

ADVANCEMENTS

In Organ Donation Research

Research Updates

We are delighted to present the latest Issue of Advancements in Organ Donation Research. Despite its obvious challenges linked to COVID-19 pandemic, years 20-21 have been two of the most exciting years in organ donation research. The arrival of mRNA vaccines to fight against COVID-19 and the future use for a variety of cancers, the significant increase in the number of Donation after Circulatory Death (DCD) organ donors, and huge leaps toward the use of DCD hearts for transplantation are just a few to name. Another significant development in organ donation research is the establishment of new CMS metrics for OPOs performance. The fact that the use of the pancreas for research would be counted as a transplanted organ will have a transformational effect on metabolic disorders including diabetes. In addition, the field of pancreatic cancer will significantly benefit from the increased availability of pancreatic samples for research.

During the last year, the ORDC was fortunate to be able to organize a number of webinars dedicated to the use of organs for research. These webinars were possible by the active participation of a number of academic and non-academic researchers. The entire ODRC leadership was delightfully surprised by a significant number of OPOs participating in these rather educational webinars.

It must be noted that the only way for continuation and expansion of OPOs' research is active participation by all members throughout the country. We would like to use this opportunity to invite all OPOs interested in research activities to reach out to the ODRC for a variety of tasks including formation of subcommittees dealing with different aspects of research and education, and the formation and contents of future ODRC webinars and newsletters.

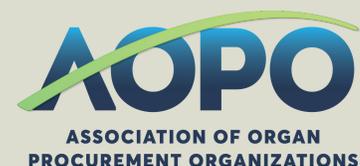


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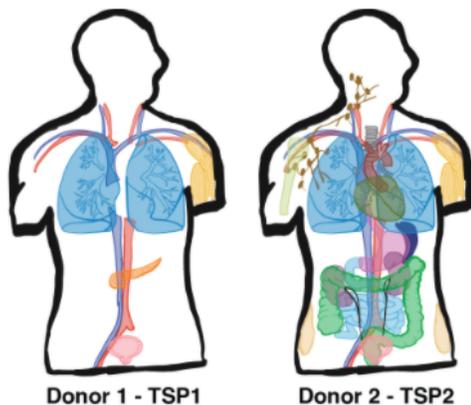
An Open Access Multi-Center Research Project

In 2018, a group of scientists primarily at Stanford University published an article in the journal Nature entitled “Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris”. In this study, the Tabula Muris Consortium provided a compendium of single-cell transcriptomic data from the laboratory mouse comprising more than 100,000 cells from 20 organs and tissues. This amazing resource put forward a tool to directly explore and compare gene expression in numerous cell types including lymphocytes and endothelial cells. This impactful study is considered a cornerstone for an atlas of transcriptomic cell biology and enabled the researchers to simultaneously survey thousands of cells in mice. The next logical step was to expand this atlas in mice (Tabula Muris) to humans (Tabula Sapiens). This atlas would be the result of studying two million cells from 25 organs of eight normal subjects. Obtaining numerous organs and tissues from the same donor would control for genetic background, age, and environment.

CONSORTIUM MEMBERS



Fig. 1) Centers involved in the Tabula Sapiens Project



To achieve this, a consortium of researchers from numerous laboratories at Stanford University, University of California San Francisco, University of California Berkeley, and Chan Zuckerberg Initiative approached Donor Network West for a pilot project. This large collaborative network of PI's with deep expertise at the preparation of diverse organs, enabling study of numerous non-transplanted organs from consented donors.

Fig. 2) Schematic representation of organs and tissues used in two donors (TSP1 and TSP2) for single-cell RNA sequencing.

As a result, the logistics and infrastructure were built capable of tracking hundreds of samples from tissues through sample preparation, library construction, and sequencing. The goal was to make sequence data rapidly and broadly available to the scientific community.

A significant amount of data has currently been posted on the Chan Zuckerberg Initiative's website from two authorized donors referred to as TSP1 and TSP2.

<https://tabula-sapiens-cellxgene.ds.czbiohub.org/all/>
<https://chanzuckerberg.github.io/cellxgene/>

As shown below, Cellxgene i.e. an interactive system for single-cell transcriptomics data was used to visualize the data enabling scientists across the world to collaboratively explore and understand single-cell RNA-seq data. The system equips developers with scalable, reusable patterns and frameworks for visualizing large scientific datasets and will be followed by a far more comprehensive data on additional donors widely available to the scientific community.

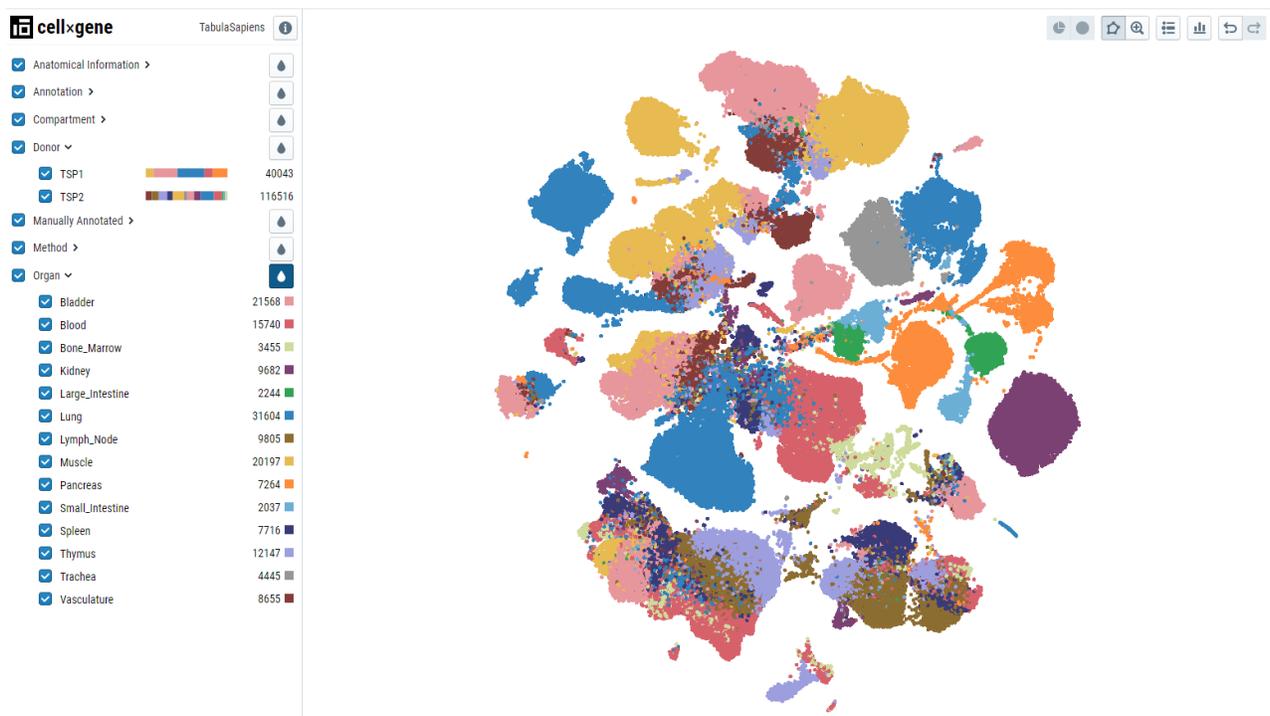


Fig. 3) Visualization of single-cell RNA-seq data using Cellxgene.

Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial

<https://www.nejm.org/doi/full/10.1056/NEJMoa2031532>

Ex situ Dual Hypothermic Oxygenated machine Perfusion (DHOPE) has been proposed as a means of reducing hepatobiliary graft injury in the setting of liver transplantation. Small studies have suggested that machine-based preservation can reduce the ischemia-reperfusion injury that contributes to these complications, but no rigorous clinical trials comparing DHOPE to conventional static cold preservation have been performed. This article presents the results of a multicenter, randomized controlled study (the DHOPE-DCD trial) comparing DHOPE with static cold preservation during transplantation of livers from donors after circulatory death (a high-risk group in whom the incidence of biliary strictures has been reported to be three times higher than that observed with brain-dead donors).

The trial was conducted at six transplant centers in Europe. Adult patients undergoing liver-only transplantation and receiving a graft from a donor after controlled circulatory death were randomly assigned to receive a liver preserved either with DHOPE (after static cold preservation during transportation) or with cold preservation alone.

The study was supported by a Dutch foundation with the machine-perfusion fluid provided by Bridge to Life. Each transplant center purchased their own perfusion device, with the manufacturer providing training of the perfusionists. This device (Liver Assist) enabled dual oxygenated perfusion through the portal vein and hepatic artery using cold Belzer machine-perfusion solution at 10 degrees C. The minimum duration of perfusion was two hours. The primary end-point was incidence of symptomatic nonanastomotic biliary strictures at 6-months after transplantation; this was assessed by the transplant teams based on symptoms and MR cholangiography.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2031532>

The study assessed 245 patients for eligibility, of whom 160 underwent randomization. After four transplant cancellations, 78 donor and recipient pairs were included in each arm. Groups were well balanced; donor risk index was median 2.12 in both groups and laboratory MELD scores were 14 in perfusion vs. 16 in control groups. Static cold-ischemia was just over six hours. Symptomatic biliary strictures were reduced by two-thirds, from 18% in the conventional arm to 6% with DHOPE ($p=0.03$). Intraoperative postreperfusion syndrome was also reduced from 46% to 28% and early allograft dysfunction from 40% to 26% (both significant). There were no differences in rates of re-transplantation or death within six months, although the study was underpowered for these outcomes.



In conclusion, this study demonstrates that use of hypothermic oxygenated machine-perfusion reduces the rate of ischemia-reperfusion injury (manifested by intraoperative instability, early allograft dysfunction, and nonanastomotic biliary strictures) when livers from donors after circulatory death are transplanted. Limitations to this approach include the inability to assess marginal livers for suitability, as may be possible with normothermic perfusion techniques. Future studies are assessing DHOPE for livers from donors after brain-death are underway. Additional studies could test whether sequential hypothermic then normothermic perfusion could allow benefits of both approaches to be realized. Cost-effectiveness of this approach to high-risk liver transplantation also needs to be assessed.

AGREEMENTS WITH RESEARCH ENTITIES



Through a series of online meetings in 2020, the ODRC's Standardization Subcommittee discussed and identified a number of critical issues that need to be addressed in any standard research agreements between OPOs and various research entities. Here we briefly list the most critical aspects of research agreements.

The issue of **Donor Privacy** and protection of donor information through de-identification proved to be an important issue. The protected health information (PHI) [names, dates, except year, telephone numbers & FAX numbers, geographic data, social security numbers, Email addresses, medical record numbers, account numbers, health plan beneficiary number, certificate/license numbers, full face photos and comparable images, vehicle identifiers and serial numbers including license plates, Web URLs + device identifiers and serial numbers, Internet protocol addresses, and biometric identifiers) must be redacted in communications with research entities.

The fact that HIPAA Privacy Rule protects the individually identifiable health information of donors for 50 years following the date of death was highlighted and must be addressed in any agreements.

The multi-OPO members reiterated the clarification of **Responsibility** in agreements. The responsibilities include but not limited to obtaining authorization, recovering samples, packaging, and shipment of biospecimens.

Another issue discussed was the description and clarification of the **Scope of Research** in agreements. The recommendation was that projects that involve genomic or proteomic profiling with the potential identification of the donors are not generally covered by standard agreements and need their own agreements.

An additional subject matter needing special attention in agreements was developing and commercialization of **immortalized cell lines**. Strict biosafety protocols, documented tracing of individual research samples, and indemnification of OPOs from claims linked to the use of samples were critical subjects that were recommended to be addressed in standard agreements.

The appropriate **Acknowledgement** of the donors and OPOs in any publications (in print or online) resulting from the work done on samples were also included in subjects discussed in standard agreements.

To facilitate the establishments of new research agreements, a template Agreement has been developed by the ODRC's Standardization Subcommittee and it will be posted on ODRC's AOPOplus page.



If you are interested in being more involved in future efforts of the ODRC, please contact Kayla Gray at kayla.gray@dnaz.org.

To join the AOPOplus community or to join the ODRC, please contact Roxane Cauwels at rcauwels@aopo.org.

THE CURRENT STATUS OF OPO RESEARCH ACTIVITIES

The review of a questionnaire collected during 2020 from OPOs across the country revealed around 1/3 of OPOs surveyed had a position dedicated to research. While this does not necessarily mean that OPOs devoid of any research staff have no research activities or their viewpoint toward research, instead it may show that a large number of OPOs have yet to find it necessary to build a department or section dedicated to research.

There is certainly an immense opportunity here for the ODRC to further facilitate research and provide support to OPOs that plan to dedicate more staff and funds to support research activities. During the last year, the ODRC has organized a number of educational webinars, worked on streamlining the standardization of processes, and published several newsletters highlighting new research projects.

Considering the extremely high quality of bio-specimens that OPOs can provide to researchers across the country and the modification of a number of regulatory processes by the US government to become more research-friendly, there is no doubt that the number of OPOs with a dedicated research organization will be on the increase.

