BIOGRAPHICAL SKETCH

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NAME: Soto-Gutierrez, Alejandro

eRA COMMONS USER NAME (credential, e.g., agency login): ASOTO1

POSITION TITLE: Associate Professor, Department of Pathology, University of Pittsburgh.

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Guadalajara, Mexico	MD	02/1998-03/2004	Medicine
Okayama University, Japan	PhD	04/2004-09/2007	Bio-pathological Science
Okayama University, Japan	Clinical Fellowship Surgery	04/2005-09/2007	Surgery
Massachusetts General Hospital, Harvard Medical School, Boston, USA	Research fellowship	11/2007-10/2009	Surgery & Bioengineering
University of Pittsburgh, Pittsburgh, USA	Instructor of Surgery	11/2009-06/2011	Cell & Regenerative Therapies

A. Personal Statement

The goal of our laboratory is to develop new methodologies to treat liver disease with multi-cellular cues for complete and stable repopulation of livers and maturation of stem-derived liver cells to engineer functional human liver tissue in vitro and in vivo to use it for modeling liver disease, drug discovery and transplantation. I have the expertise, leadership and motivation necessary to successfully carry out the proposed work. I have a broad background in liver cell therapy, liver tissue engineering, hepatic differentiation, and biology with the clinical know-how with specific training and expertise in key research areas for this application. The subject of my PhD thesis was stem cell therapies and experimental transplantation, which involves hepatic differentiation of mouse and human pluripotent stem cells and utilization in cell transplantation therapies. I have focused on hepatic development and the molecular pathways of human pluripotent stem cell differentiation towards mature hepatic phenotype. I designed a simple and effective differentiation protocol involving natural stages of liver development by the addition of soluble factors and the co-culture of a combination of non-parenchymal liver cell lines for improved maturation and developed novel biological and surgical approaches in hepatic cell therapies. Early in my career, I recognize the main obstacles in the field of stem cell derived hepatocyte function and I believe the engineering of human liver tissue from stem cells hold enormous potential for modeling the cues of a whole organ. The success of my early work with surgery and transplantation convinced me that my background in stem cells and experimental and clinical cell transplantation would provide me with the fundamental skills and knowledge required to develop such approaches. Further, my medical training would help me consider practical issues for hepatic functions and applications. Therefore, I decided to pursue postdoctoral training at the Harvard Medical School. I focused my efforts on developing protocols and techniques to engineer liver tissue using the natural liver Extracellular matrix and primary isolated cells. A critical finding of my work was that the quality of the matrix is vital, especially if stem cells are going to be used. Upon completion of my postdoctoral training, I accepted a position at the University of Pittsburgh, an institution with one of the largest multidisciplinary groups of scientists dedicated to liver biology. Here, I have coax my cellular biology expertise with tissue engineering and genetic engineering to understand hepatocyte functions relevant to human disease (e.g. cirrhosis, liver failure, fatty liver) and recently obtained my tenure as an Associate Professor. In addition, I have successfully administered my own projects (e.g. staffing, research protections, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. In summary, I have a demonstrated record of accomplished and productive research projects in an area of high relevance for liver engineering, and my expertise and experience have prepared me to lead the proposed project.

B. Positions and Honors

Positions and Employment

1999-2002 Clinical Research Fellow, University Hospital, University of Guadalajara, Mexico.
2002-2003 Medical Intern, University Hospital, University of Guadalajara, Mexico.
2003-2004 General Medicine Practitioner, National Health Department of Mexico.
2004-2007 PhD Student, Bio-pathological Science, Okayama University, Japan.
2007-2009 Surgery Research Fellow Harvard Medical School, Boston, MA, USA.
2009-2011 Instructor of Surgery, University of Pittsburgh, Pittsburgh, PA, USA.
2011-present Assistant Professor, Department of Pathology, University of Pittsburgh, Pittsburgh, PA, USA.
2012-present Editor-in-Chief of "Organogenesis", Taylor&Francis Editorial House
2012-present Director of the Cell Therapy Course at the University of Pittsburgh School of Medicine.
2013-present Co-Founder of Wholeorgan.org and Facilitator of "The Whole Liver Research Community" www.wholeorgan.org
2015-present Past-Chair and Founder. Transplant Regenerative Medicine Community of Practice (TRM COP) at the American Society of Transplantation,
2016-present Associate Director, Cellular & Molecular Pathology (CMP) Graduate Program in the Department of Pathology.
2017-present Associate Professor (Tenured) Department of Pathology, University of Pittsburgh.

Honors

2004 Doctoral Course Scholarship, "Monbukagakusho" Ministry of Education, Science and Culture, Japan.
2005 Young investigator award of the International College of Surgery. Sapporo, Japan.
2007 Yuki award for research excellence of the Medical Association of Japan.
2007 "Martin de la Cruz" award, University of Guadalajara, Mexico.
2008 Clinical Research Award in Transplantation from the New England Organ Bank.
2009 NIH Pathway to Independence (PI) Award (K99/R00)
2009 Thomas E. Starzl, Research Award from the American Liver Foundation
2011 BD Biosciences Stem Cell research award
2012 AST (American Society of Transplantation) Basic Science Faculty Development Grant
2013 The Competitive Medical Research Award from the UPMC Health System
2016 The Pittsburgh Liver Research Liver Center Seed Grant award 2016-2017
2016 University of Pittsburgh Physicians (UPP)/UPMC Academic Foundation Research Grant

Patents

- Isolated adult cells, artificial organs, rehabilitated organs, research tools, organ encasements, organ perfusion systems, and methods for preparing and utilizing the same. Publication #: WO2011002926
- Methods For The Treatment And Prevention Of Liver Disease. Publication #: US20140249209
- Method of preparing artificial organs, and related compositions. Publication #: WO2015168254
- Human induced pluripotent stem cells for high efficiency genetic engineering. Application, No. PCT/US2017/044719
- **Methods of engineering human induced pluripotent stem-derived livers in rats and uses thereof.** Application, No. PCT/US2018/018032

Professional activities

Advisory Boards

-Scientist member- University of Pittsburgh's Human Stem Cell Research Oversight (hSCRO) Committee. March 1, 2013- May 28, 2018.
-Scientist member- American Society of Transplantation, Vascular Composite Allotransplantation Advisory Council (VCA). May 20, 2013-April 30, 2016.
- Chair and founder- American Society of Transplantation, Transplant Regenerative Medicine Community of Practice (TRM COP). January, 2015-December, 2018.
- Committee Member- Cellular Approaches for Tissue Engineering and Regeneration (CATER) program. Training Grant from the National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health. January, 2015-Present
- Committee Member - The Health Sciences Tissue Bank (HSTB), University of Pittsburgh.

Other Service:

Reviewer for American Society of Transplantation, January 2014, four year appointment
Reviewer for the European Research Council (2013, 2014)

-Reviewer for the American Association for the Advancement of Science (AAAS)
- Invited Reviewer for the Center for Scientific Review Special Emphasis Panel
Small Business: Digestive Sciences, Consortium on Targeting And Regeneration (Human Islet Research Network (HIRN)), and the Hepatobiliary Pathophysiology Study Section (HBPP) at the National Institutes of Health.

C. Contribution to Science (from 88 peer-reviewed publications), H-index, 36.
My contributions to science are in three major research areas: 1) Generation and hepatic differentiation of pluripotent stem cells for the treatment of liver failure; 2) Tissue and organ bioengineering for transplantation; 3) Understanding and prevention of hepatocyte failure.

1. Generation and hepatic differentiation of pluripotent stem cells for the treatment of liver failure. We have designed simple and effective hepatic differentiation protocol involving natural stages of liver development by the addition of soluble factors and the co-culture of a combination of non-parenchymal liver cell lines for improved hepatic maturation of pluripotent-derived liver cells. Additionally, we have evaluated the reprogramming capacity of different stages of development of human liver cells and established differentiation protocols of patient-derived iPS cells to study alpha-1-anti-trypsin deficiency.

1: Collin de l'Hortet A, Takeishi K, Guzman-Lepe J, Morita K, Achreja A, Popovic B, Wang Y, Handa K, Mittal A, Meurs N, Zhu Z, Weinberg F, Salomon M, Fox IJ, Deng CX, Nagrath D, **Soto-Gutierrez A***. Generation of Human Fatty Livers Using Custom-Engineered Induced Pluripotent Stem Cells with Modifiable SIRT1 Metabolism. **Cell Metab. 2019** Aug 6;30(2):385-401.e9. PMID: 31390551. ***(Corresponding Author)**

2: Zabulica M, Srinivasan RC, Vosough M, Hammarstedt C, Wu T, Gramignoli R, Ellis E, Kannisto K, Collin de l'Hortet A, Takeishi K, **Soto-Gutierrez A*,** Strom SC. Guide to the Assessment of Mature Liver Gene Expression in Stem Cell-Derived Hepatocytes. **Stem Cells Dev. 2019** Jul 15;28(14):907-919.
PMCID: PMC6648222. ***(Corresponding Author)**

3: Tafaleng EN, Chakraborty S, Han B, Hale P, Wu W, **Soto-Gutierrez A,** Feghali-Bostwick CA, Wilson AA, Kotton DN, Nagaya M, Strom SC, Roy-Chowdhury J, Stolz DB, Perlmutter DH, Fox IJ. Induced pluripotent stem cells model personalized variations in liver disease due to α1-antitrypsin deficiency. **Hepatology. 2015;**62(1):147-57. PMCID: PMC4482790

4: Basma H, **Soto-Gutiérrez A,** Yannam GR, Liu L, Ito R, Yamamoto T, Ellis E, Carson SD, Sato S, Chen Y, Muirhead D, Navarro-Alvarez N, Wong RJ, Roy-Chowdhury J, Platt JL, Mercer DF, Miller JD, Strom SC, Kobayashi N, Fox IJ. Differentiation and transplantation of human embryonic stem cell-derived hepatocytes. **Gastroenterology. 2009;**136(3):990-9. PMCID: PMC2732349.

5: **Soto-Gutiérrez A,** Navarro-Alvarez N, Zhao D, Rivas-Carrillo JD, Lebkowski J, Tanaka N, Fox IJ, Kobayashi N. Differentiation of mouse embryonic stem cells to hepatocyte-like cells by co-culture with human liver nonparenchymal cell lines. **Nat Protoc. 2007**;2(2):347-56. PMID: 17406596.

6: **Soto-Gutiérrez A,** Kobayashi N, Rivas-Carrillo JD, Navarro-Alvarez N, Zhao D, Okitsu T, Noguchi H, Basma H, Tabata Y, Chen Y, Tanaka K, Narushima M, Miki A, Ueda T, Jun HS, Yoon JW, Lebkowski J, Tanaka N, Fox IJ. Reversal of mouse hepatic failure using an implanted liver-assist device containing ES cell-derived hepatocytes. **Nat Biotechnol. 2006**;24(11):1412-9. PubMed PMID: 17086173.

2. Tissue and organ bioengineering for transplantation. I also targeted my research efforts toward the development of strategies to deliver the cells as tissue-like structures, using tissue-engineering technologies. My laboratory also focus my on developing protocols and techniques to engineer whole livers for transplantation using the liver natural matrix and isolated cells.

1: Ono Y, Pérez-Gutiérrez A, Yovchev MI, Matsubara K, Yokota S, Guzman-Lepe J, Handa, K, Collin de l'Hortet A, Thomson AW, Geller DA, Yagi H, Oertel, M., **Soto-Gutierrez A*.** Regeneration and Cell Recruitment in an Improved Heterotopic Auxiliary Partial Liver Transplantation (APLT) Model in the Rat. **Transplantation. 2017**;101(1):92-100. ***(Corresponding Author)**

2: Collin de l'Hortet A, Takeishi K, Guzman-Lepe J, Handa K, Matsubara K, Fukumitsu K, Dorko K, Presnell C,S., Yagi H, **Soto-Gutierrez A***. Liver Regenerative-Transplantation: Regrow and Reset. **Am J Transplantation. 2016;**16(6):1688-96. ***(Corresponding Author)**

3: Yagi H, Fukumitsu K, Fukuda K, Kitago M, Shinoda M, Obara H, Itano O, Kawachi S, Tanabe M, Coudriet GM, Piganelli JD, Gilbert TW, **Soto-Gutierrez A*,** Kitagawa Y. Human-scale whole-organ bioengineering for liver transplantation: a regenerative medicine approach. **Cell Transplant. 2013** ;22(2):231-42. ***(Corresponding Author**)

4: **Soto-Gutierrez A*,** Wertheim JA, Ott HC, Gilbert TW. Perspectives on whole organ assembly: Moving towards transplantation on demand. **J Clin Invest. 2012** 1;122(11):3817-23. ***(Corresponding Author**)

5: **Soto-Gutierrez A*,** Zhang L, Medberry C, Fukumitsu K, Faulk D, Jiang H, Reing J, Gramignoli R, Komori J, Ross M, Nagaya M, Lagasse E, Stolz D, Strom SC, Fox IJ, Badylak SF. A whole-organ regenerative medicine approach for liver replacement. **Tissue Eng Part C Methods. 2011**, 17(6):677-86. PMCID: PMC3103054. ***(Corresponding Author**)

6: Uygun BE, **Soto-Gutierrez A,** Yagi H, Izamis ML, Guzzardi MA, Shulman C, Milwid J, Kobayashi N, Tilles A, Berthiaume F, Hertl M, Nahmias Y, Yarmush ML, Uygun K. Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix. **Nat Med. 2010** Jul;16(7):814-20. PMCID: PMC2930603.

7: Navarro-Alvarez N, **Soto-Gutierrez A**, Chen Y, Caballero-Corbalan J, Hassan W, Kobayashi S, Kondo Y, Iwamuro M, Yamamoto K, Kondo E, Tanaka N, Fox IJ, Kobayashi N. Intramuscular transplantation of engineered hepatic tissue constructs corrects acute and chronic liver failure in mice. **J Hepatol. 2010**;52(2):211-9.

3. Understanding and prevention of hepatocyte failure. My laboratory have pioneered and patented ways to examined the metabolic breakdown that takes place in liver cells during late-stage cirrhosis and found clues that suggest new treatments to delay liver failure. By forcing expression of the genes that control liver cell function and resetting liver transcriptional program, we have been able to reverse chronic liver failure.

1: Guzman-Lepe J, Cervantes-Alvarez E, Collin de l'Hortet A, Wang Y, Mars WM, Oda Y, Bekki Y, Shimokawa M, Wang H, Yoshizumi T, Maehara Y, Bell A, Fox IJ, Takeishi K, **Soto-Gutierrez A*.** Liver-Enriched Transcription Factors Expression Relates to Chronic Hepatic Failure in Humans. **Hepatology Commun. 2018** 23;2(5):582-594. ***(Corresponding Author)**

2: Tobita T, Guzman-Lepe J, Takeishi K, Nakao T, Wang Y, Meng F, Deng CX, Collin de l'Hortet A, **Soto-Gutierrez A*.** SIRT1 Disruption in Human Fetal Hepatocytes Leads to Increased Accumulation of Glucose and Lipids. **PLoS One. 2016**, 18;11(2):e0149344. ***(Corresponding Author)**

3: Wang RH, Zhao T, Cui K, Hu G, Chen Q, Chen W, Wang XW, **Soto-Gutierrez A**, Zhao K, Deng CX. Negative reciprocal regulation between Sirt1 and Per2 modulates the circadian clock and aging. **Sci Rep. 2016** Jun 27;6:28633.

4: Nishikawa T, Bell A, Brooks JM, Setoyama K, Melis M, Handa K, Tian J, Kaestner KH, Vodovotz Y, Locker J, **Soto-Gutierrez A*,** Ira J. Fox. Resetting the transcription factor network reverses terminal chronic hepatic failure. **J Clin Invest**. **2015**; 125(4):1533-44. ***(Corresponding Author**)

5: Nishikawa T, Bellance N, Damm A, Bing H, Zhu Z, Handa K, Yovchev MI, Sehgal V, Moss TJ, Oertel M, Ram P, Pipinos II, **Soto-Gutierrez A***, Fox IJ, Nagrath D. A switch in the source of ATP production and a loss in capacity to perform glycolysis are hallmarks of hepatocyte failure in advance liver disease. **J Hepatol**. **2014** Jun;60(6):1203-11. ***(Corresponding Author**)

6: Liu L, Yannam GR, Nishikawa T, Yamamoto T, Basma H, Ito R, Nagaya M, Dutta-Moscato J, Stolz DB, Duan F, Kaestner KH, Vodovotz Y, **Soto-Gutierrez A**, Fox IJ. The microenvironment in hepatocyte regeneration and function in rats with advanced cirrhosis. **Hepatology. 2012** May;55(5):1529-39. PMID: 22109844

Complete List of Published Work in My Bibliography
http://www.ncbi.nlm.nih.gov/pubmed/?term=soto-gutierrez+a

D. Research Support
Ongoing Research Support

- R01DK117881 (Taylor, L) PI (Soto-Gutierrez, A) Co-I 07/1/2018 - 06/30/2023
NCATS/NIDDK
"Investigating a Therapeutic Strategy for Non-Alcoholic Fatty Liver Disease (NAFLD) in a Human Liver Microphysiology System" The goal of this application is to develop human liver microphysiology system to study NASH

- U01TR002383 (Wikswo, J) PI (Soto-Gutierrez, A) Co-I 07/1/2018 - 06/30/2023
NCATS/NIDDK
"Harnessing human brain and liver microphysiological systems for testing therapeutics for metastatic melanoma"
This research project will utilize the a neurovascular unit, a liver-on-chip, and brain and liver organoids (which in addition to hiPSC-derived liver or brain cells includes endothelial cells) to study how the tissue microenvironment affects the growth of metastatic melanoma cells and their response to drugs.

- UG3DK119973 (Taylor, L) PI (Soto-Gutierrez, A) Co-I 09/1/2018 - 07/30/2023
NCATS/NIDDK
"Human Microphysiology Systems Disease Model of Type 2 Diabetes Starting with Liver and pancreatic Islets"
Our proposal has a strategic plan to optimize the migration from primary human cells in the UG3 phase to iPSC-derived cells in the later stages of the UH3 phase, including collaborative integration of relevant progress in the iPSC field.

- P01 DK096990 (Perlmutter, D) PI (Soto-Gutierrez, A) Co-I 04/1/2019 - 03/30/2024
NIH/NIDDK
"New Therapies for Liver Fibrosis and Hyperproliferation in Alpha1-AT Deficiency"
We will investigate patients who have undergone liver transplantation who are MZ heterozygous for AT and have no other explanation for severe liver disease.

Completed Research Support (Since 2009)

-R01 DK099257-01A1 (Soto-Gutierrez, A) PI 04/01/2014 – 07/31/2018
NIH/NIDDK
"Mini-Livers Derived from Human IPS Cells for Modeling Steatosis and Therapy"
Overall the goal is to develop an organ culture system for liver graft engineering and transplantation, using decellularized rat liver extracellular matrix populated by human induced pluripotent stem (iPS) cells to study steatosis or fatty liver disease. Role: PI

-R01 ES022606 (Runge-Morris, M) PI (Soto-Gutierrez, A) Co-I 01/01/2014 – 10/31/2018
NIH
"Expression, Regulation and Function of the SULT1C Carcinogen-Activating Enzymes"
Overall goal is to investigate the expression and function of many different fetal liver processes including drug metabolism and detoxification pathways and hepatocyte transport processes. Role: Co-Investigator

-R01DK107697 (Shapiro E) PI (Soto-Gutierrez, A) Co-I 09/23/2015 – 07/31/2019
NIH/NIDDK
"Quantitative molecular and cellular MRI of hepatocyte transplantation"
Overall goal of this proposal is to develop a quantitative molecular MRI to dynamically monitor and even quantify Hepatocyte transplantation.