

ADVANCEMENTS

In Organ Donation Research

Research Updates

During the 2019 Organ Donation Research Council (ODRC's) meeting in St Louis, it became apparent that there was a paucity of information on the scale and nature of research in OPOs across the country. As a council, it was decided that collecting basic information about the scale of OPO's Research involvement would drastically benefit the OPO community and allow the ODRC to better address specific needs and more accurately predict trends in OPOs' research. In response, the ODRC developed a comprehensive Questionnaire regarding research among OPOs.

In response, 48 OPOs completed the survey, representing 83% of all OPOs nationwide. We encourage other non-responding OPOs to act and participate in the future. We believe that it is an absolute necessity for the ODRC to reflect research activity across the country.

We are delighted to note that 94% of all responding OPOs, participate in some capacity in supporting research. While there are significant differences in terms of the extent of OPOs' Research Teams, type of Research positions, the project that they support, more than 70% plan to expand their Research activities in the near future. It is noteworthy to mention that more one-third of OPOs have at least one staff dealing with Research activities.

Research education including designing processes, project verifications, and activating new research projects are in great demand. In fact, more than 80% of respondents are motivated to participate in research-related educational activities.

ODRC, as an active AOPO Council seems to be popular among OPOs. In fact, around half of OPOs have already been participating in the ODRC. It is encouraging to note that one-third of non-members have expressed interested in joining ODRC. We encourage all interested OPOs to join the ODRC Team and plan to directly contact interested OPOs.



ASSOCIATION OF ORGAN
PROCUREMENT ORGANIZATIONS

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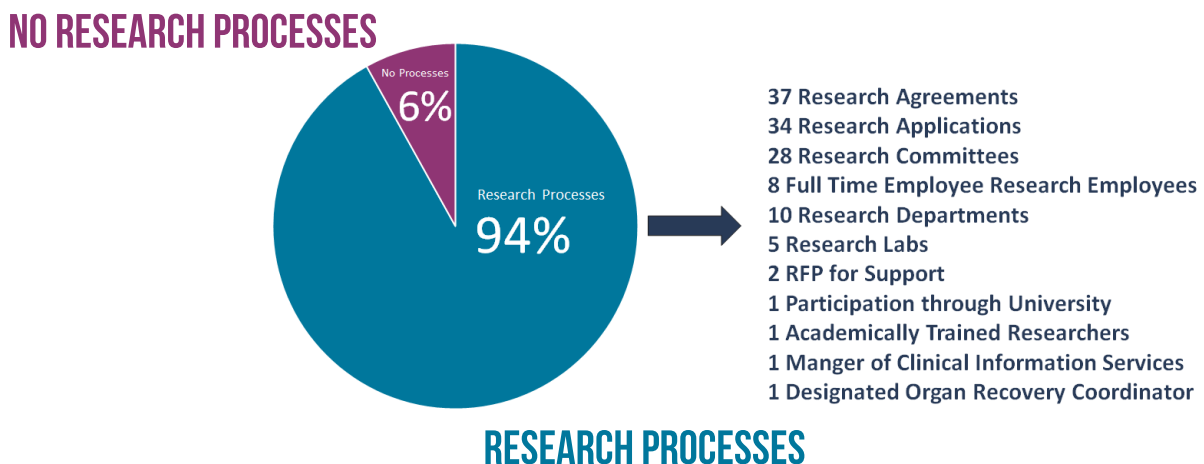
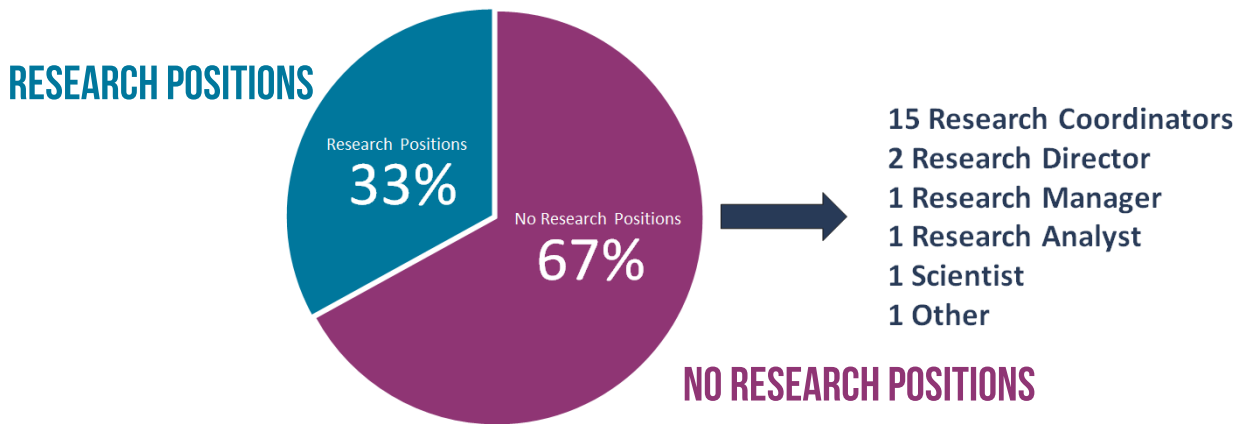
In response to these results, the ODRC is looking into new mechanisms to drastically expand educational resources and become more involved in process design and educational activities. Accordingly, the ODRC leadership has recently created a subcommittee dealing with standardization of research-related agreements to allow better harmonization among OPOs across the US.

In order to expand educational resources, the ODRC is also looking into organizing webinars that include invited speakers, project highlights, and an open forum to exchange ideas.

The ODRC is open to all members for involvement and the leadership of the council invites your involvement.

If you are interested in being more involved in any future efforts of the ODRC (e.g. joining subcommittees, providing content for future webinars or the newsletter, etc.), please contact Kayla Gray at kayla.gray@dnaz.org.

To join the AOPOPlus community or join the ODRC, please reach out to Roxane Cauwels at rcauwels@aopo.org.



ODRC COMMITTEES

Since its inception, the ODRC has been aiming to better understand the need for research activities and help to initiate and maintain active research programs in OPOs across the country.

This year, despite unprecedented limitations imposed on us by the COVID-19 pandemic, the ODRC has been working diligently to further support research activities and foster new partnerships between public and private research entities and OPOs. In order to do that, we have worked on forming a number of ODRC sub-committees to better identify the issues and problems and come up with recommendations to remedy them.

The first sub-committee was the Standardization Group. Through a series of online gatherings during the last several months, a number of issues related to research agreements and their standardizations took place. Within a short period, it became clear that issues that commonly concern the research program include donor privacy, safety, indemnity, and the nature of research projects. These issues were compounded by the wide availability of new genomic and proteomic methods that potentially affect donors' privacy in the future.



STANDARDIZATION COMMITTEE

Members

- Ahmad Salehi, MD
- Roxane Cauwels
- Gary Morgan
- Chuck Zollinger
- Darla Welker
- Immanuel Rasool
- Kayla Gray
- Glen A Franklin, MD
- Gary Marklin, MD
- Marty Sellers, MD
- Nissa Casey

Goals

During the next 4 weeks, The ODRC Leadership will send a draft document that involves a template for research agreements to all participating OPOs and will seek their comments and suggestions. At the end of this period, the recommended template will be posted at the AOPO Plus and all participating OPO Research programs can freely use this template as a guide to establishing agreements with their research partners across the country.

If you are interested in becoming more involved in this subcommittee or would like to share any thoughts on future subcommittees, please reach out to Ahmad Salehi at asalehi@dnwest.org

ODRC WEBINAR SERIES

The ODRC held a webinar, titled “Research Studies” on September 29, 2020 that was attended by 143 participants.

The goal of this webinar was to present ongoing research studies involving the OPO community, highlighting challenges but also opportunities for collaboration. There were three speakers: Jocelyn Phillips, Clinical Trainer at Southwest Transplant Alliance, Dr. Gary Marklin, chief medical and research officer at Mid-America Transplant, and Dr. Claus Niemann, Professor of Anesthesia and Surgery at UCSF. The speakers noted that some of the greatest challenges in multi-center trials included variability in approval processes for such studies across OPOs, the need to obtain IRB approvals (primarily for recipient data) and the creation a data and ethics monitoring committee to oversee such studies. These presenters then participated in panel discussion regarding OPO research as whole.

One particular area that came up was how the ODRC could engage and facilitate OPOs participating in such collaborative research. Another ongoing initiative highlighted was the opportunity and advantages of standardizing OPO research processes and practices.



Jocelyn Phillips, Clinical Trainer

Southwest Transplant Alliance

Ms. Phillips presented some important lessons learned in getting a complex study up-and-running, including the importance of identifying key stakeholders and responding to challenges. She specifically spoke on her experience related to the APOLLO Study.

Gary Marklin, MD, Chief Medical & Research Officer

Mid-America Transplant

Dr. Marklin presented about the upcoming multi-OPO randomized trial of T4. This unblinded study will randomize heart-eligible donors requiring vasopressor support to intravenous T4 or saline placebo. The primary outcome will be whether a higher proportion of hearts are transplanted.

Claus Niemann, MD, Professor of Anesthesia & Surgery

University of California, San Francisco

Dr. Niemann presented on the ongoing randomized control hypothermia study for kidney donation. The goal of this study is to test whether hypothermia is as effective as machine perfusion and will wrapping up enrollment by the end of 2020.

The goal of APOLLO is to make kidney transplantation have an even greater positive impact by learning more about genetic variations that are found in some people of African descent.

It has been known for decades that African Americans have higher risk for end-stage renal disease and require dialysis treatments 3 to 4 times more often than other racial and ethnic groups. In 2010, a major research discovery showed that small changes in a single gene, the APOL1 gene, contributes to this increased risk of kidney disease in African Americans. Preliminary data suggests that variation in the APOL1 gene can also impact outcomes after kidney transplantation and affect the safety of living kidney donation for the kidney recipient. Based on this, the National Institutes of Health is launching the APOLLO study or the APOL1 Long-term Kidney Transplantation Outcomes Network.

The purpose of APOLLO is to improve the lives of those who donate or receive a kidney by learning more about the genetic variations in the APOL1 gene that are found in some people of African descent. This collaborative effort engages the existing network of Organ Procurement Organizations and HLA Laboratories, a community advisory council comprised of kidney donors, recipients and advocates, and approximately 240 transplant programs across the United States all with the sole mission of better understanding the impact of the APOL1 gene on kidney transplantation outcomes.

Results of the APOLLO study have the potential to improve outcomes for all people with end-stage renal disease. There may be more kidney transplants and the safety of living kidney donation may be improved as a result of this research.

For more information visit: <https://www.theapollonetwork.org>

Contact APOLLOstudy@wakehealth.edu



WE ARE SHARING HOPE

The use of an anti-rejection drug additive to a standard UW preservation solution will lead to first-in-class priority preservation solution for broad application in all solid organ transplants to pre-treat, rather than simply preserve, organs for transplantation.

As most transplanted organs are procured from deceased donors, an organ must be stored and preserved until it can be transplanted into a recipient. Preservation times vary with the different organs; with hearts and lungs, transplants must occur within 6 hours of recovery while kidneys can be stored safely for 24-48 hours. Over the last 20 years, many methods and solutions have been developed to preserve donor organs for transplantation. The most widely utilized preservation solution is the University of Wisconsin (UW) solution. The components of UW solution, as with the other solutions, are utilized to maximize organ function after blood flow is re-established in the recipient. They do nothing to mitigate the injury suffered as a consequence of organ donation nor do they prepare the donor organ for the oncoming attack from the recipient's immune system.

Currently available preservation solutions aim to prolong organ viability and allow for donor organ transportation. None of the currently available organ preservation solutions provide protection from injury or load anti-rejection drugs into the donor organ prior to transplant. Our team has capitalized on these unique findings and has developed a bioengineered solution to optimally deliver antirejection medications, specific to the donor organ, by the addition of a nanoparticle carrying anti-rejection drugs (Targeted Rapamycin Micelles or TRaM) contained within the UW preservation solution. The use of such an additive to a standard UW preservation solution will lead to first-in-class priority preservation solution for broad application in all solid organ transplants to pre-treat, rather than simply preserve, organs for transplantation.

For more information visit www.SharingHopeSC.org

Contact Darla Welker: welkerd@sharinghopesc.org



SOUTH CAROLINA ORGAN & TISSUE RECOVERY SERVICES

MIROMATRIX

The need for transplantable organs outpaces the ability to recover transplantable organs. The prospect of bioengineered organs to meet that need is tantalizing.

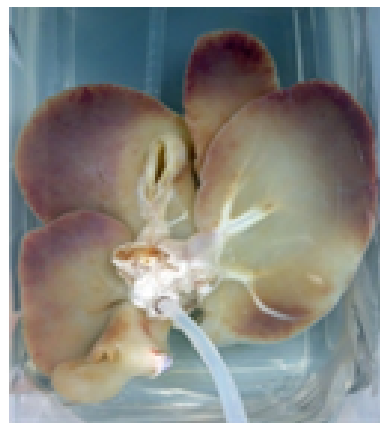
Miromatrix is a regenerative medicine company leading the way toward bioengineering transplantable human organs. Perfusion decellularization and recellularization technology allows them to remove all cellular material from a porcine organ, a kidney for example, leaving behind a pristine kidney scaffold with an intact vascular structure. They then perfusion recellularize the kidney with primary kidney parenchymal cells, for example, endothelial cells, podocytes, and mesangial cells. This is accomplished in a bioreactor and results in a functional human kidney. Miromatrix currently has active research programs for liver and kidney and has demonstrated the ability to bioengineer an intact vascular system, repopulate the porcine scaffold with functional primary cells, and in vivo functionality. To date the Miromatrix research team has been developing bioengineering processes using hybrid organs composed of human endothelial cells and porcine parenchymal cells. As they transition to a bioengineered organ to help people, they are now working with human parenchymal cells and are thus in need of acquiring donated organs which are not suitable for transplant. This research program is intended to increase the supply of transplantable organs. Miromatrix estimates that one donated kidney can be bioengineered into 4-8 transplantable kidneys. With shared missions of increasing the transplantable organ supply and making the most of the gift of life, Miromatrix is eager to build research partnerships with OPOs who can supply organs for this effort.

For more information visit: <https://www.miromatrix.com/>

Contact M. Mason Macenski: mmacenski@miromatrix.com



0 Hours



8 Hours



24 Hours

Time series of a pig liver undergoing perfusion decellularization, with complete decellularization at 24 hours leaving a perfectly intact liver scaffold complete with vasculature.

Photo Courtesy of Miromatrix

There are no known conflicts of interest with Miromatrix within AOPO or ODRC.

Research Spotlights are here to show the impact that organ procurement professionals and their respective OPOs have created that have resulted in a scientific publication. The Advancements in Organ Donation Research newsletter will spotlight a few of the articles each edition and provide space on AOPO Plus where you can easily access the abstracts, authors and links to the full articles. These publications may include authors from the OPO community or have utilized research organs, tissues, eyes or data for their research. The ODRC leadership invites you to share any current or past publications that you have participated in to be featured or added to AOPO Plus for archival purposes.

This edition, we want to spotlight a group of transplant and organ procurement professionals worked together to approach the issue of best practices associated with this type of donation. With the help of the ODRC, a survey went out to OPO leadership and transplant surgeons alike in the hope of creating a more standardized way of approaching DCD donors. In doing so, the leaders of this project were able to publish an impactful article with 83% of OPOs participating.

This publication truly highlights the importance of collaboration among OPOs, specifically in regards to research. When we work together towards standardization and discovering new techniques in the field, the OPO community truly makes a lasting impact in both organ procurement and medical advancements as a whole. The ODRC is in place to help facilitate projects, like this one, and promote the innovation that OPOs are pioneering and participating in across the country and world.

A Step toward Standardization: Results of two National Surveys of Best Practices in Donation after Circulatory Death Liver Recovery and Recommendations from The American Society of Transplant Surgeons and Association of Organ Procurement Organizations

Clinical Transplantation

Mark J. Hobeika, Robert Glazner (AZOB), David P. Foley, Steven Hanish, George Loss, Cristiano Quintini, Eling Eidbo (AOPO), Charles Zollinger (UTOP), Jay Ruterbories (PATF), Daniel J. Lebovitz (OHLB), David Axelrod

Donation after circulatory death (DCD) liver allografts remain underutilized. Inconsistent processes for DCD procurement may contribute to allograft discard. Optimal surgical and organ procurement organization (OPO) practices for DCD liver recovery should be developed and adopted. DCD practice surveys were distributed to transplant surgeons and OPO leadership. DCD liver recovery best practices were assembled based on survey data, literature review, and subject-matter expert consensus opinion. Data were obtained from transplant surgeons (n = 188) and OPO leadership (n = 48 OPOs). Surgeons preferred attending physician presence at recovery (72.4%); while only 27.7% of OPOs require this. Pre-withdrawal communication huddle (Surgeons: 88.7%; OPOs: 93.8%) and administration of pre-withdrawal heparin (Surgeons: 90.6%; OPOs: 84.8%) are widely accepted. Surgical preference for withdrawal of support is in the operating room (89.3%); OPO practice varies dependent upon hospital and family requirements. Functional donor warm ischemic time (fDWIT) start time is variable, while fDWIT end time is agreed upon as initiation of aortic flush by surgeons (81%) and OPOs (81%). DCD liver recovery practices including mandatory communication huddle, pre-withdrawal heparin administration, and clearly defined start and end of fDWIT should be implemented nationally. Creating a set of best practices for DCD recovery guidelines is necessary for improving DCD liver utilization.

Point-of-care blood gas analyzers have an impact on the acceptance of donor lungs for transplantation.

The Scandinavian Journal of Clinical and Laboratory Investigation

Gary F. Marklin (MOMA), Robert Bresler(MOMA), Rajat Dhar (MOMA)

An organ donor PaO₂ above 300 mm Hg is generally required for lung transplantation. Point-of-care (POC) blood gas analyzers are commonly used by organ procurement organizations (OPO) but may underestimate the PaO₂ at high levels. We hypothesized that changing to a more accurate blood gas analyzer would result in additional lungs transplanted. All PaO₂ measurements on organ donors managed at one OPO's recovery center were performed on an i-STAT POC analyzer prior to October 2015, and on a GEM 4000 subsequently. For 24 weeks, all blood gases were tested simultaneously on both analyzers. We compared lung outcomes of 147 donors in the year prior to this change (using the i-STAT) with 56 donors in the 24-week study period (using the GEM 4000 for lung allocation). When the PaO₂ was above 300 mm Hg, the i-STAT PaO₂ was 54 mm Hg lower on average than the GEM 4000. When the GEM PaO₂ measured between 300–375 mm Hg, the corresponding i-STAT PaO₂ value registered less than 300 mm Hg 25 out of 48 times (52%), with an average difference of 55 mm Hg (S.D. 22). The rate of lungs transplanted using the GEM 4000 was 48% compared with 35% in the year prior using the i-STAT (p=0.11), with equivalent recipient outcomes. The i-STAT analyzer underestimated the PaO₂ above 300 mm Hg and changing to a more accurate PaO₂ analyzer may increase lungs transplanted.

<https://doi.org/10.1080/00365513.2020.1821395>

Moving From Organ Donation to Knowledge Donation: A Novel Opportunity for Surgical Education Following Organ Donation

Cureus

Peter Wu, Rebecca Rieger, Margaret M. McBride,
Kayla Gray(AZOB), James Mankin

The objective of this article is to share how our institution implemented the use of organ donors for surgical education following organ recovery. Despite technological advances, realistic surgical simulation models are lacking, leaving little opportunity to practice a procedure prior to performance on a living patient. Utilization of organ donors following organ donation offers an opportunity for life-like surgical simulation. We developed a pathway to use organ donor tissue in the post-recovery period for robotic simulation. We obtained support from our local Institutional Review Board, Ethics Committee, and organ procurement organization to create a “knowledge donor” program. Our knowledge donation program provided learners hands-on experience with a novel procedure and also provided organ donors another opportunity to express their altruism. We found that the process was well accepted by donor families and learners. We implemented a knowledge donation program at our hospital that provides valuable surgical experience. We discuss future directions for knowledge donation at our institution.

<https://doi.org/10.7759/cureus.10473>

RESEARCH MADE POSSIBLE BY OPO'S

Functional Organization of Midget and Parasol Ganglion Cells in the Human Retina

bioRxiv

Research Partnership with Department of
Neurosurgery at Stanford University

Abstract: The functional organization of diverse retinal ganglion cell (RGC) types, which shapes the visual signal transmitted to the brain, has been examined in many species. The unique spatial, temporal, and chromatic properties of the numerically dominant RGC types in macaque monkey retina are presumed to most accurately model human vision. However, the functional similarity between RGCs in macaques and humans has only begun to be tested, and recent work suggests possible differences. Here, the properties of the numerically dominant human RGC types were examined using large-scale multi-electrode recordings with fine-grained visual stimulation in isolated retina, and compared to results from dozens of recordings from macaque retina using the same experimental methods and conditions. The properties of four major human RGC types -- ON-parasol, OFF-parasol, ON-midget, and OFF-midget -- closely paralleled those of the same macaque RGC types, including the spatial and temporal light sensitivity, precisely coordinated mosaic organization of receptive fields, ON-OFF asymmetries, spatial response nonlinearity, and sampling of photoreceptor inputs over space. Putative smooth monostratified cells and polyaxonal amacrine cells were also identified based on similarities to cell types previously identified in macaque retina. The results suggest that recently proposed differences between human and macaque RGCs probably reflect experimental differences, and that the macaque model provides an accurate picture of human RGC function.

Involvement: The human eye was provided by **Donor Network West** (San Ramon, CA). We are thankful for the cooperation of Donor Network West and all of the organ and tissue donors and their families, for giving the gift of life and the gift of knowledge, by their generous donations.

<https://doi.org/10.1101/2020.08.07.240762>

The ex vivo human lung: research value for translational science

JCI Insight

Research Partnership with
Cardiovascular Institute at
University of California, San Francisco

Abstract: Respiratory diseases are among the leading causes of death and disability worldwide. However, the pathogenesis of both acute and chronic lung diseases remains incompletely understood. As a result, therapeutic options for important clinical problems, including acute respiratory distress syndrome and chronic obstructive pulmonary disease, are limited. Research efforts have been held back in part by the difficulty of modeling lung injury in animals. Donor human lungs that have been rejected for transplantation offer a valuable alternative for understanding these diseases. In 2007, our group developed a simple preparation of an ex vivo-perfused single human lung. In this Review, we discuss the availability of donor human lungs for research, describe the ex vivo-perfused lung preparation, and highlight how this preparation can be used to study the mechanisms of lung injury to isolate primary cells, and to test novel therapeutics.

Involvement: The authors thank donor families for their gift to research and **Donor Network West** and **Tennessee Donor Services** for their assistance in obtaining organs for research.

<https://doi.org/10.1172/jci.insight.128833>

RESEARCH MADE POSSIBLE BY OPO'S

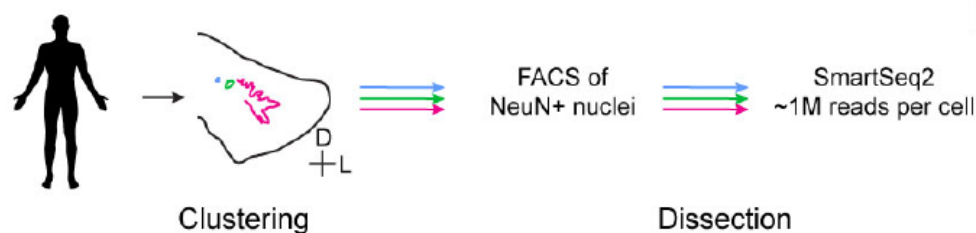
Cerebellar nuclei evolved by repeatedly duplicating a conserved cell type set

bioRxiv

Research Partnership with Department of Neurosurgery at Stanford University

Abstract: How have complex brains evolved from simple circuits? Here we investigated brain region evolution at cell type resolution in the cerebellar nuclei (CN), the output structures of the cerebellum. Using single-nucleus RNA sequencing in mice, chickens, and humans, as well as STARmap spatial transcriptomic analysis and whole-CNS projection tracing in mice, we identified a conserved cell type set containing two classes of region-specific excitatory neurons and three classes of region-invariant inhibitory neurons. This set constitutes an archetypal CN that was repeatedly duplicated to form new regions. Interestingly, the excitatory cell class that preferentially funnels information to lateral frontal cortices in mice becomes predominant in the massively expanded human Lateral CN. Our data provide the first characterization of CN transcriptomic cell types in three species and suggest a model of brain region evolution by duplication and divergence of entire cell type sets.

Involvement: Human samples were obtained from **Donor Network West** and were deemed exempt from IRB regulations by Stanford University.



This figure shows an overview of workflow for human snRNAseq. The three CN are separately dissected from frozen tissue, and processed for snRNAseq of NeuN+ nuclei as done for mouse and chicken CN.

<https://doi.org/10.1101/2020.06.25.170118>

Characterizing relaxin receptor expression and exploring relaxin's effect on tissue remodeling/fibrosis in the human bladder

BMC Urology

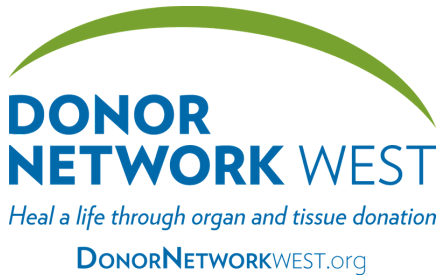
Research Partnership with Department of Urology, Stanford University Medical Center

Abstract: Relaxin is an endogenous protein that has been shown to have antifibrotic properties in various organ systems. There has been no characterization of relaxin's role in the human bladder. Our objective was to characterize relaxin receptor expression in the human bladder and assess relaxin's effect on tissue remodeling/fibrosis pathways in bladder smooth muscle cells.

Involvement: IRB exemption and external approval from **Donor Network West's** (federally designated organ procurement organization) Internal Research Council and Medical Advisory Board Research Subcommittee was obtained for collection of primary bladder tissue from brain dead cadaveric organ transplant donors.

<https://doi.org/10.1186/s12894-020-00607-4>

SPECIAL THANKS TO THE FOLLOWING OPO'S FOR THEIR SUBMISSIONS



Tennessee Donor Services
an extraordinary commitment to science, health and hope



A Division of
DCI Donor Services

