Human organoids: a new dimension in cell biology


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ABSTRACT Organoids derived from stem cells or tissues in culture can develop into structures that resemble the in vivo anatomy and physiology of intact organs. Human organoid cultures provide the potential to study human development and model disease processes with the same scrutiny and depth of analysis customary for research with nonhuman model organisms. Reconstructing the complexity of the actual tissue or organ, patient-derived human organoid studies may accelerate medical research, creating new opportunities for tissue engineering and regenerative medicine, generating knowledge and tools for preclinical studies, including drug development and testing. Biologists are drawn to this system as a new “model organism” to study complex disease phenotypes and genetic variability among individuals using patient-derived tissues. The American Society for Cell Biology convened a task force to report on the potential, challenges, and limitations for human organoid research. The task force suggests ways to ease the entry for new researchers into the field and how to facilitate broader use of this new model organism within the research community. This includes guidelines for reproducibility, culturing, sharing of patient materials, patient consent, training, and communication with the public.

EXECUTIVE SUMMARY

Advances in stem cell biology have heralded a revolution in biology and medicine. As these technologies expanded into human cells, they paved the way for discoveries in fundamental human biology and advancement in medical care. A major recent step in this revolution has been the development of methods to generate, under controlled cultured conditions, three-dimensional (3D) structures, known as organoids, that recapitulate development and tissue organization and resemble organs in the body. Organoids originate from renewable tissue sources that self-organize in culture to acquire in vivo-like organ complexity. Organoids can be generated from human cell sources, including adult tissue-specific stem cells, embryonic stem cells (hESCs), and induced pluripotent stem cells (hiPSCs). Therefore, they have the potential to overcome a number of previous limitations in biomedical research aimed at gaining mechanistic insights into human development, producing accurate models of human disease, and generating patient-matched tissue sources for regenerative medicine.

To optimize the potential of these powerful new developments for scientists, The American Society for Cell Biology (ASCB) asked a task force of ASCB members, including researchers, several of whom play critical roles in developing organoid systems; ethicists; and patient advocates to identify opportunities for organoid research for
biologists, highlight obstacles to progress, and challenges, as well as generate recommendations and best practices to increase the impact of this emerging, rapidly expanding, and highly promising field. Discussion by the task force, as well as the results of a questionnaire sent to the ASCB membership, acknowledge the enormous potential of these new “model systems,” while also demonstrating the challenges for science and society that come with this opportunity. For the composition of the task force, see Supplemental Information 1; for a summary of questionnaire results, see Supplemental Information 2.

Opportunities

• Organoids offer the possibility to study human tissues at the same level of scientific scrutiny, reproducibility, and depth of analysis as has been customarily possible only with nonhuman model organisms.

• Organoids allow investigators to recapitulate morphogenetic events in human development that lead to tissue and organ formation.

• Organoids can be used to study mechanisms of disease acting within human tissues, generating knowledge and tools applicable to preclinical studies, including drug testing.

• Organoids can be generated from any individual, allowing the study of variability among human individuals at the tissue level, as well as the cellular mechanisms leading to complex disease phenotypes.

• Organoids resembling the complexity of tissues and organs offer numerous applications for tissue engineering, drug discovery, and regenerative medicine.

We propose that human organoids have the potential to provide basic scientists with the opportunity to perform mechanistic studies within a “human model” system, with acceptable ethical constraints.

Challenges and recommendations

• Organoids recapitulate only part of the entire body and may not faithfully capture the stereotypic and complex functions of individual organs. Thus, in contrast to whole animal models, organoids offer only an approximation of the biology of an entire organ and do not mimic the behavior of the complete organism. They lack key in vivo features such as defined body axis, a functional immune system, and complete physiological networks. Therefore, results from organoids have to be complemented by whole organism studies in model systems and compared with actual human development, tissue organization, and physiology.

• “Gold standards” and best practices must be defined for the study of organoids. The protocols for the derivation and culture conditions of organoids have to provide sufficient details to enable reproducibility. Criteria need to be developed that allow investigators to compare cell types and structures in an organoid to the composition and organization of the respective organ.

• The long-term advancement of organoid research relies on the distribution of tissue sources that are renewable and readily comparable between laboratories. Particularly important for the study of disease is the establishment of tissue banks (biobanks) that distribute hiPSCs from different patients with the same disease. Such biobanks could also be distribution hubs for control samples from both unaffected individuals and genetically modified patient-derived tissue samples.

• For patient-derived tissue samples, patient consent needs to specify the requirement that materials will be shared among different institutions, investigators, and countries.

• The entry of new researchers at different career stages into this field should be encouraged and facilitated by establishing training sites where investigators can acquire and adapt organoid technology. Because of the rapid advancement in tissue culture techniques and the intricacy of materials and time frame needed to generate an organoid from a renewable tissue source, either existing facilities or practicing laboratories may offer better opportunities for training than more traditional training courses.

• The potential of organoids for research and medicine brings with it ethical uncertainty and public concern. A clear definition of what organoids are and what they are not, as well as a realistic description of the opportunities they offer, should be articulated by scientists and scientific organizations in their communications.

BACKGROUND: BIOLOGY AND DERIVATION OF ORGANOIDS

Organoid definition

We study organoids because they represent minimal and reproducible models of complex human tissue dynamics during development, homeostasis, and disease. These models can be used by multiple labs and are easily manipulated, imaged, and subjected to biomolecular analysis without the confounding complexity associated with studies in vivo. When grown from human cells, they facilitate the transition from animal models to human biology with acceptable ethical constraints.

What defines organoids is the use of a renewable tissue source that 1) is derived from stem cells or primary tissue, 2) is cultured in a defined environment, 3) self-organizes into a structure that mimics the healthy or diseased modeled tissue, 4) incorporates many aspects of the cellular complexity of the modeled tissue, and 5) can be propagated and shared either as a culture itself or through a defined stem or progenitor cell population.

A brief history

Organoid culture is firmly based on 3D cell culture methodology developed over the past century. As early as 1906, the so-called hanging drop method allowed cells to be cultured in 3D (see Harrison, 1906, and Simian and Bissell, 2017, for a detailed historical perspective). The current boom of organoid research results from the ability to grow organoids from cells or tissues derived from individuals, revealing their enormous potential for human biology and medical research (Dekkers et al., 2013; Lancaster et al., 2013). For the purposes of this report, we focus primarily on the opportunities and challenges with regard to human organoids, rather than on organoids generated from animal cells and tissues.

Human organoids as a new model organism for research

For the past several decades, biomedical research was almost exclusively carried out in animal models. Although this has led to a deep understanding of many fundamental biological processes, it has left gaps in our mechanistic understanding of human-specific developmental, cell biological, physiological, and disease-related events. Furthermore, the diversity of human individuals is in sharp contrast with the genetic homogeneity of inbred animal models, leading to a deficiency in our knowledge about population diversity. Indeed, this lack of human model systems may have contributed to the low success rate in clinical trials of pharmaceutical compounds developed in animal models.
With the advent of human organoid models, this situation seems poised for change. For the first time, organoids offer the possibility to study the assembly of human tissues in a personalized manner. Organoids allow the recapitulation of many morphogenetic events leading to tissue formation. They can potentially be generated from any individual, whether healthy or diseased. Thus, both the variability among human individuals and the human-specific cellular mechanisms that lead to disease phenotypes can be analyzed directly.

However, human organoids have limitations as a model system. In contrast to animal models, organoids offer only an approximation of the biology within a human body. They lack key in vivo features such as a defined body axis, a functional immune or nervous system, or a functional vasculature. Therefore, although organoids can teach us about human-specific aspects of organ development and physiology, at present they are less useful for uncovering aspects of biology that rely on integrated physiological systems and the complex interplay of human organ systems. Whatever results we find in organoids will be useful only relative to the background of knowledge defined in other model systems. In that sense, organoids are themselves a new model system that is complementary rather than superior to existing animal models.

Organoids can be generated in different ways, recapitulating either organ development or organ regeneration. In their simplest form, organoids are generated from adult tissue stem cells cultivated in the presence of growth factors and matrix normally provided by the stem cell niche. Such cultures can contain all cell types derived from stem cells in vivo, either during normal tissue turnover or during repair after injury, and can recapitulate aspects of their 3D arrangement. Alternatively, organoids can be generated from PSCs including ESCs or induced pluripotent stem cells (iPSCs). This is achieved by culturing them in a specific series of growth factor or media cocktails that induce organ-specific cell fates in a sequence that mimics normal development. The final conglomerate of organ-specific cell types can arrange itself in a way similar to that found in the actual organ, allowing the analysis of morphogenetic and physiological processes “in a dish.”

A survey of ASCB members (see Supplemental Information 2) found that whereas more than 90% of respondents use human cells in culture, less than 30% use human organoids. Among the main bottlenecks that respondents listed were difficulties in growing organoids and the availability of human tissue with which to initiate cultures. A significant number of comments pointed to issues of reproducibility and cost, and many respondents questioned how well organoids actually model human biology. In this report, we lay out opportunities for organoid research, address concerns, and make recommendations for the use of human organoids to add to the “model organism” repertoire.

APPLICATIONS FOR ORGANOID RESEARCH

Organoids offer many exciting experimental applications ranging from gaining a better understanding of human development to generating clinical models for drug testing and regenerative medicine. Given the rapid progress so far, we believe the applications below will provide a glimpse of what is likely to come in the future.

Human developmental biology

The study of human development has largely been limited to observational studies on preimplantation embryos or progenitor cells and tissue isolated from aborted fetuses. For example, in the latter case, organ-specific progenitor cells are isolated from fetal tissues and grown in culture under conditions in which they continue to grow and differentiate (Nikolic et al., 2017). However, the advent of a variety of organoid models derived from iPSCs has provided a path toward dynamic observation and mechanistic studies of human development.

There are two basic approaches to studying human development using organoid models derived from iPSC. In the first, organ-specific progenitors are generated from iPSCs by passing them through a sequence of exposures to defined factors. After further culture, the progenitors self-organize into organoids representative of the developing organ. This approach has already provided a wealth of insight into the morphogenesis of several organ systems, and more intriguingly, is beginning to shed light on how human genetics impact developmental diseases of the brain, lung, and gut (Perez-Lanzon et al., 2018).

In the second approach, iPSCs are coerced to form cellular aggregates that mimic the early preimplantation embryo itself. These structures, known as embryoids or gastruloids, autonomously undergo the early stages of development. Progress in this area has dramatically accelerated in recent years, even pushing against the rule that limits the culture of human embryos beyond 14 d, a stage when mesodermal cells are normally generated in the primitive streak (Hyun et al., 2016). These studies have revealed distinctions between the earliest stages of development in humans and model organisms such as the mouse, for example, in the establishment of the embryonic axes and the specification of primordial germ cells (Irie et al., 2015; Kobayashi and Surani, 2018; Martyn et al., 2018). They offer the possibility of further insights into early human development, enable evolutionary studies of the species-specificity of early developmental events, and establish a new model system relevant to the underlying causes of early human pregnancy loss.

Human disease modeling

Beyond modeling human development, the cellular complexity and 3D organization of organoids provide a unique platform for identifying the mechanisms of adult human disease. The cellular organization of organoids can be studied at the systems level with advances in functional genomics and proteomics, including single-cell analysis and high-throughput transcriptomics, proteomics, and large-scale characterization of chromatin domains and transcription regulatory elements. This level of detailed analysis is difficult to achieve with human tissue taken in situ and will provide a more complete understanding of the development and cellular composition of organoids. Moreover, this information would enhance their relevance as models to study organ morphology, function, and disease and would open up new avenues in drug development and regenerative medicine. For example, the cellular diversity of developing brain organoids was leveraged to model genetic microcephaly (Lancaster et al., 2013), to identify potential mechanisms by which the Zika virus leads to microcephaly (Dang et al., 2016; Garcez et al., 2016), and colon organoids have been used to explore the mutational steps underlying tumor initiation and progression (Drost et al., 2017). Last, patient-derived organoids have been used to recapitulate the disease progression of retinitis pigmentosa (Deng et al., 2018), to study the role of neuroglia in neurodegenerative disease (Abud et al., 2017), and to model cystic fibrosis in human airway organoids (McCauley et al., 2017).

Tissue engineering and regenerative medicine

iPSC-derived organoids have tremendous potential for applications in tissue engineering and regenerative medicine. These small tissues have many characteristics of embryonic tissues, which have been previously shown to have regenerative potential when implanted in vivo. For example, hiPSC-derived intestinal organoids comprising
both endoderm and mesoderm differentiate into fully vascularized guts when implanted into immune-compromised mice. Moreover, the implanted organoids incorporate high-level structural features such as villi that are not observed when organoids are cultured in vitro (Spence et al., 2011; Munera et al., 2017). Additional tissues that have been shown to have regenerative potential are the lung, skin, and hair (Hirsch et al., 2017). Other researchers are investigating organoids as regenerative therapies for diseases of the liver (organ buds) and eye (optic cup) (Huch et al., 2017; Mandai et al., 2017).

**Personalized medicine**

One intriguing application of patient-derived organoids—whether from iPSCs or from adult stem/progenitor cells—is patient-specific clinical models to aid in identifying drugs or combinations of drugs for treating disease. This concept has already found some success. For example, gut organoids have been used to identify patients who are uniquely responsive to an expensive therapy for cystic fibrosis (Dekkers et al., 2013).

**Preclinical disease modeling/drug screens**

A report by the Tufts Center for the Study of Drug Development describes the average cost of developing a prescription drug for market approval at $2.6 billion. This expense is driven mainly by the high failure rates (~88%) for drugs that are tested in human subjects (DiMasi et al., 2016). Organoids therefore may provide a unique model for human tissue disease for use in drug screens or preclinical models. For example, a screening of more than 6000 approved drugs in hiPSC-derived cortical neural progenitor cells identified a handful of compounds that were protective when tested in human brain organoids (Zhou et al., 2017). In addition to potentially repurposing existing drugs, organoid-based screening can also be used for new drug target discovery.

Several critical challenges must be overcome in order to take full advantage of the enormous potential that organoid research has to offer. These challenges include reproducibility, the development of gold standards for different organoid systems, standardized mechanisms of sharing tissues and experience, means of patient consent, and transparency in communication with the public. These issues are discussed in detail below.

**REPRODUCIBILITY IN ORGANOID RESEARCH**

The utility of organoids in biomedical research depends on a large extent on how reproducibly they perform in various assays or differentiation protocols. This is true whether the studies are carried out in the same laboratory or in different laboratories using shared cells or experimental protocols. The factors affecting reproducibility will vary according to the type and complexity of the assay and the source of the initiating cells, for example, whether these are well-characterized cell lines or are primary stem cells derived from fetal or adult tissues. Quality control to reduce variability is extremely important if organoids are to be grown in large quantities for clinical trials.

It is not possible here to discuss all potential sources of variability in organoid culture, but some of the most important considerations are summarized below. It is assumed that academic investigators are following the basic tenets of “rigor and reproducibility” in their experiments. These principles include standardization of nomenclature, number of replicates, statistical analysis, randomization, blinding, sample-size estimates, and transparency in reporting.

**Genetic and epigenetic variability in human cells**

Genetic variability is less of a concern in the reproducibility of assays using inbred mouse cell lines. The same is true for primary stem cells as long as they are derived from inbred strains. A number of well-characterized hESCs are also readily available for studies, for example, HUES1 and HUES9 (https://grants.nih.gov/stem_cells/registry/current.htm; http://stemcelldistribution.harvard.edu/). To some extent these lines, which were derived from embryos generated by apparently “normal” donors, can be considered as a gold standard for testing the reproducibility of organoid assays among different labs.

Potential variability in assays due to genetic background may arise with hiPSCs, especially those derived from patients carrying mutations associated with risk for an inherited disorder that has variable severity and penetrance. In these cases, the phenotype of differentiated cells may depend on the genetic background in which the mutation lies. Theoretically, iPSCs derived from different patients with the same mutation may behave differently in organoid cultures. Consequently, organoid studies should use iPSC lines derived from several patients, and, ideally, investigators should be willing to share these different lines with other labs so that results can be compared. For diseases in which the specific genetic defect is known, “disease model” cell systems could be established and shared where the genetic defect is corrected by CRISPR-Cas9 in patient cells, or the genetic defect is recreated in normal control cells. Proof of principle studies have been provided by patient cell lines from muscular dystrophy and cystic fibrosis patients (Simsek et al., 2016; Min et al., 2019).

**Isolation of stem cells from primary tissues**

Some organoid assays use stem cells isolated from primary human tissues. Variability may come from the methods used to isolate and purify the cells. For example, clinical samples may sit around for different times, the proteases used to dissociate the tissue may vary in potency, or conditions of cell sorting may vary in different ways (such as nozzle size, flow pressure, gating, and source of the antibodies to surface markers; reviewed in Hines et al. [2014]). It is therefore important that as many technical details as possible are included in isolation protocols.

**Conditions under which cell lines or stem cells are maintained**

Investigators new to cell culture and organoid assays need to be aware that cells can change over time in culture, including losing the ability to differentiate. For example, there may be selection of fast-growing variants or changes in behavior due to different compositions of commercially available media (e.g., different glucose and calcium levels), different batches of fetal bovine serum, serum replacement components, and growth factor and mycoplasma contamination, etc. These potential sources of variability are covered in basic manuals of cell culture. Cell lines should be frozen in aliquots and detailed records kept of the numbers of passage and other variables.

**Performance of organoid assays**

An important source of variability, both between laboratories and from one experiment to the next, can be the conditions in which organoids are grown. Problems fall into several categories, including batch variability in growth factor purity, differences in exposure of cells to oxygen levels in multiwell trays, and variability in the degree and rate of maturation of differentiated cell types. These variables may be compounded if the organoids are derived from a combination of different cell types, such as “multiplex” organoids in which epithelium, stromal, endothelial, and immune cells are aggregated together. Variability can also come from using different...
induction protocols. For example, a protocol developed to induce human hindgut endoderm from iPSCs also generates a small amount of mesoderm that is correctly patterned as posterior lateral plate and gives rise to smooth muscle, whereas protocols to induce anterior endoderm do not generate associated mesoderm (Munera and Wells, 2017; McCauley et al., 2018).

Importantly, organoids are useful only if they come close to recapitulating the actual organ in situ. Various criteria have been used for comparison, such as a description of the cell types formed using RNA expression at the single-cell level, antibodies or genetically encoded markers; a 3D to 4D reconstruction of the complete organoid to determine the overall morphology, layering and regional patterning; and finally, developing assays to evaluate the physiology and function of the specific organoid. The latter may include transplantation and functional integration into a host animal as was shown for intestinal models (Fumagalli et al., 2017; Munera et al., 2017). Robust verification is achieved by comparing these structural and functional measures with the respective organ in another model system, such as mouse, pig, and nonhuman primate, or in actual human tissue.

Conclusions and recommendations
Given the potential sources of variability discussed above, a number of recommendations can be made:

• It is critical that organoid protocols are described in great detail in initial publications and the sources are provided for the reagents used at every stage (cell isolation; organoid culture conditions; differentiation induction methods; isolation of differentiated cell types).
• Transfer of knowledge is most efficient by means of lab visits, facilities, and repositories that routinely culture and grow organoids (for further discussion see Training in organoid research below).
• Criteria (transcriptomic profiles, surface antibody arrays, 3D reconstruction, single-cell analysis, and behavior after transplantation) need to be established for comparing the differentiated cell types and structures obtained in organoids with cell types and tissue organization present in normal tissues.
• It is likely that genetic background can affect the behavior of iPSCs carrying disease-associated mutations. It is therefore recommended that lines are derived and banked from multiple patients. To maximize the utility of these banks, patient consent should include allowing them to be shared among different institutions and investigators (for further discussion see Tissue sourcing and patient consent in organoid research and Sharing materials and results below).

Tissue still in situ is taken from either living or nonliving humans
For living humans, taking tissue in situ involves intrusion into their bodies and requires voluntary and informed consent. To touch a living person’s body without proper consent and in a manner that might be harmful or offensive is an interference with commonly held notions of personal autonomy and is illegal in many national systems of law, including those of the United States.

Tissue taken from deceased individuals may raise questions about who—if anyone—has the authority to consent to donation. In many legislatures, such as the United States, a deceased person is not considered a human subject of research for the purpose of triggering federal research ethics rules. Nonetheless, some jurisdictions treat the tissue as under the dispositional authority of someone other than the state or the research community, so that, for example, consent from a near relative might be required. Finally, because of religious, ethnic, or national customs it may be an offense to take tissue from the deceased, or certain types of research (e.g., investigating past population movements and settlement patterns) may pose a cultural or even political challenge.

Ex vivo tissue
Ex vivo tissue includes “abandoned tissue,” such as surgical waste or “gifted tissue,” when taken pursuant to consent, as above, or fundamentally “altered tissues,” such as cell lines. National rules vary on whether it is considered to be some form of property of the person from whom it was taken. Such rules may apply if there is sufficient information embodied in or attached to the sample, such that the original source/donor is identifiable. When that is the case, the source/donor is a subject of study whenever the tissue is studied, and unless the identity is sufficiently obscured, it will trigger approval and protections for the donor’s interests.

Regulatory boards
In general, if the tissue is taken specifically for research purposes, national rules for research will apply, and in many systems, this will entail not only informed consent but also some form of independent oversight to ensure the research is sound and the interests of participants are protected. In the United States, for example, it will in most cases be subject to institutional review board (IRB) oversight and some federal regulations embodied in the Common Rule. Federal regulation and IRB requirements are formally triggered when the research is funded by one of the federal agencies and departments that have adopted the Common Rule, but in many other cases, the research is conducted in a setting where voluntary compliance is undertaken.

Even when consent is obtained, it may be necessary to see whether the consent extends to all research or, at least, to the particular research being contemplated. Some organoid research might be sufficiently alarming to some members of the public such that this will become relevant. For this reason, the process of obtaining tissue from donors may need to include information about the range of envisioned uses and the possibility of future uses not yet contemplated. For example, working with tissue obtained from a tissue bank may require attention to whether source/donor identities are knowable and, if they are, whether the identities can be obscured. If not, then consent may need to be obtained, unless consent can be waived based on exceptions for situations such as minimal risk and unreasonable costs for contacting the donor. For more information on how to
manage tissue consented prior to the establishment of iPSC or organoid research, please refer to the discussion in Lomax et al. (2015).

For specific research objectives, it may be advisable for institutions to have specialized research boards that have specific knowledge of stem cell technologies and applications. Specific human embryo research now possible with new culturing methods may require additional oversight committees that review, approve, and monitor any research involving organoid studies on early human development or aim to produce human gametes with the implicit goal to study fertilization or use in in vitro fertilization (IVF).

Several guidelines and discussions on the topic of consent have been published; see, for example, Guidelines for Stem Cell Research and Clinical Translation published by the International Society for Stem Cell Research www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf.

Elements of consent
When a research participant or a parent/guardian of a research participant consents, the following should be addressed:

- What are the immediate research purposes and any contemplated future uses, along with known risks and benefits (if any) to this information being collected?
- Does the donor wish to be recontacted for additional uses in the future, or would s/he prefer to allow the tissue to be used without further consent? The participant should also be asked whether there are any particular uses to which the donor does not consent.
- If the tissue donor is to be identifiable, how will medical and personal information and donor identity be stored? How will it be protected, and what are the rules under which it will be held confidential or distributed to other researchers? In addition, is there any plan to return research results to participants? If so, the circumstances triggering such a return should be discussed.
- If the tissue donor will be unidentifiable from research on the sample, the donor should understand that deidentified data and biospecimens will be distributed to researchers and/or deposited in central databases and biobanks.
- The participant should be informed that blood cells, skin biopsies (fibroblasts), or other tissues (i.e., hair) may be used to generate iPSC and organoids, especially if the tissue is collected in the context of a larger study (genetic/genomics, for instance), and samples will be frozen for future use. An opt-in consent where the donor or their kin explicitly agrees to the use or, more desirable but less likely, an opt-out consent where exclusions have to be specified, should be provided.
- The participant should be asked for permission to link any medical, clinical, and genetic data to the biospecimens and their derivatives. The participant should also be asked to link any medical, clinical, and genetic data to those of their family members, if they are also enrolled in the same research study.
- The participant should be given the possibility to withdraw from the study with the understanding that material might have already been distributed, been used, or may be used in the future for research purposes and communicated in published journal articles or at conferences.
- Organoid research can yield important insight about specific diseases and even treatment. Thus, patients who donated their cells or tissue with broad consent should nevertheless have the option to learn about the results from their organoids.

Guidelines for future collection
Regulations for the need and extent of consent vary broadly based on the source of the tissue. We will only discuss consideration for future collection of tissues.

- For living donors, unidentifiable tissues (often the case of surgical waste, where the only information collected is about the disease) should be distinguished from identifiable tissues (where information about the donors can be obtained through studying the tissue).
- For deceased individuals, consent should be based either on prior expressed wishes of the deceased person or consent of next of kin.
- For unidentifiable tissue, no consent should be needed, but consent may be necessary if the type of research (e.g., transplantation, generation of embryoids, gastruloids, or germ cells/gametes) might be upsetting if the donor had considered it. For this type of research, it is advisable to discuss with the IRB (or equivalent oversight body, if outside the United States) whether it is important to go back to the donors for additional consent.
- For identifiable tissue, consent should be given for use, with preference to the broadest possible consent for anticipated and unanticipated uses, including sharing broadly among institutions worldwide. Note that this requires some degree of imagination when describing possible future uses of the tissue.
- If the broadest consent cannot be obtained, tissue should either not be collected or only distributed noting the specific restrictions. Emerging electronic recording technologies may make it easier to manage varying restrictions placed by each donor.
- A unique identifier, such as GUID (global unique identifiers), originally developed by the autism research community, generates a common subject identifier for research participants across research laboratories and repositories and is recommended for researchers in other fields as a tool to share data (https://ndar.nih.gov/tools_guid_tool.html)

SHARING MATERIALS AND RESULTS
Research progresses by communicating and sharing results and data. We propose strong guidelines for the sharing and communication of results and materials obtained by organoid research and propose increased use of federally supported biobanks as centers to enhance and coordinate distribution, training, and sharing. Distribution via data and tissue banks is highly advisable in the future. A few organoid banks and centers already exist in Japan, the United States, and Europe (van de Wetering et al., 2015; Sachs et al., 2018; Takebe et al., 2018; Yan et al., 2018).

These biobanks can offer several advantages for organoid research:

- Set standards for quality of material preservation.
- Develop standard procedures for organoid culture.
- Engage in training.
- Respect and enforce restrictions made by the donor through data depositories.
- Facilitate communications with the donor for special consent (i.e., transplantation, embryoid generation, or germ cells/gamete manipulations).
- Distribute materials with accurate information, detailing quality-control protocols used for cell, tissue, organoid generation, and maintenance.
Collect and distribute biospecimens for broad distribution that were modified by individual labs, for example, to correct a specific genetic defect.

**Guidelines for communication and sharing**

- Data and samples for research should be available for use by approved investigators without geographical restrictions.
- Data and biospecimens should be distributed after the request of approved researcher and their institution have agreed to and signed an appropriate Material Transfer Agreement (MTA) and, if needed, submitted an IRB approval/exemption from their institution.
- In the interest of rapid dissemination of data and findings, advancement of knowledge, and replicability of data, the MTA should include language in support of data sharing.
- Investigators should agree to return generated data and modified biospecimens to a biobank or make materials available within an agreed-upon time or by the time of publication, whichever comes first. The sharing language could encourage or require the deposition of results in www.bioRxiv.org or a similar preprint server to facilitate free access.

**TRAINING IN ORGANOID RESEARCH**

The success of any research area, technique, or application is directly dependent on the relative experience and training of the scientists carrying out the work. Experimental approaches that are simple to implement are also easier to disseminate, with or without commercialization. More complex protocols—including the generation and characterization of organoids—require extensive experience in enabling procedures prior to mastery. With such technologies, “failure” to replicate prior work does not necessarily mean that the previously published studies were flawed; it is equally likely that the “art” of conducting the procedure was not successfully communicated to and/or mastered by the second set of researchers. This fundamental challenge has severe implications for any field reliant on complicated experimental protocols.

Increasing the number of scientists trained to work with organoids will be essential for several key issues:

- Solving challenges and uncertainties associated with reproducibility. Until a critical mass of researchers at different institutions are trained in dependable and consistent techniques to generate organoids, it will be challenging to understand the extent to which variability arises because of technical differences versus genetic (or biological) ones.
- Alleviating bottlenecks in organoid research. Until training is reliable and easy to come by, the number of labs carrying out research using organoids will remain limited, which directly limits the number of questions that will be asked using this technology.
- Expanding the use of organoids into translational areas, including screening for novel therapeutics and regenerative medicine.
- Using organoids to expand the next frontiers of research. This could include, for example, a comprehensive description of the cell types in the body and their organization into tissues. Tissue-engineering efforts may result in more realistic organoids that more closely resemble the in vivo organ including vascularization, innervation, and immune system support.

The field will thrive only once we have reliable and dependable methods of training. We recognize that there are both challenges and opportunities associated with developing and implementing training opportunities. The challenges include the fact that hands-on training in these protocols is difficult and protocols can be challenging to reproduce at different geographic locations. The development of well-structured organoids requires long periods of time (many months to years) and is not easily translated from one type of organoid to the next. Furthermore, derivation and culturing organoids requires infrastructure, multiple experienced personnel, and institutional buy-in. These challenges make dissemination of detailed knowledge in organoid culturing to new laboratories difficult in typical short-term practical courses such as those currently used to teach experimentation with model organisms.

Thus, alternatives to existing training methods need to be found and indeed already exist in limited locations. These include stem-cell core facilities that could be expanded to provide a teaching platform that could include visiting programs open to people from different institutions. Such programs could essentially solidify art into practice through the protocols they choose to teach and could include topics such as the culture and derivation of hPSCs, isolation of tissue-specific stem cells or tissue explants, differentiation into human organoids, genetic manipulations including those based on CRISPR, and functional genomic approaches with single-cell resolution. Such facilities would also provide a mechanism and medium for the exchange of knowledge and collaboration by bringing together experts in organ culture, robotics and engineering, microscopy and image analysis, cryopreservation, and animal model studies. For examples of collaborative facilities striving toward clinical translation, see Takebe et al. (2018) and Yan et al. (2018).

**Conclusions and recommendations**

- Training facilities need to drive the dissemination of the art of organoid culturing and promote sharing of expertise and knowledge among researchers between institutions.
- Sharing of source material is critical for training and dissemination.
- Best practices for organoid research have to be in place to train and increase the number of researchers in the next generation in this arena.

**PUBLIC OUTREACH**

Since the beginning of medical science, incremental steps forward in understanding the treatment or mechanics of disease have delivered major advances in medical care. These advances, however, have often pushed the envelope of what is considered socially acceptable, and have not always been met with immediate public acceptance.

Public wariness and cultural and religious barriers often stand in the way of immediate acceptance of some of these advances. Examples include organ donation and transplantation, IVF, and other cutting edge medical research procedures. This public uncertainty—sometimes outright opposition—has often resulted in decreased public acceptance of new medical advances and in recent years has led to politically motivated efforts to place policy restrictions (funding bans and in some cases criminal penalties) on scientific research. Examples include recombinant DNA (1970s), stem cell research (2000s), fetal tissue research (1990s, 2016–present), gene editing (2016–present), and mitochondrial replacement therapy (2016–present).

A large fraction of research using organoids is funded by the National Institutes of Health, the European Union, Japan’s Ministry of Education, and other public funders. Scientists, therefore, have a
responsibility to be transparent with the public about the results of their research and its implications without over-sellimg it. Researchers should also be transparent about the sources of material used to generate organoids. Acknowledgment of ethical issues associated with the field is also important.

During the debate in the United States regarding federal support of research using hESCs, the proresearch advocates, including scientists, were careful to not promise cures resulting from research that was only in its nascent stages at the time. Scientists were encouraged to discuss the potential and the promise of the field if their research was successful.

It is critical that scientists know their audience. In general, public opinion of scientists and support for science is quite positive, but can vary widely based on race, gender, age, education, region, and political affiliation. Public audiences are also more likely to be initially wary of new areas of research. Americans became more accepting of hESC research over time as the public and political debate continued between 2000 and 2013 because they had time to learn about and become more comfortable with the area of research.

Since organoid research is an emerging field and provides investigators with new tools for their research, they should share their excitement about the ways in which these tools will help them reach their research goals. It is also important to assure nonexperts about what organoids are not. For example, brain organoids are not complete brains. They cannot replace the complete function of the brain, and the field is not replicating consciousness in a dish. The same can be said for organoids of other organs of the body. Intestinal organoids do not replicate the intestine, and retinal organoids are not eyes and do not have vision. Support will not be gained by one lecture. Like other areas of research, it will take time for the general public to adapt, and the scientific community will have to commit to a continued effort at education and dialogue, particularly as advances continue.

As the research progresses and clinical applications become more apparent and real, organoid research will receive increased attention from the media. This will play an important role in educating the public and will help shape any emerging political debate. Organoid researchers should, therefore, consider educating reporters about this area of research even though they may be hesitant to do so. Researchers without prior experience or media training may be concerned about having their conversation accurately reported by a reporter, particularly one not familiar with the science. The complicated nature of the science surrounding organoids may also serve as a barrier for discussion between scientists and reporters. Too many scientists are not able to describe their research in the most basic terms let alone show experience in working with reporters or media training. Societies such as the ASCB, or institutional public information and communication offices, are willing to and should be consulted.

We suggest that scientists working on organoids consider focusing on the following talking points when communicating with public audiences about organoids:

- Describe what organoids are and what they are not.
- Clearly describe the potential opportunities of organoids to your research.
- Articulate key discoveries that have resulted from organoids that would not have been possible using other approaches.
- Acknowledge the unknowns and challenges.
- Avoid talking about unpublished, non-peer-reviewed results.
- Consult with researchers in other cutting-edge fields about their experiences working with the press and other audiences. What experiences have they had in similar areas of cutting-edge science? What suggestions do they have for you based on those experiences?
- The members and staff of the ASCB are able to provide you with professional guidance (www.ascb.org/advocacy/).

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