Weill Cornell Medicine

Generation of Human Glomerular Endothelial Cells for Kidney Disease Research and Treatment

Lead Inventors:

Shahin Rafii, M.D.
Professor of Medicine
Arthur B. Belfer Professor in Genetic Medicine
Chief, Division of Regenerative Medicine
Director, Ansary Stem Cell Institute

Sina Rabbany, Ph.D.
Dean of the DeMatteis School of Engineering and Applied Science at Hofstra University
Adjunct Associate Professor of Bio-Engineering in Medicine, Weill Cornell Medicine

Raphael Lis, Ph.D.
Assistant Professor of Reproductive Medicine in Medicine, Medicine, Weill Cornell Medicine
Assistant Professor of Reproductive Medicine, Reproductive Medicine, Weill Cornell Medical College

Business Development Contact:

Louise Sarup
Associate Director, Business Development and Licensing
(646) 962-3523
lss248@cornell.edu

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Background & Unmet Need

- >800 million people worldwide suffer from chronic kidney disease[1], which can progress to end-stage renal disease, requiring dialysis or transplantation
- Many patients with end-stage renal disease undergo complications related to hemodialysis, such as infection, or never receive a kidney transplant
- Kidney organoids could provide an avenue for development of new therapeutics for renal disease, but the heterogeneity of kidney vasculature is a major hurdle for their generation
- The kidney is vascularized with highly specialized and zonated (region-specific) endothelial cells that are essential for its filtration functions, including glomerular endothelial cells
- **Unmet Need:** Methods for generating functional kidney vasculature and tissue for research and therapeutic purposes

Technology Overview

- **The Technology:** Method to reprogram human umbilical vein endothelial cells (HUVECs) into human glomerular endothelial cells (HGECs) by expressing the transcription factor Tbx3
- Tbx3 can be used alone or in combination with additional transcription factors—Prdm1, Gata5, and Pbx1—with the best results observed when all four factors are co-expressed
- HGECs could, for example, be co-cultured with kidney podocytes and mesangial cells to construct functional glomeruli
- **The Discovery:** Tbx3 was identified as a crucial mediator of glomerular development and function through high-throughput bulk single-cell RNA sequencing of kidney vasculature
- **PoC Data:** Overexpression of Tbx3, alone or in combination with Prdm1, Gata5, and Pbx1, in HUVECs results in gene expression profiles that closely match those found in the human glomerulus

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David Barry
Raphael Lis
Balvir Kunar

Patents:
US Application
EP Application

Publications:
Barry et al. *Nat Commun*. 2019.

Biz Dev Contact:
Louise Sarup
646-962-3523
lss248@cornell.edu

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[1]Kovesdy. *Kidney Int Suppl (2011)*. 2022.

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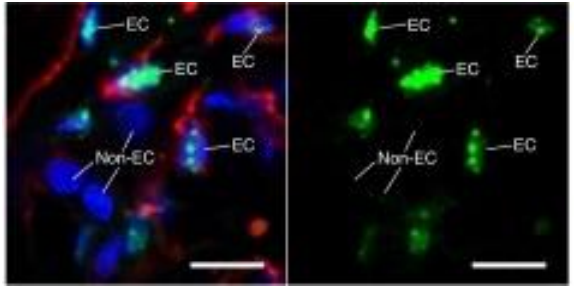
Technology Applications

- Co-culture of HGECs with kidney podocytes and mesangial cells to construct functional glomeruli
- Use of HGECs in high throughput screening for chronic kidney disease drug discovery
- Use of HGECs to build vascularized kidney organoids to model functions of the kidney
- Therapeutic transplantation of HGECs or functional glomeruli to regenerate damaged kidney tissue

Technology Advantages

- HUVECs are readily obtainable as a starting source for HGEC generation
- Flexibility in the methodology used to overexpress Tbx3, Prdm1, Pbx1, and/or Gata1

Supporting Data / Figures



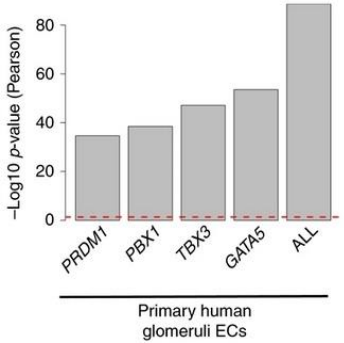


Figure 1: Top: Immunofluorescent staining in human kidney tissue confirms that Tbx3 protein (green) is restricted to endothelial cells in glomerular capillaries **Bottom:** Measure of overlap between glomerular-specific genes and those differentially expressed after Tbx3, Prdm1, Pbx1, and Gata1 overexpression.

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HGECs: Human Glomerular Endothelial Cells.
HUVECs: Human Umbilical Vein Endothelial Cells.

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