unique group of model organisms as they are natural hosts of many severe viral pathogens that infect humans. Airway[273,274] and intestinal[275–277] organoids from bats have for example recently been developed to model SARS-CoV-2 and other viral infections. Of note, the first turtle organoids, representing liver, were recently reported in a preprint publication for modeling hypoxia-induced injuries.[278]

For the welfare of pet animals, dog-derived organoids have been used to study common canine diseases such as type 1 diabetes,[279] copper storage disease,[280] and cancers.[281–284]

Table 1. Additional research organisms used for organoid and OoC models.

Organisms	Main research interests	Organoids	OoC
Ape	Research model of primates Including chimpanzees and orangutans	11	0
Monkeys	Research model of primates Mainly rhesus, with a few studies on marmoset, and cynomolgus monkeys	19	0
Dogs	Disease modeling for pet welfare	25	4
Cats	Disease modeling for pet welfare	8	1
Cattle	Research model of mammals. Health and productivity of farm animals	30	6
Pigs	Research model of mammals. Health and productivity of farm animals	77	3
Horses	Health and productivity of farm animals	13	1
Sheep	Health and productivity of farm animals	4	0
Rabbits	Research model of mammals	6	0
Bats	Research model for SARS-CoV-2 and other viral infections	5	0
Birds	Research model of vertebrates Exclusively chicken	35	1
Fish	Research model of vertebrates and for toxicology Mainly zebrafish; a few rainbow trout	14	5
Snakes	Studies on snake venoms and venom gland development	2	0
Frogs	Research model of vertebrates	3	0
Flies	Research model *Drosophila melanogaster*	3[a)]	0

[a)] Of the three research articles classified as being on flies, two mention the organoid as a future prospect, and the remaining one article appears to use the term to mean an organ-like structure.

Among farm animals, pigs have been used either as animal models to study human diseases such as fibrosis,[285] or for modeling porcine diseases such as deltacoronavirus infections.[286] Publication counts recently increased in porcine gastrointestinal organoids, largely because porcine intestinal and colonic organoids are suitable for modeling bacterial and viral infections.[287] Some bovine gastrointestinal organoid publications report modeling gastrointestinal nematode infections.[288] Organoids from snake venom glands also have been reported, where venom produced might be used for anti-venom vaccines as well as for targeted development of new venom-based drugs.[289,290]

OoC platforms for reproductive organs have focused on improving the fertility of pet and farm animals including dogs, cats,[291] and cattle.[292,293] Additionally, OoC using pig-derived cells has been developed for cardiovascular tissues.

2.6. Global Distribution and Trends in Research

2.6.1. Organoid Research

To analyze the geographical distribution of organoid and OoC research, articles were grouped under the first-level organ categories and attributed to countries/regions where the research was performed. The USA is the largest contributor to organoid research, accounting for 37% of research articles overall (**Figure 5**). The European Research Area (ERA) as a whole made the second largest contribution with 31% of research articles. Although China, the third largest contributor, only accounted for 11% of organoid research articles, the number has been increasing twice as fast as the global average, while little year-on-year growth has been observed in the USA and ERA.

In the ERA, countries with the highest publication counts are Germany, the Netherlands, and UK, while Belgium and Sweden show recent above-average increases. In Asia, Japan follows China in the publication count, while South Korea shows an above-average upward publication trend. Overall, the top research countries are almost all among the high-income economies as defined by the World Bank. Among the countries considered to be emerging economies (i.e., BRICS, consisting of Brazil, Russia, India, China, and South Africa), only China and Brazil show significant presence in the research area. Brazil is the only country from South America qualifying as a top 20 research country in organoid research, largely due to research on brain organoids.

When organoid research contributions are measured per capita (shown as grayscale of the country map), the Netherlands, Luxembourg, and Switzerland in this order show the highest publication activity. The Netherlands, pioneers in organoid technology, maintain strong research activity in particular within gastrointestinal organoid research. Switzerland's high academic productivity can be explained in part by its combined strength in academia and biomedical industry, represented for example by the pharma research and development department headed by organoid pioneer Hans Clevers and by the recently-founded Roche Institute of Human Biology led by bioengineering pioneer Matthias Lütolf.

A majority of countries/regions share comparable distributions of published organ models in organoid research, with gastrointestinal organoids being by far the most studied, followed by either HPB, or neural organoids (Figure 5). However, there are also noteworthy variations among countries. For example, France and UK have higher publication counts on ocular organoids, while Austria and Brazil show greater focus on neural organoid research. For Austria, this is explained by the pioneering work of Knoblich et al. and Lancaster et al.,[68,294] while for Brazil this is largely due to studies by Rehen and co-workers using brain organoids for example to model Zika virus infection.[70] Australia excels in urinary organoid research, largely due to high productivity of Melissa Little and colleagues.[295] Belgium has a particular focus on male fertility[296] which resulted in a high proportion of reproductive organoid research. Hence, while organoid research as a whole is largely driven by globally shared research interests, regional differences due to the original productivity of some individual research groups, or because of societal needs, are clearly recognizable.

2.6.2. OoC Research

In OoC research, a similar overall pattern is seen for the most productive countries/regions, with a few exceptions. The top country is again the USA (accounting for 35% of research articles), followed by ERA (32%, of which the Netherlands and Germany

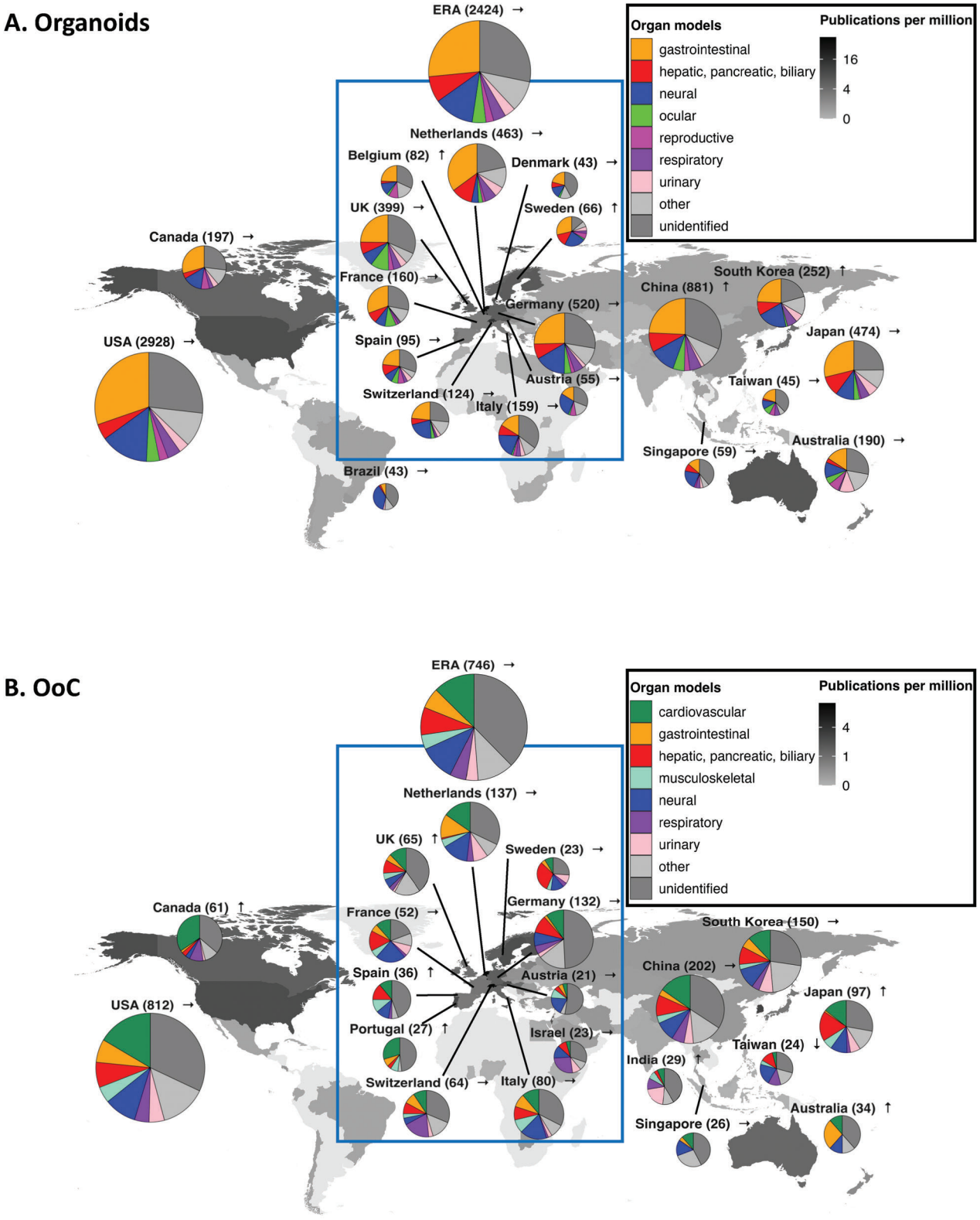


Figure 5. Global trends in organoid and OoC research. World map of A) organoid and B) OoC research and trends of countries/regions in A) organoid and B) OoC research. Pie charts of selected countries/regions are shown along with number of research articles. Arrows indicate recent trends of publication counts. For better visibility of smaller pies, diameters of the pie charts are in a cube root scale such that the area nonlinearly correlates with the number of research articles. The grayscale gradient on the map shows the sum of fractional counts of contributions of each country, adjusted for the population size. "Unidentified" as an organ model category consists of research articles in which the algorithm did not detect an organ model type.

each contribute 6%), and China (9%). Countries/regions with upward trends in the publication counts include Australia, Canada, India, Japan, Portugal, Spain, and UK. When research contributions are measured per capita, Switzerland, the Netherlands, and Luxembourg in this order, show the highest activity in OoC research. South Korea is also conspicuous, having the fifth highest publication count per capita and fourth highest overall publication count (6%). This is 50% higher than that of Japan (4%), a country with an active hiPSC research program and double the population. In most of the leading research countries/regions, OoC research predominantly focuses on cardiovascular and HPB OoC models. However, the Netherlands has an unusually high publication count on gastrointestinal OoC models, reflecting its pioneering track record and research strength in gastrointestinal organoids. Other regional characteristics are largely explained by the presence of particularly active laboratories, such as gastrointestinal OoC research in Australia by Benjamin Thierry,[297] urinary OoC in India by Rao et al.,[298] and respiratory OoC in Israel by Sznitman et al.[299] and in Switzerland by Guenat et al.[300]

3. Conclusion

While organoid and OoC is seen as a transformational technology, a meta-analysis of the field has been largely lacking. By performing a comprehensive text-mining-based analysis of more than 16 000 publications in organoid and OoC research, our work provides a multi-level categorization of the field, maps trends, and connects developments at a scale that would have been impossible by manually reviewing the literature. In particular, the algorithm identifies and tracks 149 and 107 organs/substructures modeled as organoids and OoC, respectively, as well as 130 disease conditions (see supplementary data in the GitHub repository), cell sources, and organisms including those other than human and mouse in which organoid/OoC technology has been applied. While the analysis has mainly focused on trends in organoid and OoC areas, the study also identifies relatively underrepresented research subareas. For example, although respiratory conditions are leading causes of death globally, the corresponding organ system is only the fourth and fifth most researched in organoid and OoC research, respectively. Finally, the algorithm allows geographic mapping of the research showing that although USA, ERA countries, and Japan have been the major drivers of research for both systems, China and South Korea are now among significant contributors in particular with high publication increases in organoid research. Researchers can increase the granularity of the analysis by applying the algorithm that is provided with their specific research questions.

Although the tools we developed for this task enable unbiased automated analysis of the organoid and OoC fields, there are some limitations with the approach we describe. First, due to access and copyright issues, the analysis only focuses on titles and abstracts, and so cannot capture the level of details that a full text analysis would provide. Second, the algorithm is dependent on the terminology used by authors. Thus, our corpora may miss some publications in which "organoid," "OoC" or similar terms were not used in titles/abstracts. Additionally, downstream classifications of organoid/OoC subtypes show a degree of variation, which may be relevant in some pioneering pre-2015 publications that did not use the term organoid. Third, the analysis inherits some of the features/weaknesses of literature databases, such as the article type classification that occasionally lacks a clear distinction between primary and review articles. Lastly, as with any natural language processing approach, the algorithm cannot interpret human language with 100% accuracy. This led to some misclassification and misinterpretation, particularly in relation to distinguishing research results from research intentions which required manual correction.

Nevertheless, our study pioneers the automated categorization and analysis of organoid/OoC models and provides an essential tool for tracking the rapidly expanding field.

4. Experimental Section

Data and Code Availability: i) A list of DOIs of all academic publications used in this study, ii) literature metadata under the Creative Commons Attribution Licenses, and iii) all original code were deposited at GitHub (https://www.github.com/jyshoji/text_analysis_organoids; https://doi.org/10.5281/zenodo.8138389) and are publicly available as of the date of publication.

Methods: Collecting Academic Publications on Organoids and OoC: Metadata of academic publications on organoids and OoC were collected from the following four literature databases.

- EMBASE via Ovid (https://www.ovidsp.ovid.com)
- PubMed (https://www.pubmed.ncbi.nlm.nih.gov)
- Scopus (https://www.scopus.com/)
- Web of Science (https://www.webofscience.com/)

Metadata of preprint publications were collected from bioRxiv (https://www.biorxiv.org).

The following two sets of search terms were used to identify academic publications on organoids.

- organoid OR enteroid OR colonoid OR assembloid OR gastruloid OR iblastoid OR tumoroid (including plural forms; 2011 to present)
- (blastoid OR blastoids) AND embryonic (2018 to present)

"Cardioid" and "cerebroid" were considered but not included as search terms, because they mostly retrieved academic publications unrelated to 3D culture model systems.

In order to broadly identify academic publications on OoC, which use a wide range of nomenclature, academic publications on the on-chip technology were first identified and retrieved; from these, OoC publications (see below for details) were subsequently selected. Academic publications on microphysiological systems (MPS) were also identified; this is a broad term for complex cellular systems often cultured in 3D. Among MPS are OoC which is distinguished by the inclusion of microfluidic flow in the device or system. Collectively, the following two sets of search terms were used to identify academic publications.

- "on-chip" OR "on-chips" OR "on-a-chip" (2011 to present; note that hyphens were replaced with white space for some databases)
- "microphysiological system*" OR "microphysiology system*" OR "microphysiologic system*" OR "micro physiological system*" OR "micro physiology system*" OR "micro physiologic system*" (where * works as a wildcard character; 2011 to present)

The formatted search strings that were actually used for each database can be found at the GitHub repository in the file (./raw_data3/README-raw_data3.md).

Metadata of academic publications were only collected that were written in English and were classified in the databases as "article" and/or "review" while excluding "comment", "editorial", "retracted article" and "retraction notice" when possible. Hereafter, collected non-review academic

publications are referred to as "research article." The literature search and collection were performed on 6 September 2022. Additionally, the literature corpus was updated on 5 June 2023 during the revision of the paper by adding publications published after 1 January 2022 and filtering out duplicate publications. The nine-months overlap of publication periods (January to September 2022) between the two data acquisitions was introduced to handle changes in the publication year, which tend to occur when publication status changes from electronic to printed publication. Accordingly, if a publication in the existing corpus had a new copy in the newly added corpus, the publication year was changed according to the latter, before the new copy was discarded as a duplicate document.

The metadata, including titles and abstracts, of the identified publications were exported as either .ris (EMBASE), .nbib (PubMed), or .bib (Scopus, Web of Science, and bioRxiv) file formats using the export function of each database. In metadata files originating from PubMed or Scopus, all occurrences of em- and en-dash were replaced with standard dash, and non-breaking space was replaced with standard space as these characters would have been skipped when the files were imported to R.[301] As the terms of use of some of the databases do not allow publishing the set of metadata, provided instead is: i) a list of DOIs and titles of the academic publications along with full results of the analysis, and ii) a subset of publication metadata under the Creative Commons Attribution Licenses which can be readily analyzed by the code that is published alongside. Clarivate, the owner of the Web of Science, allowed the sharing of all metadata for review purposes after the deduplication step below (the all_corpus file, see below), with a statement clarifying the data attribution. Please note that the metadata originated from Web of Science is attributed to Clarivate and is subject to their terms of use.

Metadata Cleanup and Deduplication: Analyses were performed using R[301] (version 4.0.5) on RStudio[302] (version 2023.03.1+446) using the tidyverse package.[303] The complete code used for this section can be found at ./R/ formatting.R of the repository and be opened and run on RStudio.

The metadata corpora of organoids, blastoids, on-chip technology, and MPS were separately loaded on R using the revtools package.[304] The organoid and blastoid corpora were combined to give the integrated organoid corpus. In the metadata corpora, character strings corresponding to URL (e.g., https://www.dx.doi.org/) were deleted from the DOI field when present to homogenize the style. In each corpus, extra copies of the same documents were identified based on the DOI field, and removed (i.e., deduplicated) using the revtools package by the following steps.

- Removing documents originating from Web of Science when there were extra copies of the same document from another database. Metadata of recent publications from Web of Science sometimes contained typographical errors
- DOI-based detection and removal of extra copies of documents from all databases

After the DOI-based deduplication, following changes were made in the on-chip corpus in order to subsequently identify academic publications on OoC.

- Inserting a new column "text_all_mod_lower" to accommodate combined titles, keywords, and abstracts, which are referred to as combined texts below.
- Changing all occurrences of the terms "on a chip," "on-a-chip," "on chip," "on-chip," "on chips," and "on-chips" in the combined texts to "onchip" to standardize the writing style

Subsequently, a list of all words was identified and compiled that preceded the term "onchip" in the combined texts across the on-chip corpus. This word list, consisting of over 3000 words, was manually evaluated, and each word was classified as either: i) words to include, ii) words to consider, iii) words to exclude (see ./csv/ pre_onchip_all_F.csv). Within the category words to include were (multi-)cellular structures or processes such as liver, angiogenesis, and cancer that were considered relevant for organs/tissues or their equivalents. Within the category words to consider were words that were conditionally considered organ equivalents depending on the context, such as abbreviations, and potential parts of two-word organ/tissue names. The context was subsequently examined that they appeared in, and reclassified them in the category words to include when appropriate, along with a preceding word when necessary (e.g., "node" was included only when preceded by "lymph"). Words to exclude were words that are not related to organs/tissues. Overall, 243 single words or two-word combinations as organ equivalents were considered. From the on-chip corpus, metadata of academic publications were selected in which the term "onchip" in the combined texts was preceded by one of the words to include in the above list, and considered them as academic publications on OoC. This selected corpus was combined with the MPS corpus to give the integrated OoC corpus, which was further deduplicated based on the DOI field.

The organoid and OoC corpora, excluding preprint publications, were further deduplicated based on the title field by the following steps.

- Title-based detection of extra copies of documents from all databases
- Manual inspection of the extra copies that were detected in the previous step to identify true duplicates
- Removal of the manually confirmed extra copies that were identified in the previous step

In the organoid corpus, the title-based deduplication combined with manual inspection identified additional 235 extra copies that needed removing, which were not detected by DOI-based deduplication due to the articles either lacking or having mismatches in the DOIs. The title-based deduplication alone without manual inspection would have led to the erroneous removal of nine unique documents. In the OoC corpus, the title-based deduplication with manual inspection identified additional 57 extra copies that needed removing. The title-based deduplication without manual inspection would have led to the erroneous removal of four unique documents.

The organoid and OoC corpora were further refined using the following steps for subsequent analyses.

- Removing documents with empty entries in the author or abstract fields
- Removing documents with "Anonymous" entry in the author field
- Replacing the keywords field with the author keywords field when the latter had an entry
- Removing long, computer-generated keywords that had over 250 characters from the keyword field
- Removing authors' declarations from the abstract field, when applicable
- Removing documents on nevus sebaceous (a type of birthmark that is also known as organoid nevus) as they are not related to 3D culture models
- Deleting white space and hyphens after "non" in titles, keywords, and abstracts, such that, for example, "non-human" is changed into "non-human" and therefore not detected as "human" at later steps.
- In abstracts, replacing "." followed by a number with "," to distinguish between a full stop and a decimal point.
- Replacing "on chip", "on-chip", "on a chip", "on-a-chip", "on chips", and "on-chips" in titles, keywords, and abstracts with "onchip" to standardize the writing style.
- Making a new column "text_all_mod" to encompass combined titles, keywords, and abstracts, which are referred to as combined texts below.
- Making new columns ("_key" columns) to list titles, keywords, or abstract sentences that contain one or more of key terms. The key terms for the organoid corpus are: organoid, enteroid, gastruloid, colonoid, blastoid, tumoroid, assembloid, embryoid, cerebroid, and cardioid. The key terms for the OoC corpus are: onchip, OoC, and microphysiological system with writing style variations.

The resulting processed metadata file (./R_results/all_corpus) was used for subsequent analysis.

Identification of Organ Models:Identification of Organ Models The relevant code for this section can be found at ./R/organ_types.R of the repository. The code uses the above all_corpus file as input.

To identify the organ types of the researched organoid and OoC models, first, phrases that preceded the term "organoid" or "onchip" were extracted, and organ/tissue names were then identified in the extracted phrases. To achieve this, a list of all words that preceded the terms "organoid" (for the organoid corpus) or "onchip" (for the OoC corpus) in the combined texts was identified and compiled. This word list was manually evaluated, and each word was classified as either: i) words to include, ii) words to consider, iii) words to exclude (see ./csv/pre_words_F.csv). Within the category words to include were either organ/tissue names (e.g., brain, alveolar), or words that may follow organ/tissue names that modify the later "organoid" or "onchip" (e.g., "tumor" as in brain tumor organoid, or "derived" as in intestine-derived organoid). Within the category words to consider were potential part of two-word organ/tissue names (e.g., "duct" as in breast duct, or "unit" as in neurovascular unit). Words to exclude were words that are not likely to follow organ/tissue names that modify the later "organoid" or "onchip" (e.g., large, developed). For words to consider, an additional preceding word was extracted from the documents to identify two-word organ/tissue names. The identified two-word organ/tissue names were merged to make them a single word by removing the intermediate white space (e.g., "breast duct" was changed to "breast duct") and subsequently added to the list of *words to include*. The two-word organ/tissue names were also merged in the title, keywords, abstracts, and combined text fields of the metadata corpora. Overall, 683 single words or two-word combinations as words to include were considered.

Next, the tidytext package[305] was used to extract phrases that consist of a few words ending with either "organoid" or "onchip" in one of the following styles, where "000" means any one word and "AAA" means a word to include from the above list.

- (start of a sentence) AAA organoid (or onchip)
- 000 AAA organoid (or onchip)
- 000 and AAA organoid (or onchip)
- 000 or AAA organoid (or onchip)

For example, in the sentence "a drug targeting liver promoted organoid maturation," "liver" is not extracted because "promoted" is not a word to include, thus avoiding the misclassification of the document as using liver organoid. In contrast, in a sentence "we generated liver epithelial organoids," "liver" is extracted because "epithelial" is a word to include, thus allowing the document to be classified as using liver organoid. Similarly, "liver" is extracted from "liver and pancreatic organoid", whereas it is not extracted from "the drug affected liver and suppressed organoid growth," because "pancreatic" is a word to include while "suppressed" is not. The extracted phrases were stored at new columns ("pw_" columns).

To accommodate the wide variation of nomenclature, a nested list of organ/tissue names was made by selecting organ/tissue names from the above list of words to include, and supplementing with synonyms and different word forms. The resulting nested list has two levels: the first level contains organ/tissue names, of which each element encompasses a second-level list containing synonyms and different forms. For example, the nested list has liver and stomach in the first-level list, which respectively includes liver, livers, hepatic, hepatocyte, etc. and stomach, and gastric as second-level lists. Note that the actual second-level lists were written in the regular expression. In a subsequent step, words/phrases in the second-level lists were captured in text fields of the metadata corpus and translated as corresponding organ/tissue names in the first-level list, such that, for example, hepatic organoids and hepatocyte organoids were both interpreted as liver organoids. In addition, disease names (e.g., tumor, fibrosis) and abbreviations (e.g., CNS as central nervous system) were included in the list. The complete lists are found in (./R/organ_types.R).

The words/phrases belonging to the second-level lists of the nested organ name list were captured in each document in the following four locations.

- Extracted phrases preceding "organoid" or "onchip" in titles ("pw_" column)
- Extracted phrases preceding "organoid" or "onchip" in keywords and abstracts ("pw_" column)
- Extracted sentences containing "organoid," "onchip," or similar terms in titles ("_key" column)
- Extracted sentences containing "organoid," "onchip," or similar terms in keywords and abstracts ("_key" column)

Organ type classifications of the organoid or OoC models researched were made for each document at each of the above four steps (see below for details). The final classification was made with the first step having the highest priority and the fourth step the lowest priority. Therefore, a document was first classified based on extracted phrases in titles, and when this failed classification was based on extracted phrases in keywords and abstracts, and so forth.

For each of the above four steps, organ-type classifications were made with the following considerations.

- Word boundary was set for each word/phrase in the second-level lists, such that, for example, "delivery" is not matched by "liver."
- Abbreviations were only captured when the corresponding full terms appeared somewhere in the combined texts.
- Disease names were captured, and subsequently broken down into an organ- and disease type prior to classification when possible. For example, "glioblastoma organoid" was translated as "brain organoid" with the "tumor" attribute.
- Organ/tissue type categories were subsequently arranged as a hierarchical classification tree (./miscs/organ_classification_final.xlsx; see Figure S2, Supporting Information as an example). For example, the neural category encompasses lower categories of brain, nerve, and others, of which the brain category includes lower categories (e.g., forebrain, brainstem).
- If only one organ/tissue name was captured at one of the above steps, the document was classified according to the captured organ/tissue name. If more than one organ/tissue names appeared at the same step, classification was made based on following rules.
- ○If the multiple organ/tissue names belonged to the same branch of the hierarchical classification tree (i.e., when an organ/tissue is a subcategory of the other; as for example, brain and cerebrum), it was assumed that the multiple organ/tissue names were used to describe a single entity, and classified the document according to the lower-level category (e.g., cerebrum).
- ○If the multiple organ/tissue names belonged to different branches within the same organ system (e.g., cerebrum and cerebellum), it was assumed that the multiple organ/tissue names were used to describe different entities, and classified the document according to the highest-level category (e.g., neural).
- ○If the multiple organ/tissue names belonged to different organ systems (e.g., brain and intestine), the document was classified as using models for "multiple organs".

In addition, the following terms were conditionally captured.

- "ganglionic" was included as "ganglion" only when not followed by "eminence."
- "epidermal" was included as "epidermis" only when not followed by "growth."
- "hair" was included as "hair follicle" only when not followed by "cell."
- "mesonephros" was included as "mesonephros" only when not following "aorta-gonad-."
- "aorta" was ignored when the document mentions "aorta-gonad-mesonephros."
- "embryonic" was considered as a type of organoid/OoC only when not followed by "stem."
- "cortex/cortical" was captured only when either brain or cerebrum was mentioned in the combined texts.

- "choroid" was included as "choroid" of the eye only when "choroid plexus" is not mentioned.
- "sinusoid" was interpreted as the sinus of the lymphatic system when it appeared with the lymph node, but was interpreted as a hepatic structure when it appeared with liver.
- "valve" was interpreted as the heart valve only when it appeared with heart/cardiac.
- "antrum," "fundus", and "corpus" were considered as "gastric antrum," "gastric fundus," and "gastric corpus", respectively, only when "gastric/stomach" appeared in the combined texts.
- "lobule" was interpreted as the hepatic lobule only when "liver/hepatic" appeared in the combined texts.
- "glomerulus" was interpreted as the structure in the kidney only when "kidney/renal/nephron" appeared in the combined texts.

Finally, documents classified with the "tumor" attribute were assigned to the "tumor organoid" or "tumor-on-chip (ToC)" *corpora*, whereas the remaining documents were assigned to either "organoid" or "OoC" corpora. Note that documents in the tumor organoid and ToC corpora were not included for the analysis in this paper, except for Figure S1 (Supporting Information) that shows publication counts of each corpus. The result of the analysis in this section can be found at ./R_results/organ_types_P.

For validation, organ model types were manually classified in three subsets of documents ($n = 24$ for each), and compared the outcome with the algorithm-based classification. Note that manual classification could also give different results depending on how much a reader would read between the lines. For example, if an abstract says "Non-alcoholic fatty liver disease was studied using organoid models," a reader may assume that liver organoids were used, which may or may not be correct. The manual and algorithm-based classifications showed 83 ± 8% and 89 ± 16% matches in organoid and OoC corpora, respectively, when a reader read between the lines. If a reader did not read between the lines the manual and algorithm-based classifications showed 96 ± 4% and 94 ± 6% matches in organoid and OoC *corpora*, respectively. In addition, all documents were manually checked that were classified as using infrequently researched organ/tissue models (appearing in less than five documents) to avoid misreporting non-existent organ models (classification adjusted in 11 out of 131 academic publications).

Identification of Cell Sources:Identification of Cell Sources The code used for this section can be found at ./R/cell_types_F.R of the repository. The code uses the all_corpus file as the input.

Overall, the following eight cell types and cell sources were assigned to articles in the corpora: i) induced pluripotent stem cells, ii) embryonic stem cells, iii) adult stem cells, iv) pluripotent stem cells, v) progenitor cells, vi) tissue, vii) tumor cells, and viii) stem cells. The category "pluripotent stem cell" encompasses both "embryonic-" and "induced pluripotent stem cells" categories, as well as articles where the type of "pluripotent stem cell" was not specified by the authors. Similarly, the category "stem cell" encompasses embryonic, adult, pluripotent, and induced pluripotent stem cells as well as "stem cell" without further specifications by authors. Note that "mesenchymal stem cell" were excluded from the "stem cell" category since there is broad consensus in the stem cell field that these do not meet the definition of stem cell.[306] The abbreviation "ASC" was also excluded which is commonly used for adult stem cells, because this abbreviation also appeared with different meanings in the corpora (e.g., adipose-derived mesenchymal stem cell, apoptosis-associated Speck-like protein containing a CARD, autism spectrum condition, etc.).

In addition, words (indicated as *000* below) that appear in the following styles were extracted across the corpora, manually checked, and included in the corresponding cell source categories.

- 000-derived stem cell (included in adult stem cell)
- 000-derived organoid (included either in tissue or tumor cell. For example, "small intestine-derived organoid" was interpreted as being made from tissue, rather than stem cells.)
- 000 stem cell (included either in adult stem cell or tumor cell)

A nested list of cell types was made, with a word boundary being set for each word/phrase in the second-level lists. The nested list was used to capture cell sources in the following two locations, with the above step having a higher priority.

- Extracted sentences containing "organoid", "onchip," or similar terms in titles ("_key" column)
- Extracted sentences containing "organoid," "onchip," or similar terms in keywords and abstracts ("_key" column)

The result of the analysis in this section can be found at ./R_results/cell_types_P. For graphical visualizations in figures, i) adult stem cells, ii) progenitor cells, and iii) tissue categories were combined as the "adult cell" category for simplicity.

For validation, cell sources were manually classified in three subsets of documents of the organoid corpus ($n = 24$ for each). The manual and algorithm-based classifications showed 72 ± 13% matches when the reader read between the lines, and 83 ± 2% when the reader did not. The cell source classification of OoC corpus in this paper was not shown as OoC platforms typically use primary cells whereas the cell source classifications aimed to determine types of stem cells.

Identifying Research Organisms:Identifying Research Organisms The code used for this section can be found in ./R/organism_F.R of the repository. The code used the all_corpus file as the input. Overall, the following fifteen groups of organisms were identified: i) human, ii) mouse, iii) monkeys, iv) apes, v) dogs, vi) cats, vii) cows, viii) pigs, ix) horses, x) sheep, xi) rabbits, xii) snakes, xiii) fish, xiv) flies, and xv) frogs.

First, phrases were identified that contained organism names that should not be considered as research organisms (e.g., bovine serum albumin). To this end, the tidytext package[305] was used to identify phrases containing organism names and manually selected phrases that are not to be captured. The selected phrases were deleted from the text fields prior to classification. In addition, "guinea pig" was changed to "guineapig" so that it is not captured as "pig." In the end, guinea pig was not considered as a research organism because no papers describing guinea pig-derived organoids/OoC were found at the time of the analysis .

A nested list of organism names was made, with word boundary being set for each word in the second-level lists. The nested list was used to capture research organisms in the following four locations.

- Extracted sentences containing "organoid" or "onchip" in titles ("_key" column)
- Extracted sentences containing "organoid" or "onchip" in keywords and abstracts ("_key" column)
- Titles
- Keywords and abstracts

The final classification was made by integrating the above four steps, with a later step being only considered when the article was not classified by earlier steps. All research articles that were classified as using one or more rare research organisms (i.e., all organisms except human and mouse) were manually checked, and the research organism classification was corrected when necessary to only consider an organism when it was a source of organoids or OoC (adjusted in 118 out of 337 research articles).

The result of the analysis in this section can be found at ./R_results/organisms_*P*. For validation, research organisms were manually classified in three subsets of documents ($n = 24$ for each). The manual and algorithm-based classifications showed 68 ± 2% and 78 ± 9% matches in organoid and OoC corpora, respectively, when the reader read between the lines, and 81 ± 6% and 97 ± 2% when the reader did not.

Identifying Countries/Regions of Authors' Affiliations:Identifying Countries/Regions of Authors' Affiliations The code used for this section can be found at ./R/country_F.R of the repository. The code uses the all_corpus file as the input.

Prior to the identification of countries/regions, the following changes were made to the address field of the metadata corpora.

- "People's Republic of China" was changed to "China", so that it is not captured by "Republic of China."
- "Republic of China" was changed to "Taiwan", so that it is not captured by "China."
- "Northern Ireland" was changed to "UK," so that it is not captured by "Ireland."
- "Russian Federation" was changed to "Russia" to homogenize the writing style.
- "Tbilisi, Georgia" in various styles was changed to "Georgia_c," in order to distinguish it from "Georgia" as the state of USA. Note that all authors from Georgia as a country were from Tbilisi.
- "Korea" was changed to "South Korea." Note that there were no authors found from North Korea.
- All state names of USA, including abbreviated forms, were changed to "USA."

Next, a list of names of all countries/regions was made, and used for extracting country/region names from the address field. Note that country names were captured only when they were either followed by "." or at the end of the address field, in order to avoid capturing country names appearing as a part of research institute names (e.g., Royal Netherlands Academy) or author's name (e.g., France). Subsequently, the following changes were made to the extracted country/region names to homogenize writing styles.

- "United States of America" was changed to "USA."
- "United States" was changed to "USA."
- "United Kingdom," "England," "Scotland," and "Wales" were changed to "UK."
- For documents originating from Web of Science, the first country/region name in the address field was removed, as it represents the corresponding author's country/region which as a result appears twice in the address field.

Next, the number of times each country/region name appeared was counted for each document. The country/region with the highest number of occurrences was determined in each document to be the main research country. Where more than one country/region was found with the same number of occurrences, the country/region mentioned earliest was chosen which typically represented the first author's country. Research articles from one of the countries affiliating to the European Research Area (ERA) were also grouped and summarized as an additional pie chart in Figure 5. ERA here was defined as the participants of the Horizon 2000/Europe, consisting of 27 EU member states (including the former member UK) and 18 associated countries (including the former member Switzerland).

Fractional counts of country's contributions were also calculated for each document as defined by the number of occurrences of a country/region name divided by the total number of occurrences of all country/region names. For Figure 5 showing global trends in research, the fractional counts of contributions were further adjusted by country's population, which was taken from Wikipedia.[307]

The result of the analysis in this section can be found at ./R_results/countries_P.

Identifying Research Topics:Identifying Research Topics The code used for this section can be found at ./R/research_topics.R of the repository. The code uses the all_corpus, cell_types_P, organ_types_P, and organisms_P files as the inputs.

First, biomedically important research topics were identified in the corpora by using the tidytext package[305] to make lists of words and n-grams including bigrams (i.e., a pair of consecutive words such as "stem cell"), trigrams (i.e., a group of three consecutive words), tetragrams (four words) and pentagrams (five words) that occurred in the corpora. Words and n-grams containing stop words (i.e., very common words such as "are," "we," etc.) were ignored. Frequently occurring words and n-grams were selected from the lists with varying cut-off scores (occurring in >50 academic publications for individual words, >30 for bigrams, >9 for trigrams, >4 for tetragrams, >2 for pentagrams). The resulting lists were manually inspected to extract biomedically important research topics such as disease names, and research interests. In addition, n-grams ending with any of the following terms (disease, disorder, syndrome, infection, injury, failure, or dystrophy) were specifically examined (occurring in >2 publications). Further, bigrams that contain "development" as the second word were selected and organ names that appeared as the first word were identified. At a later step, "development" was considered as organ development when preceded by one of the organ names identified here. Research topics were also selected from phrases that occurred in the keyword field (occurring in >4 publications).

Next, a nested list of research topics was made, with the word boundary being set for each word/phrase in the second-level lists. The nested list was then used to detect the research topics in each document of the corpora. The output of this analysis was further supplemented with columns from previously generated files that included organ mode types, research organisms, cell sources and countries of authors. The result of the analysis in this section can be found at ./R_results/research_topics_P.

Graphical Visualization of the Results: The code used for this section can be found in files starting with "fig_" at ./R/ of the repository. The circular packing graph (Figures 1 and 2 and Figure S6, Supporting Information) and diagrams (Figure 3 and Figures S3, S5, and S7, Supporting Information) were drawn using the igraph,[308] ggpp,[309] and ggraph[310] packages. World maps showing global research trends (Figure 5) were drawn using the rworldmap package.[311] The R Graph Gallery[312] was referred to for inspiration of visualization methods.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

C.L.M. has advisory roles in HeartBeat.bio AG, Angios GmBH, Mogrify Limited and Sartorius AG. C.L.M, and R.P.D. declare research funding from Sartorius AG; however, this is for an unrelated study. S.K. holds a patent on an organ-on-chip platform. J.Y.S. declares that he has no competing financial interests or personal relationships.

Keywords

metaanalysis, microphysiological systems, organoids, organ-on-a-chip, organ-on-chip, stem cells, text mining

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