Meeting Report

Increasing the Availability of Quality Human Tissue for Research

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Advances in 3D and other *in vitro* tissue model platforms have led to fundamental improvements in research on human disease, development of novel therapies, and safety testing. In addition, histological and cellular investigations of human tissues continue to serve as keystones in understanding disease and health processes. In recognition of the importance of human tissues in research, the Physicians Committee for Responsible Medicine held a workshop. Working closely with key stakeholders from the research community, regulatory agencies, and organ procurement organizations, the goal was to explore, understand, and address the barriers to increased use of human organs, tissues, and cells in research. Workshop participants were tasked with identifying the challenges of accessing and qualifying tissues for research purposes and creating a strategy to help meet the needs of the research communities to increase the availability and quality of human tissues in biomedical and translational research. Break-out groups identified significant challenges in the areas of policy, scientific development, and public engagement with respect to the provision and application of tissues and cells for scientific advancement. Following working group recommendations, stakeholders concluded that there is a need to facilitate the availability and quality of human tissues for the research community, as well as provide a framework for education of the public, medical professionals, and researchers to foster donation and utilization for research in place of animal models. The success of these new initiatives will facilitate greater access to high-quality human tissues for biomedical and translational research and help ensure the transition away from the dependence on animal models.

1 Introduction

It is increasingly recognized that advanced *in vitro* models using human tissue or cells contribute to a better understanding of human health and disease and drive the development of safe and effective medical products (Freedman et al., 2015; Jackson et al., 2018; McAleer et al., 2019). There has been a noticeable paradigm shift away from the reliance on whole animal models to study human pharmacology, pathology, and toxicology toward the utilization of human tissue and cell-based model systems (Sistare et al., 2011; US EPA, 2019). In addition to immediate therapeutic uses, such as organ transplantation, human tissues are critically important resources in biomedical research, education, quality control, and the production of therapeutic and diagnostic aids. Most organs and tissues are recovered from consented, deceased donors, but not all donors qualify for tissue or organ donation. However, additional consent for research purposes allows an alternate path for the donor gift to be honored. Healthy and diseased tissue samples are, for many applications, the preferred model system to conduct in-depth analyses of human biological processes (Jackson et al., 2018; Reuben et al., 2015). As the demand for using more human tissues for numerous applications has grown, national policies and guidelines are necessary to ensure that there are readily available sources of a variety of human tissues and cells, as well as quality standards and specifications for their successful use.

From the research perspective, the most widely cited barrier preventing greater adoption of human tissue and cell-based approaches is lack of access to reliable sources of tissues (Holmes et al., 2015). Improving accessibility to larger quantities of high-quality human tissues will enable the use of human-based models to better support basic research and inform regulatory decisions in a timelier fashion. Collectively, stakeholders are placing more of an emphasis on sourcing, distributing, and supporting research with tissues that come from common disease states, shifting the paradigm away from thinking that everything needs to be tested on "healthy individuals" to everything needs to be tested across the health spectrum. This shift in emphasis would further aid in enhancing new medical discoveries while also reducing tissue discards. There is, furthermore, a strong need to address the communication and coordination challenges between tissue providers and end users.

To encourage discussion and further understand the challenges in procuring and obtaining high-quality human tissue for scientific research, the Physicians Committee for Responsible Medicine (PCRM) sponsored a one-day roundtable on October 23, 2018 held at the PCRM headquarters in Washington, DC. The roundtable was attended by a broad group of 23 subject-matter experts including scientists, physicians, policy experts, representatives from U.S. regulatory agencies, industry, and non-governmental organizations. To our knowledge, this roundtable represented the first meeting in the U.S. to bring together key stakeholders from the full spectrum of tissue research – from a transplant surgeon who initiates the recovery in the operating room to an end-user who uses human cells to study drug development for preclinical trials – to discuss the challenges and current state of human tissues in research. The main goal of this roundtable was to identify the scientific, reg-

ulatory, and policy needs to facilitate access and use of human tissues in research that can be effectively utilized for human risk assessment by regulatory agencies. Another key focus was to discuss how to standardize methods and quality control metrics for the recovery and provision of human tissues and cells.

Plenary presentations that opened the roundtable addressed the challenges faced by organ procurement organizations (OPOs), research tissue organizations (RTOs), and end users of human tissues. The speakers provided in-depth context and first-hand experiences regarding the impact that human tissues have had on research in their respective fields. Common themes that recurred throughout the opening presentations included (1) challenges of incorporating human tissues and cells into research projects, (2) issues with using animals in research, (3) difficulty in recovering tissues, (4) unknown variability in tissues that can impede research conclusions, (5) lack of standardized methods on the sourcing of human-derived biomaterials, (6) difficulty of obtaining in-depth medical history data accompanying tissues, and (7) the need for database systems that would allow donor health and disease history data to be captured and mined for current and future efforts toward qualifying specific donor materials to fit particular needs in the laboratory or clinic.

The presentations were:

- *Setting the Stage: Increasing the Availability and Quality of Human Tissues in Research:* Edward L. LeCluyse, PhD, Principal Scientist, LifeNet Health
- *Hepatocyte Function: Lessons Learned from Transplantation:* Timothy L Pruett, MD, University of Minnesota, Division of Transplantation
- *Role and Function of an Organ Procurement Organization*: Thomas Buersmeyer, Vice President of Partner Relations, LifeNet Health
- *Research Tissue Organizations Supporting the Needs of the Medical Research Community:* Gina Dunne Smith, Executive Director, International Institute for the Advancement of Medicine
- *Characterization of Isolated Cells from Human Liver Tissue*: *Understanding and Leveraging Donor Heterogeneity*: Sharon Presnell, PhD, President, Amnion Foundation
- *Human Cells for Therapeutics Discovery and Development:* G. Sitta Sittampalam, PhD, Senior Advisor to the Director, National Institutes of Health, National Center for Advancing Translational Sciences
- *Regulatory Considerations:* Scott A. Brubaker, Director, U.S. Food and Drug Administration, Division of Human Tissues
- *The Sources of Variability: The Good, the Bad, and the Ignored:* Jean-Louis Klein, PhD, Scientific Director, GlaxoSmithKline

After the plenary presentations, participants attended one of three breakout groups to facilitate deeper discussion into three key topic areas: (1) scientific and technical, (2) legal and policy, and (3) education and training of the public and medical personnel. These discussions focused on the critical factors hindering broader access to human tissues and factors that impact the quality of donated tissues for research purposes, as well as what steps could be taken to enhance or improve these important endeavors. The following sections describe the diverse themes of the plenary presentations, which mainly addressed the current challenges and opportunities for the provision and use of human tissues and cells in basic and translational research applications. In addition, we summarize the main outcomes of small group discussions and report the key recommendations for addressing the range of challenges that we face.

2 Plenary presentations

2.1 Towards greater adoption of more human-relevant models

There is a need to overcome a cultural and historical reliance on using animals in research. Human pathological, pharmacological, and toxicological events often cannot be mimicked in animals due to inherent genetic, molecular, anatomical, and physiological differences between species (Herrmann and Jayne, 2019; Sousa et al., 2017). The scientific case against the use of animals in research and testing grows more compelling with exponential progress in the development of human biology-based methods and new research technologies (Herrmann and Jayne, 2019). There has also been growing recognition and support for a move away from the total reliance on whole animal systems and towards the use of human-relevant model systems (US EPA, 2019). Various 3D models exist and continue to be developed using human tissues and cells to better understand human biology and study disease pathogenesis, drug efficacy and toxicity, and much more. For many purposes, *in vitro* systems employing human tissue are the most scientifically relevant, providing a much more accurate representation of human function and development than animal studies (Farahany et al., 2018).

The evaluation and use of human tissue models can help reduce the reliance on animals in research and strengthen more translationally relevant testing strategies. As with the integration of any new method or technology, raising awareness will incentivize researchers to adopt human-relevant models in regulatory, academic, and industry settings. This can be done by continuing to provide evidence to researchers, increasing funding specifically for human tissue research, and increasing acceptance from regulators that human tissue models are comparable or better than the current methods using animals. Sharing experience, data, best practices, and standard operating procedures through forums and open source reference databases can be an effective way of supporting human tissue models and providing evidence of validity (ICCVAM, 2018). However, greater acknowledgement and support from funding bodies for these types of activities are necessary to accelerate the transition (Holmes et al., 2015).

2.2 Limited supply of human tissues for research purposes

The global shortage of human organs and tissues places major logistical limitations on transplantation, regenerative medicine, drug discovery, and a variety of other rapidly growing areas in biomedical research. Thousands of organs from deceased donors are discarded every year because they are deemed unsuitable for transplantation (Gill et al., 2017). There is an overarching need to

increase the accessibility of human tissues through increasing tissue donor authorization rates for research purposes. The majority of the U.S. population is familiar with organ donation for transplantation; in fact, 95% of U.S. adults support donation, yet only 58% are registered as donors (HRSA, 2020). The percentage is presumably even smaller for adults who are registered to donate for research if transplantation is not feasible. The current system is focused (and biased) towards clinical applications, however an overall increase in organ donation is required to have a major impact on overall public health as well as biomedical research opportunities.

Under the Uniform Anatomical Gifts Act, the U.S. operates its organ and tissue donation system under an explicit consent or opt-in framework whereby the individual, or the next of kin, or their surrogate after the individual's death, must register to donate organs and tissues (National Academies of Sciences, Engineering, and Medicine, 2017). Within the U.S., the donor registration consent form is overseen at the state level, and each state governs its registry independently. However, not all states address the utilization of donated tissue for research purposes in their statutes, and it is left up to the local OPO to discuss post-mortem donation options with families. OPOs are federally-designated entities, regulated by the Centers for Medicare and Medicaid Services that are responsible for increasing the number of registered donors for transplantation and other clinical applications and coordinating the donation process (HRSA, 2020). In 2013, Donate Life America conducted a survey of state donor registries, including Puerto Rico and the District of Columbia. Twenty-six of the 52 state registries surveyed included authorizations for research in the general state donor registration. Improvements to state donation infrastructure, working towards the development of an integrated nationwide network, and public education may facilitate greater acceptance, participation, and promotion of tissue donation for research, as discussed below.

One approach to increase donation for research is to move towards an all-inclusive model in which an individual automatically consents to donation of organs and tissues for transplantation, research, and education, rather than the current practice of an opt-in framework. Several European (e.g., Austria, Belgium, France, and Spain) and South American (e.g., Argentina and Colombia) nations utilize the concept of a presumed consent or an opt-out system that presumes donor authorization and participation in the absence of an explicit objection (National Academies of Sciences, Engineering, and Medicine, 2017). This system may reduce the amount of discarded non-transplantable viable organs and tissues and improve their availability for research. However, enforcing an opt-out policy raises many ethical questions, and implementation would be resource-intensive, requiring a large amount of time and energy (Prabhu, 2019).

The urgency for improvement of tissue procurement and coordination with medical and research centers is highly evident. Data from the transplant waiting list is often cited as a means to quantify the magnitude of the organ and tissue shortage. However, these data fail to capture the true scale of this crisis, because it is not conceivable to compute the number of lives that could be saved with the biomedical technologies that rely on human organs and tissues to make discoveries that improve human health. Technologies such as microphysiological systems and bioprinted tissues depend on human cells and have the potential to have a dramatic impact on scientific advancement in precision medicine and research on diseases such as Alzheimer's, cancer, fatty liver disease, and diabetes (Edington et al., 2018). Escalating costs and a greater than 95% failure rate in drug discovery are also exacerbated by limited availability of human tissue models, which more accurately translate to clinical results in patients (Giwa et al., 2017). If the development of tissue resources is allowed to remain a primarily grassroots, regionally isolated endeavor, it will stifle research innovation that is sorely needed in medicine.

2.3 Improving the coordination and distribution of human tissues

Human tissue for research is either obtained from deceased donors (after brain death determination or cardiac death) or living donors (as surgery discard). Tissues are available in a variety of forms suitable for numerous and diverse implementations and may be prepared fresh, frozen, or fixed (e.g., paraffin embedded) depending on the application of use. Researchers can source tissue from OPOs, RTOs, and tissue repositories.

Well-preserved human tissues that maintain the integrity of the original organ are in high demand for their direct relevance to human health and application to a broad range of research, including investigations into disease pathophysiology, drug target validation, safety and efficacy assessment, biomarker discovery, and diagnostic development (Clotworthy, 2012). Having sufficient supply of high-quality human organs and tissues to meet public health needs has been the subject of widespread efforts in medicine, science, and policy. Stakeholders are aiming to increase organ donation, improve donor organ utilization, and expand perception of scientific advancement using human specimens (Giwa et al., 2017).

The success of these efforts is intertwined with the need for proper handling and preservation of organs and tissues during recovery, storage, transport, and other steps of the chain of stewardship in order to maintain the tissue integrity and meet logistical requirements. In the U.S., organ donation and recovery are coordinated and orchestrated by the United Network of Organ Sharing (UNOS) via a network of 58 OPOs located throughout the country. However, OPOs often do not have the resources, expertise, or infrastructure to effectively support recovery of tissue for research applications. Working closely with the key stakeholders of the scientific and regulatory communities, including the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA), as well as establishing best practices and universal protocols for the recovery, preservation, and distribution of human tissues and cells for research applications would represent an important start toward acceptance and adoption among the OPOs and other tissue provider communities. Securing adequate funding and implementation of legislation in the U.S. would allow for the improvement of infrastructure to better support the use of non-transplantable, post-mortem, and surgical discard tissue for research applications.

2.4 Barriers to the application of human tissues for basic research

Donor heterogeneity and variation in tissue handling and processing, coupled with a lack of standardized cell isolation and characterization techniques, compromise reproducibility and limit the utility of donor tissues and cells for medical research advancements (National Academies of Sciences, Engineering, and Medicine, 2019). Organs and tissues for research applications are similarly susceptible to stressors introduced by donor health issues and/or transit time (e.g., cold ischemia time) from recovery to the laboratory as those utilized for transplantation (Grizzle et al., 2010). Deviating from best practices during the recovery, preservation, and storage of tissues, combined with the lack of universal acceptance and training of standardized methods in centers that do not use OPOs, can cause subcellular changes or other artifacts that may be misinterpreted as disease-related or disease-specific findings.

Roundtable participants identified poor recovery and preservation processes, long warm and cold ischemic times, and lack of clinical documentation of patient medical and social history as obstacles to working with human tissue for medical research. Organ or tissue recovery is an urgent, time-sensitive process. Effective recovery and delivery of tissue to the laboratory requires researchers to be available at undesirable hours (i.e., nights, weekends, and holidays), and requires laboratories to have the associated infrastructure for delivery and handling of tissue at short notice (Holmes et al., 2015).

Inadequate and inaccurate tissue recovery and donor medical information puts research at risk of being irreproducible, a major problem that consumes over 28 billion research dollars in the U.S. each year (Freedman et al., 2015; Edington et al., 2018). Harmonizing methods and developing cross-industry standardization of best practices for the recovery, storage, and transport of tissues will improve their integrity and maximize their potential in research. Supporting biorepositories, the development of new human tissue preservation technology, and raising awareness in the scientific and regulatory communities are fundamental ways in which the barriers to greater acceptance and application of human tissue models for translational research can be overcome.

2.5 Breakout group discussions

Roundtable attendees participated in one of three breakout groups to discuss key legal, scientific, and educational challenges and delineate recommendations. These discussions are summarized below.

Legal and policy

A clear understanding of applicable laws, regulations, and independent polices for obtaining, accessing, and using human tissues for research is critical to lend confidence to regulated industry and other stakeholders, ensure transparency, and build trust within the public and donor communities. This breakout group was organized to examine existing policies and, to the extent possible, determine where improvements can be made.

Members of this group considered how to broaden and streamline donor consent and authorization practices. Discussants recommended the inclusion of language to enhance donor and donor family understanding and support of research applications, including genetic research and bioengineering of cells. Currently, every OPO's consent/authorization policy, as well as each state's donor registration and first-person consent process operates independently; there was a general consensus that it would be beneficial to standardize the current system to better support donation across the U.S. and harmonize the consent/authorization form language. Simplifying consent/authorization wording, making donation forms inclusive of donation for transplantation, research, and education, and increasing the transparency of how human tissues are used in research applications could improve donor comprehension and, subsequently, donation rates.

This breakout discussion also addressed the need to revise federal policies that mandate or encourage research or tests using animals as the preferred method. While there have been some improvements over the past decade, acceptability of data from human biology-based methods by regulatory bodies in the U.S. is limited. To improve communication, regulatory agencies should work to develop policies that reflect acceptance of human-relevant research methods.

Scientific and technical

For several roundtable participants, teasing out technical versus biological variability is a major challenge. Representing the inherent biological variability between individuals is important in pharmacological and toxicological research, especially to produce physiologically relevant models, and should be documented from the time the biological sample is collected to the time it is processed for use. Undesirable technical or artefactual variability due to differences in handling or preparation should be minimized as much as possible during the entire recovery, preservation, and storage of tissues. To minimize variability in these steps, methods should be consistent, reproducible, and well-documented. Donated samples should be collected using procedures appropriate for the type of specimen being collected and the intended uses. Guidelines for handling and recovery should be developed in keeping with best practices for sample collection, preservation, storage, and shipping specifications for all recovery sites to adopt for research applications.

Another recurring theme of the breakout session was the need to better define and standardize the nomenclature, characterization, and quality control metrics for human tissues. To better understand true differences in normal versus diseased tissue, a definition for tissue quality and "what is normal" needs to be established, including baseline histological criteria and measures of key biomarkers. This is particularly challenging when diseases and disorders remain ill-defined or are largely dependent on the clinical symptoms that may not have molecular or structural biomarker correlates. Quantitative metrics are imperative to assess quality and stratification of tissues, and minimum quality performance specifications should be established and adopted by the scientific community to increase confidence in human tissue research. The question of how and what to standardize for

specific tissues needs further exploration and input from all key stakeholders.

Proposals on how to approach this issue include creating several tiers of product quality, standardizing by cell type or technology platform intended for use, such as standard 2D or microphysiological systems. Another possibility is to begin standardizing quality metrics or performance specifications by organ, tissue, or cell type and intended research purpose, in a fit-for-purpose approach. It was acknowledged that defining and dictating the same standards for academia, industry, and regulatory agencies may not be practical at this stage due to highly variable objectives and levels of resources. In order for these ideas to be widely applied, proposals for quality control guidelines should be endorsed and publicized by funding agencies and peer-reviewed scientific journals.

An additional focus of discussion and concern for this breakout group was the absence of industry-wide agreement on quality standards and best practices to preserve the integrity of tissue samples for research purposes. Specimen quality would best be upheld by implementing best practices for sample collection, processing, transport, storage, and retrieval. While individual organizations may have internal standard operating procedures that represent best practices for each of these key stages, the broader scientific community would benefit from a cohesive, unbiased universal guidance document outlining best practices that are reviewed and endorsed by the key stakeholders, namely OPOs, regulatory, academia, and industry.

Training and education

Training and education at all levels is critical to improve public perception of research, increase donation rates for research, expand skill sets of the recovery teams, preserve quality of samples, and develop communication pathways between providers and researchers. This breakout group discussed the importance of communicating with the public to educate potential donors and family members about the imperative role tissues and organs play in medical and basic research. Health professionals would benefit from strategies on how to introduce conversation with patients and their families regarding donation options early on. Improved communication pathways and partnerships between researchers and tissue providers are also essential to improving the current system.

A common theme during the breakout session was the notion of creating and strengthening partnerships. This is especially vital between OPOs, RTOs, and end users. Creating accountability regarding any tissue or cell product that is being delivered to the end user would help certify that the success of one entity is dependent upon the success of the other. One proposed solution to improve accountability was to instigate a professional certification program that could be administered through educational workshops and hands-on training, overseen by professional organizations such as the North American Transplant Coordinators Organization (NATCO).

RTOs, such as the International Institute for the Advancement of Medicine (IIAM) and LifeNet Health, host surgical workshops to train experienced donation coordinators on proper recovery methods to procure organs for research. These workshops improve surgical skill sets and competency to perform detailed recovery and preparation of samples for research requests in an effort to fully maximize the donor gift and stress the importance of educating recovery teams to treat organs and tissues for transplantation and research equally.

3 Recommendations

Breakout group discussions led to the development of the following recommendations:

1. States and OPOs should simplify language and streamline donation consent forms to a single-approval check box to include donation for transplantation, research, genetic engineering or manipulation, and education.
2. All stakeholders should gain a better understanding of the value of human tissue for research purposes and the need for quality tissues, while working towards dispelling negative connotations around scientific research. Surgeons and other medical professionals, transplant coordinators, and scientists should improve their communication pathways and conduct more public outreach.
3. OPO personnel should receive intensive continuing education to improve the process of collecting human organs and tissues for research. This could be achieved in coordination with similar program initiatives within the scientific community and regulatory agencies.
4. To identify sources and to access human tissues for specific research projects, stakeholders should create a program that includes a database for researchers to input their tissue needs, such as the quantity, time parameters, and processing technique. Tissue providers can choose to participate in the program to access this database and pick up the request (or bid on request). Providers would also be required to meet a certain set of standards to qualify for participation in the program.
5. End users in conjunction with RTOs should establish a set of quality control criteria and well-defined minimum performance metrics and parameter specifications for each tissue or cell type.
6. Scientific and professional societies, like the American Association of Tissue Banks (AATB), NATCO, or FDA should work with OPOs, regulatory, academia, and industry to create standardized criteria of use, language, characterization, cell type, recovery, and procurement practices. These criteria should include research tissue procurement, processing, preservation, storage, quarantine, and distribution, as well as comprehensive record-keeping, ethical credibility, proper training, safe handling, and confidentiality and be widely adopted as best practices.
7. Regulatory agencies should commit to revising current U.S. federal regulations favoring research or tests using animals, such as the recent directive by the EPA (US EPA, 2019).
8. All stakeholders, especially academia and industry, should increasingly pursue research using human tissue models and urge the U.S. Congress to prioritize human tissue research.

4 Concluding remarks

Human tissues and cells represent an invaluable resource for the scientific community as a whole and have substantial potential to be used for a variety of applications thanks to their adaptability. Tissues from healthy and diseased donors provide unparalleled opportunities for studying healthy and disease-specific tissue to conduct research and deepen our understanding of how diseases emerge, develop, and spread. A large amount of today's scientific research would not be possible without the valuable gift of organ and tissue donation (Anderson et al., 1998). Every effort should be made to encourage donation to research, as well as to develop appropriate infrastructure for their dissemination and maximal use.

Some of the key challenges to using human tissues in research include obtaining sufficient tissues of acceptable quality and quantity, with the accompanying clinical data, in the desired format, and safeguarding the results from human tissues are accepted by regulators. However, these obstacles are worth overcoming. Here we are working to acknowledge and address these issues and put forth recommendations towards creating a better, sustainable system to meet supply and demand.

References

Anderson, R., O'Hare, M., Balls, M. et al. (1998). The availability of human tissue for biomedical research: The report and recommendations of the ECVAM workshop 32. *Altern Lab Anim 26*, 763-777. https://pdfs.semanticscholar.org/5dd3/a58cb65b590fbdbe77d6b8e3a292ca6edc91.pdf

Clotworthy, M. (2012). The application of human tissue for drug discovery and development. *Expert Opin Drug Discov 7*, 543-547. doi:10.1517/17460441.2012.689282

Edington, C. D., Chen, W., Geishecker, E. et al. (2018). Interconnected microphysiological systems for quantitative biology and pharmacology studies. *Sci Rep 8*, 4530. doi:10.1038/s41598-018-22749-0

Farahany, N. A., Greely, H. T., Hyman, S. et al. (2018). The ethics of experimenting with human brain tissue. *Nature 556*, 429-432. doi:10.1038/d41586-018-04813-x

Freedman, L. P., Cockburn, I. M., Simcoe, T. S (2015). The economics of reproducibility in preclinical research. *PLoS Biol 13*, e1002165. doi:10.1371/journal.pbio.1002165

Gill, J., Rose, C., Lesage, J. et al. (2017). Use and outcomes of kidneys from donation after circulatory death donors in the United States. *J Am Soc Nephrol 28*, 3647-3657. doi:10.1681/ASN.2017030238

Giwa, S., Lewis, J. K., Alvarez, L. et al. (2017). The promise of organ and tissue preservation to transform medicine. *Nat Biotechnol 35*, 530-542. doi:10.1038/nbt.3889

Grizzle, W. E, Bell, W. C., Sexton, K. C. (2010). Issues in collecting, processing and storing human tissues and associated information to support biomedical research. *Cancer Biomark 9*, 531-549. doi:10.3233/cbm-2011-0183

Herrmann, K. and Jayne, K. (eds.) (2019). *Animal Experimentation: Working Towards a Paradigm Change*. Leiden, The Netherlands: Brill. doi:10.1163/9789004391192

Holmes, A., Bonner, F. and Jones, D. (2015). Assessing drug safety in human tissues – What are the barriers? *Nat Rev Drug Discov 14*, 585-587. doi:10.1038/nrd4662

HRSA – Health Resources and Services Administration (2020). Organ Donation Statistics. https://www.organdonor.gov/statistics-stories/statistics.html (accessed 15.03.2020).

ICCVAM – Interagency Coordinating Committee on the Validation of Alternative Methods (2018). A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. doi:10.22427/NTP-ICCVAM-ROADMAP2018

Jackson, S. J., Prior, H. and Holmes, A. (2018). The use of human tissue in safety assessment. *J Pharmacol Toxicol Methods 93*, 29-34. doi:10.1016/j.vascn.2018.05.003

McAleer, C. W., Long, C. J., Elbrecht, D. et al. (2019). Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. *Sci Transl Med 11*, eaav1386. doi:10.1126/scitranslmed.aav1386

National Academies of Sciences, Engineering, and Medicine (2017). *Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation*. Washington, DC, USA: The National Academies Press. doi:10.17226/24884

National Academies of Sciences, Engineering, and Medicine (2019). *Exploring Sources of Variability Related to the Clinical Translation of Regenerative Engineering Products: Proceedings of a Workshop*. Washington, DC, USA: The National Academies Press. doi:10.17226/25371

Prabhu, P. K. (2019). Is presumed consent an ethically acceptable way of obtaining organs for transplant? *J Intensive Care Soc 20*, 92-97. doi:10.1177%2F1751143718777171

Reuben, A., Gopalakrishnan, V., Wagner, H. E. et al. (2015). Working with human tissues for translational cancer research. *J Vis Exp 105*, 53189. doi:10.3791/53189

Sistare, F. D., Morton, D., Alden, C. et al. (2011). An analysis of pharmaceutical experience with decades of rat carcinogenicity testing: Support for a proposal to modify current regulatory guidelines. *Toxicol Pathol 39*, 716-744. doi:10.1177/0192623311406935

Sousa, A. M., Zhu, Y., Raghanti, M. A et al. (2017). Molecular and cellular reorganization of neural circuits in the human lineage. *Science 358*, 1027-1032. doi:10.1126/science.aan3456

US EPA – United States Environmental Protection Agency (2019). Directive to Prioritize Efforts to Reduce Animal Testing. 10 September 2019 memo. https://www.epa.gov/research/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

Conflict of interest

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Meeting Report

Innovative *In Vitro* Strategies for Food and Environmental Safety

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Our diet and the environment are relevant sources of xenobiotic exposure for humans (Alloisio et al., 2019). In recent years, the scientific community has become increasingly interested in non-occupational exposure to contaminants and their mixtures and in their adverse effects. Attention has focused primarily on chemical agents but, more recently, also on biological and physical contaminants. Several bioassays have been proposed as tools to investigate the hazards of these unintentional exposures. *In vitro* models for food and environmental safety were discussed at the meeting "*In vitro* toxicology: Innovative strategies for food and environmental safety" organized by CELLTOX Italian Association of *in vitro* Toxicology in May 2020, which was presented as a webinar in compliance with the containment measures of SARS-CoV-2 infection. The meeting was chaired by Diego Baderna and Susanna Alloisio and attracted more than 100 participants.

Francesca Caloni and **Alessia Bertero**, Università degli Studi di Milano (ESP), presented an integrated approach for testing the emerging mycotoxins beauvericin (BEA) and enniatin B1 (ENNB1), natural food and feed contaminants of emerging concern (Caloni et al., 2020; Albonico et al., 2017; Prosperini et al., 2017), using an *in vitro* strategy based on the combination of human and species-specific *in vitro* models. Models for oral and topical exposure to emerging mycotoxins, alone or combined also with traditional mycotoxins, were applied, such as human intestinal barrier with Caco-2 cells differentiated on inserts in serum-free medium (Ferruzza et al., 2012), species-specific intestinal barrier with IPEC-J2 cells cultured on inserts (Zakrzewski et al., 2013), and human reconstructed skin and cornea (MatTek Corporation). The toxicological effects of the mycotoxins on trans-epithelial electrical resistance (TEER) and cytokine release in the intestinal barriers and on cell viability (MTT) in the human reconstructed skin and cornea models were evaluated. A novel integrated *in vitro* toxicological evaluation is proposed that combines human and species-specific models (i.e., bovine granulosa cell, swine intestinal models, human barriers, etc.).

Isabella De Angelis, **Valentina Prota** and **Olimpia Vincentini**, Istituto Superiore di Sanità (ISS), described a pilot study to develop an OECD Test Guideline on an *in vitro* approach for determining the gastrointestinal fate of ingested nanomaterials. Several parameters can influence the physical-chemical properties and bioavailability of nanomaterials (NMs) during their passage through the gastrointestinal tract. Caco-2 monoculture on inserts is an ideal system for rapid assessment of intestinal permeability,