BIOGRAPHICAL SKETCH

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NAME: Silvia Vilarinho

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

POSITION TITLE: Assistant Professor of Medicine and of Pathology

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 Porto, Portugal	M.D.,	07/04,	Medicine
University of Porto, Portugal	Ph.D.	07/08	Biomedical Sciences
University of California, San Francisco, CA	Post-Doc	06/09	Biomedical Sciences
University of Minnesota, Minneapolis, MN	Intern	06/10	Internal Medicine
Yale University, New Haven, CT	Resident	06/11	Internal Medicine
Yale University, New Haven, CT	Fellow	06/15	Digestive Diseases

A. Personal Statement

I am a physician-scientist and Assistant Professor in the Departments of Internal Medicine (Digestive Diseases) and Pathology. My overarching career goal is to bridge patient care to disease-relevant research and concurrently advance the understanding of the molecular basis of liver function in health and disease. Nearly all our studies begin with patients suffering from liver diseases of unclear etiology and we use human genetics and genomics to uncover the molecular mechanism(s) responsible for disease with potential diagnostic, therapeutic and prognostic applications. We use cell-based and mouse models to determine the specific mechanism(s) linking mutant gene to disease. This research approach provides new knowledge with direct impact in improving patient care and creates a great scientific environment to train future physician-scientists and students with particular interest in human disease.

B. Positions, Scientific Appointments and Honors

Positions

1998-2004: M.D. student, Faculty of Medicine, University of Porto, Portugal

2005-2008: Ph.D. student, University of Porto (entire research studies conducted in the laboratory of Dr. Jody Baron at University of California San Francisco, CA)

2009-2010: Internal Medicine Internship, University of Minnesota, Minneapolis, MN

2010-2015: Physician-Scientist Pathway: Internal Medicine Residency and Digestive Diseases Fellowship, Yale University School of Medicine, New Haven, CT (post-doctoral research conducted in the laboratory of Dr. Richard Lifton)

2015-2016: Instructor, Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT

2016-pres: Assistant Professor of Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT

2018-pres: Assistant Professor of Pathology, Yale University School of Medicine, New Haven, CT.

2018-pres: Appointment in the Graduate School of Arts and Sciences, Yale University School of Medicine, New Haven, CT.

01/2021-pres: Associate Director, MD-PhD Program, Yale School of Medicine, New Haven, CT.

Honors and Awards

1994 Honorary member of the Portuguese Association for Phenylketonuria (PKU)

2005 Portuguese Foundation for Science and Technology PhD Fellowship

2006 Travel Award to the 2006 Meeting on the Molecular Biology of HBV

2007 Young Investigator Travel Award to the 13th International Congress of Immunology

2008 Travel Award to the Hepatic Inflammation and Immunity Meeting 2008

2014 AGA-AASLD Academic Skills Workshop Grant

2014 Fellowship2Leadership Salix Fellows' Program Travel Grant to DDW

2015 Yale Annual Samuel Kushlan Award for Excellence in Research during Fellowship Training

2015 AASLD Sheila Sherlock Clinical and Translational Research Award

2016 AASLD Young Investigator Travel Award

2017 Yale Annual Junior Faculty Samuel Kushlan Award for Excellence in Research

2017 Inaugural EASL-AASLD Masterclass Travel Grant

2018 AASLD Young Investigator Travel Award

2019 Doris Duke Charitable Foundation Clinical Scientist Development Award

2021 Inaugural Yale School of Medicine John Forrest, Jr. Prize for Mentorship in Student Research

C. Contributions to Science

1. Discovery and characterization of novel genes underlying the onset and development of portal hypertension

We study rare forms of portal hypertension that develop in the absence of any known primary liver disease or exposure as roadmap to identify the molecular underpinnings of portal hypertension pathogenesis in common forms of advanced liver disease. Thus far, we identified that recessive loss-of-function mutations in *DGUOK* or *GIMAP5* cause portal hypertension. These studies are very informative in elucidating molecular pathways driving portal hypertension and may serve the basis to identify novel therapeutic targets and develop novel therapies.

a. **Vilarinho S**, Sari S, Yilmaz G, Stiegler AL, Boggon TJ, Jain D, Akyol G, Dalgic B, Günel M, Lifton RP. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. *Hepatology*, 63(6):1977-86, 2016.

b. Drzewiecki K, Choi J, Brancale J, Leney-Greene M, Sari S, Dalgiç B, Ünlusoy-Aksu A, Evergin Sahin G, Ozen A, Baris S, Karakoc-Aydiner E, Jain D, Kleiner D, Schmalz M, Radhakrishnan K, Zhang J, Hoebe K, Su H, Pereira JP, Lenardo MJ, Lifton RP, **Vilarinho S**. GIMAP5 maintains liver endothelial cell homeostasis and prevents portal hypertension. *J Exp Med.* 2021 Jul 5;218(7):20201745. Epub 2021 May 6.

2. Discovery and characterization of novel bile acid synthesis disorders and cholestatic liver diseases

By combining genomic approaches to highly informative cohort of patients with liver disease of unknown cause, we have identified the following additional three genetic liver disorders: (1) a novel bile acid synthesis disorder due to ACOX2 deficiency, (2) a novel cholestatic liver disease due to recessive mutations in *KIF12*, and (3) the first individual with OSTα deficiency, who presented with features of cholestasis, liver fibrosis and congenital diarrhea**.**

a. **Vilarinho S**, Sari S, Mazzacuva F, Bilgüvar K, Esendagli-Yilmaz G, Jain D, Akyol G, Dalgiç B, Günel M, Clayton PT, Lifton RP. ACOX2 deficiency: A disorder of bile acid synthesis with transaminase elevation, liver fibrosis, ataxia, and cognitive impairment. *Proc. Natl. Acad. Sci. U.S.A.*, 113:11289-93, 2016.

b. Unlusoy Aksu A, Das SK, Nelson-Williams C, Jain D, Özbay Hoşnut F, Evirgen Şahin G, Lifton RP, **Vilarinho S**. Recessive Mutations in KIF12 Cause High Gamma-Glutamyltransferase Cholestasis. *Hepatology Communications*, 2019 Feb 13;3(4):471-477.
c. Gao E, Cheema H, Waheed N, Mushtaq I, Erden N, Nelson-Williams C, Jain D, Soroka CJ, Boyer JL, Khalil Y, Clayton PT, Mistry PK, Lifton RP, **Vilarinho S**. OSTα deficiency: A disorder with cholestasis, liver fibrosis and congenital diarrhea. *Hepatology* 2020 May;71(5):1879-1882.

3. Clinical Utility of Genomic Analysis in Undiagnosed Liver Disease in Children and Adults

As many liver and digestive diseases remain poorly understood and hence difficult to treat, we recognized this problem as an unprecedented opportunity to apply cutting-edge genomic techniques to uncover the molecular basis of various digestive diseases. Hence, we have demonstrated the utility of whole exome sequencing in diagnosis and management of pediatric and adult idiopathic liver diseases. Together, these studies have identified novel disease mechanisms, phenotypes, and new therapeutic approaches, and have contributed to a change in clinical practice in this field. Furthermore, we have employed exome sequencing to identify somatic *CTNNB1* and *NF2L2* mutations as drivers of hepatocellular carcinoma arisen in a child with inherited *ABCB11* deficiency, and to track the genomic evolution of hepatocellular adenoma-carcinoma transition, vascular invasion, and brain dissemination.

a. **Vilarinho S**, Choi M, Jain D, Malhotra A, Kulkarni S, Pashankar D, Phatak U, Patel M, Bale A, Mane S, Lifton RP, Mistry PK. Individual exome analysis in diagnosis and management of paediatric liver failure of indeterminate aetiology. *J Hepatol*, 61(5):1056-63, 2014.
b. **Vilarinho S**, Erson-Omay EZ, Harmanci AS, Morotti R, Carrion-Grant G, Baranoski J, Knisely AS, Ekong U, Emre S, Yasuno K, Bilguvar K, Günel M. Paediatric hepatocellular carcinoma due to somatic *CTNNB1* and *NFE2L2* mutations in the setting of inherited bi-allelic *ABCB11* mutations. *J Hepatol*, 61(5):1178-83, 2014.
c. **Vilarinho S**, Erson-Omay EZ, Mitchell-Richards K, Cha C, Harmanci AS, Yasuno K, Bilguvar K, Günel M, Taddei TH. Exome analysis of the evolutionary path of hepatocellular adenoma-carcinoma transition, vascular invasion and brain dissemination. *J Hepatol*, 67(1):186-191, 2017.
d. Hakim A, Zhang X, DeLisle A, Oral EA, Dykas D, Drzewiecki K, Assis DN, Silveira M, Batisti J, Jain D, Bale A, Mistry PK, **Vilarinho S**. *J Hepatology*, 2019 Jun;70(6):1214-1221.

4. Generation of a single cell human liver atlas website resource available to the global liver community

We have aggregated and integrated publicly available single cell RNA-sequencing of more than 36,000 cells from 28 human livers reported in five independent studies. This data allowed us to develop a user-friendly online tool for quick and easy interrogation and comparison of gene expression across different parenchymal and non-parenchymal liver cell populations. Collective, this study consists in the current largest human liver transcriptomic single cells atlas accessible for interactive visualization via an open-access web portal to the research community worldwide.

a. Brancale J, **Vilarinho S**. A single cells gene expression atlas of 28 human livers. J Hepatology, 2021; Epub May 17, 2021; DOI: https://doi.org/10.1016/j.hep.2021.03.005.

5. NKG2D and Age-dependent Immune Responses to Hepatitis B Virus

During my graduate research studies, we identified a new role for Natural Killer T (NKT) cells activating receptor NKG2D signaling in the initial innate immune response to hepatitis B virus (HBV). Blockade of an NKG2D-ligand interaction prevented HBV- and NKT cell-mediated liver injury in mice, and hence identified a potential therapeutic target for treatment of acute HBV infection, leading to a patent of the NKG2D monoclonal antibody for the treatment of HBV infection. I have also contributed to investigating the role of IL-21 in determining age-dependent effectiveness of immune responses using the same HBV mouse model.

a. **Vilarinho S**, Ogasawara K, Nishimura S, Lanier LL, Baron JL. Blockade of NKG2D on NKT cells prevents hepatitis and the acute immune response to hepatitis B virus. *Proc. Natl. Acad. Sci. U.S.A.*, 104:46, 2007.
b. Publicover J, Goodsell A, Nishimura S, **Vilarinho S**, Wang ZE, Avanesyan L, Spolski R, Leonard WJ, Cooper S, Baron JL. IL-21 is pivotal in determining age-dependent effectiveness of immune responses in a mouse model of human hepatitis B. *J Clin Invest.,*1;121(3):1154-62, 2011.

All of my published work is listed here:
https://www.ncbi.nlm.nih.gov/myncbi/1lUzy2tUMsmkg/bibliography/public/