UVA PEDIATRIC CENTER OF EXCELLENCE IN NEPHROLOGY ACCOMPLISHMENTS. Period 2012-2016

The Pediatric Center of Excellence in Nephrology at UVA has made substantial progress during years 2012-2016. Crucial findings have been made and novel methodologies have been established that were instrumental for the success of the program. The Pilot and Feasibility Program has been successful at engaging and supporting junior faculty through Pilot Projects, and attracting and retaining graduate students to research in Pediatric Nephrology. The Enrichment/Educational Program of the Center supported a number of research students, and sponsored seminars and symposia to enhance research in kidney development and disease.

RESEARCH PROJECTS

Center Project 1: Lineage relationships in the kidney vasculature: role of RBP-J
R. Ariel Gomez, M.D.

Publications

Abstracts


**Project-Generated Resources**

1) Mouse models for conditional deletion of *Notch1, Notch 2 or Jagged 1* in renin and/or Foxd1 cell lineages. *Notch1* deletion, *Notch2* deletion and *Ren1dCre* mice are available from the PI upon request.

**Center Project 2: Epigenetic mechanisms of nephron progenitor cell renewal and fate**

Samir El-Dahr, M.D.

**Publications**


Abstracts
2. Chen S, Yao X, and El-Dahr SS. HDAC1 and HDAC2 are critical in renewal and differentiation of nephron progenitor cells. Platform presentation, Society for Pediatric Research Meeting, Boston, MA, April 30th, 2012. Winner of the Basic Science Fellow Award of the SPR.

Project-Generated Resources
1. Bioinformatics resulting from our publications are made publicly available in the GEO database of the NCBI.
2. All mouse models funded by this grant are made available to investigators.
3. We have developed significant expertise in conducting chromatin-based techniques such as ChIP and ATAC. These techniques have been scaled down to a relatively small number of cells and starting nuclei. All of the protocols and bioinformatics analyses of the chromatin landscape of the nephron progenitors will be made available online on the PNCE website.

Center Project 3: Formation of atubular glomeruli by oxidant injury in murine ureteral obstruction
Robert L. Chevalier, M.D. and Maria Luisa Sequeira-Lopez, M.D.

Publications


Abstracts


6. CD44 and CD44+ cells are dispensable for the recruitment of renin expressing cells. Oral presentation, Council on Hypertension, AHA Meeting 2016.

Project-Generated Resources
1) Mouse models to trace the lineage of different nephron compartments are available upon request.

2) Training in techniques for UUO and UUO+release is currently provided to other investigators.

PILOT AND FEASIBILITY PROGRAM

The PCEN has funded several Pilot Projects. The grantees have benefited from the guidance of their respective mentors and from interactions with the other main project PIs and laboratory members who have provided training in cutting-edge techniques and discussion of research areas new to them.

Table 1. Performance of the PCEN P&F program during 2012-2016. *Belyea and Medrano shared two publications

<table>
<thead>
<tr>
<th>Category</th>
<th>Saifudeen</th>
<th>Belyea</th>
<th>Medrano</th>
<th>Adli</th>
<th>Liu</th>
<th>Charlton</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publications</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>13*</td>
<td></td>
</tr>
<tr>
<td>Abstracts</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td></td>
<td>5</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Awards</td>
<td>3</td>
<td></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Grants</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Publications

Pilot project: Epigenetic mechanisms of nephron progenitor cell renewal and fate
PI: Zubaida Saifudeen, Ph.D.
Mentor: Samir El-Dahr, M.D.


**Abstracts**


**Funding Support**

1. R56DK104779 Saifudeen (PI) 9/10/2015 - 9/9/2016
   NIH/NIDDK
   p53-Regulated Metabolic Fitness of Self-Renewing Nephron Progenitor Cells

2. U24 DK076169-09 (Pilot 25034-54) Saifudeen (PI) 10/1/2014 - 9/30/2015
   DiaComp Pilot & Feasibility Project
   p53-Regulated Metabolic Fitness of Self-Renewing Nephron Progenitor Cells

**Pilot Project: Jagged 1 and kidney vascular development**

**PI:** Brian Belyea, MD.

**Mentor:** R. Ariel Gomez, MD

**Publications**

   **Cited:** 0  **Impact Factor:** Not yet determined  **Rank:** Not available

   **Cited:** 2  **Impact Factor:** 11.47  **Rank:** 3 of 46 Multidisciplinary Sciences journals

   **Cited:** 4  **Impact Factor:** 2.856  **Rank:** 17 of 119 Pediatric journals

**Abstracts**


Honors and Awards:
1. Young Physician-Scientist Award April 2016
   American Society for Clinical Investigation

2. National Institutes of Health Loan Repayment Award August 2015

3. Robert J. Roberts Award August 2015
   University of Virginia, Department of Pediatrics
   Honoring outstanding junior faculty member

Funding Support:
NIH/NIDDK 1K08DK102914-01 Belyea (PI) 7/1/2014 – 3/31/2019
“Role of Renin Progenitors in Hematopoiesis"

Mentored Career Development Award: To study the role of renin progenitors during normal and neoplastic hematopoietic development.
Role: PI

Pilot Project: Hypoxia and kidney vascular pathology
PI: Silvia Medrano, Ph.D
Mentor: R. Ariel Gomez, MD

Publications
   Cited: 2 Impact Factor: 11.47 Rank: 3 of 46 Multidisciplinary Sciences journals

   Cited: 4 Impact Factor: 2.856 Rank: 17 of 119 Pediatric journals

Abstracts


**Project-Generated Resources**

1) mouse model with conditional deletion of Hif2α in renin cells
2) miR-330-5p deletion mice

Mice available from the PI upon request.

**Pilot Project: CRISPR mediated whole-genome knock-out screening to identify essential genes in nephrovascular development.**

**PI:** Mazhar Adli, Ph.D.

**Primary Mentor:** R. Ariel Gomez, M.D.

**Co-mentors:** Samir El-Dahr, M.D., Maria Luisa Sequeira Lopez, M.D.

**Publications**


**Submitted Articles**


**Project-Generated Resources**

The project allowed us to generate the following tools, which are either open to be freely used by the scientific community or we are happy to share or collaborate with different groups.

1. Computational tool for CRISPR design and off-target prediction: Freely available @http://www.adlilab.org/CROP-IT/homepage.html

2. CRISPR Screening libraries:
   - **Whole genome libraries:** We have both mouse and human libraries targeting ~18K genes in the genome. Each library contains ~120K sgRNAs.
   - **Focused libraries:** We also have libraries containing limited sets of sgRNAs that target nuclear genes, cell cycle genes or epigenetic regulator genes.

**Funding Support**

1. Active Research Support
   - V scholar Plus award Adli (PI) 01/10/16 – 09/30/17 (NCE)
   - The V Foundation for Cancer Research
   - Epigenetic Engineering to Correct an Aberrantly Regulated Locus in Cancer
   - The goal of this study is to use novel epigenetic engineering tools to change and reprogram aberrant chromatin state and function at specifically targeted genomic regions.
2. Completed Research Support

CaTS Pilot Project   Adli (PI)  11/01/14 – 04/30/16
UVA Cancer Center & NCI CCSG P30 CA44579

In vivo CRISPR based knock-out screening to identify essential epigenetic regulators of tumor progression in xenograft model of pancreatic cancer.

The aim of this project is to use CRISPR gene editing technology to perform knock screenings to identify essential genes involved in in vivo tumor progression and chemotherapy resistance in PDAC.

Pilot project: Histone Deacetylases 1 and 2 in Kidney Development
PI: Hongbing Liu, Ph.D.
Mentor: Samir El-Dahr, M.D.

Publications

Funding Support
1. P30 GM103337-03 Hongbing Liu (PI) 08/01/2015 – 07/31/2016
NIH/NIGMS
Translational Research in Hypertension and Renal Biology (PI: Luis Gabriel Navar). Pilot project: Histone Deacetylases 1 and 2 in Kidney Development
2. AHA Scientist Development Grant, pending

Honors and Awards
1. SSPR (Southern Society for Pediatric Research) Young faculty Award (2016)
2. 6th Biennial National IDeA Symposium of Biomedical Research Excellence (NISBRE) Young Investigator Travel Award (2016)

Pilot project: The role of the cap mesenchyme in establishing nephron number in mice born prematurely
PI: Jennifer Charlton, M.D.
Mentors: Maria Luisa Sequeira-Lopez, M.D. and Samir El-Dahr, M.D.

Publications
1. Jetton, JG; Guillette, R; Askenazi, DA; Dill, L; Jacobs, J; Kent; AL; Selewski, DT; Abitbol, CL; Kaskel, FJ; Mhanna, MJ; Ambalavana, N; Charlton, JR. Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN): Design of a Retrospective Cohort Study. Accepted for publication in Frontiers in Pediatrics.
3. Charlton, JR; Pearl, VM; Denotti, AR, Lee, JB, Swaminathan, S; Scindia, Y; Charlton, NP; Baldelomar, EJ; Beeman, SC; Bennett, KM. Biocompatibility of ferritin-based nanoparticles as targeted MRI contrast agents. Nanomedicine, NBM. 2016 April 9: epub ahead of print. PMID: 27071333. PMCID: PMC Journal – In Process.
4. Hann, B; Baldelomar, EJ; Charlton, JR; Bennett, KM. Measuring the intra-renal distribution of glomerular volumes from histologic sections. Am J of Physio. 2016. Accepted for publication.
6. Baldelomar, EJ; Charlton, JR; Beeman, SC; Hann, BD; Cullen-McEwen, L; Pearl, VM; Bertram, JF; Wu, T; Zhang, M, Bennett, KM. MRI phenotyping to nondestructively measure glomerular number and volume distribution in mice with and without nephron reduction. Kid Int. 2015 Nov 4: epub ahead of print. PMCID: PMC4854807.
Abstracts and Invited Symposia


2. Nationwide Children’s Hospital Pediatric Research Conference
   Short Term Gestation, Long Term Risk: Exploring the links between prematurity and chronic kidney disease
   Columbus, OH. November 19, 2016.

3. “The fault is not in our stars but may be in our embryos”: Glomerular number in LBW babies
   Low birth weight and the kidney: Function and Structure
   Bergamo, Italy. April 2, 2016

4. American Society of Pediatric Nephrology Annual Meeting
   Long-Term Outcomes after Neonatal Acute Kidney Injury: The Kidney and Beyond….
   Baltimore, MD. April 30, 2016

5. 2016 Advances in Renal Imaging Symposium
   MRI-iron particles to quantify glomeruli in vivo
   Indianapolis, IN. November 15, 2016.

Honors and Awards

1. NIH K Symposium Outstanding Investigator Award, 2016
2. Promotion to Associate Professor, Department of Pediatrics in July 2016

Funding Support

1. American Society of Nephrology
   Carl W. Gottschalk Research Scholar Grant
   Charlton, PI
   “Detecting renal pathology in mouse model of prematurity using MRI-based biomarkers.”
   The goal of this project is to evaluate the microstructural changes within the glomerular, vascular, and tubulointerstitial compartments by MRI in the prematurely born mouse compared to full term mice.

2. R01, PA-13-302, NIDDK
   Charlton, co-PI
   Noninvasive MRI techniques to detect pathology in murine models of renal disease
   Submitted July 2016, score: 13

ENRICHMENT PROGRAM

Student training

The PCEN is very successful in providing research exposure to college students and attracting graduate students and medical students to pediatric nephrology research. the laboratories of each PCEN PI hosted summer research students to pursue projects funded by the Administrative Supplement for Summer Students. Two predoctoral students Eugene Lin and Yan Hu from the UVA Department of Biology training in the laboratory of Dr. Gomez successfully completed their projects and graduated. Dr. El-Dahr has three predoctoral students from the interdisciplinary Biomedical Science Program at Tulane.

PCEN Summer Students

1. Project 1: Ariel Gomez
   - Eugene Lin, UVA Department of Biology graduate student
     Project: Role of Foxd1 cells in renal vascular patterning
   - Gonzalo Olaverria Salavaggione, rising senior undergraduate student, Ohio State University Biology major.
     Project: Analysis of expression of hypoxia related genes Hif 2α and Epo in the kidney.
   - Robert Paxton. BS in Biology with concentration in Biotechnology and Molecular Biology, Elon University (2016).
     Project: Cell fate in the developing kidney.
2. **Project 2**: Samir El-Dahr

- Jenny Ngo, Tulane School of Medicine, Medical student rising second year
  Project: Role of histone methyltransferases in kidney development
- Zahra Saifudeen, freshman undergraduate student, Tulane University.
  Project: Regulation of Renal Epithelial Cell Differentiation by Epigenetic Modifiers.

3. **Project 3**: Chevallier and Maria Luisa Sequeira Lopez

- Akif Shameem, UVa Class of 2016, Biology and Public Health major
  Project: Formation of atubular glomeruli by oxidant injury in murine ureteral obstruction
- Sofia Rosenzweig, University of Maryland Baltimore County undergraduate student
  Project: Lineage tracing studies on the formation of atubular glomeruli and on nephron regeneration after release of UUO.
- Jessica Moskaluk, rising junior undergraduate student, Pennsylvania State University. Forensic Science major.
  Project: Regulation of gene expression in renin lineage cells.

*Other training provided by the PCEN*

- Nathan Grainger, PhD student at the University of Nevada, Reno, School of Medicine. He came to Dr. Sequeira-Lopez's lab April 24-30 2016, to train in complete and partial UUO and release in newborn and adult mice. He had no previous surgical experience and after a one on one training for a whole week he was able to successfully perform the procedures without help.
- Members of Dr. Kevin Lynch, UVA Department of Pharmacology came to Dr. Sequeira-Lopez's lab to train in UUO techniques.
- Leon DeLalio, PhD student at the CVRC at UVA. He is working on the pannexin gene in renin kidney cells. He is receiving regular guidance and training in Dr. Ariel Gomez's in histological and molecular biology techniques in kidney.

*Seminars*

**Ambra Pozzi, PhD**, Vanderbilt University Medical Center
*Integrins in fibrotic responses: Good or bad receptors*
February 2, 2015

**Roy Zent, M.D., Ph.D.**. Vanderbilt University Medical Center
*Integrins in the kidney*
February 3, 2015

**Sergio D. Rosenzweig, MD, PhD**
Deputy Chief of the Immunology Service at the Clinical Center, NIH and the Co-Director of the Primary Immunodeficiency Clinic, NIAID, NIH
*Glycosylation, Hypogammaglobulinemia and Resistance to Viral Infections*
March 3, 2015

**Hiroko Nishimura, M.D., DMSc**
Professor, Department of Health Informatics, Niigata University of Health and Welfare, Niigata, Japan, and Professor Emeritus, Department of Physiology, University to Tennessee HSC, Memphis, TN, USA
*Does reduced nutrition during development program renal glomerular injury? -from animal study to patients*
April 3, 2015

**Ariel Gomez, M.D.**, UVA Department of Pediatrics
*The CHRC: Programs of Excellence*
September 4, 2015
Linda Mullins, Ph.D., University of Edinburgh/BHF Cardiovascular Science Centre, Queen’s Medical Research Institute, Edinburgh
*Rodent Genome Targeting: a personal perspective!*
December 4, 2015

John Mullins, Ph.D. Director, BHF Centre for Research Excellence and Chair, Molecular Physiology
University of Edinburgh
*Integrating ‘Macro’ and ‘Wide-angle’ views of renin and the RAS*
December 4, 2015

Michael J. McConnell, Ph.D.
*Single Cell Analysis of Brain Somatic Mosaicism*
March 4, 2016

Rhian M Touyz, MBBCh, Ph.D., FRCP, FRSE, British Heart Foundation Chair of Cardiovascular Medicine
Director - Institute of Cardiovascular & Medical Sciences, BHF Glasgow Cardiovascular Research Centre
*VEGF signaling, anti-cancer drugs and hypertension*
March 18, 2016

Mario Capecchi, Ph.D. 2007 Nobel Laureate, Medicine or Physiology and Professor of Human Genetics and Biology
University of Utah School of Medicine
Betsy and Stuart Houston Lecture: “Gene Targeting into the 21st Century: Mouse Models of Human Disease from Cancer to Neuropsychiatric Disorders”
April 5, 2016

Conversations with a nobel laureate: Dr. Mario Capecchi.
A lunch session where faculty and students within the UVA School of Medicine met with Dr. Capecchi to have a general discussion about scientific research.
April 5, 2016

James P Nataro, M.D., UVA Department of Pediatrics
*Strategic Planning 101 – Mentoring for Young Investigators and Fellows*
April 15, 2016

Allen Everett, M.D. Director of the Pediatric Proteome Center, Johns Hopkins University
*Proteomic Discovery and use of biomarkers in Pediatric Medicine*
April 22, 2016

4th Annual Research Trainee Competition, Department of Pediatrics
Date: Thursday, May 5, 2016

28th Annual Research Symposium; Date: Thursday, May 19, 2016
Alessio Fasano M.D., Harvard University.
“How to Choose the Right Mentor for a Successful Academic Career”
Research day “Meet the speaker” Series. Educational activities oriented to trainees and young faculty of different specialty areas. An informal open discussion about practical research topics aimed to guide attendees in the advancement of their academic careers. Department of Pediatrics, University of Virginia.
May 19, 2016.

Hiroko Nishimura, M.D., DMSc, Professor, Department of Health Informatics, Niigata University of Health and Welfare, Niigata, Japan, and Professor Emeritus, Department of Physiology, University to Tennessee HSC, Memphis, TN, USA
*Renin-angiotensin system and angiotensin receptors – Evolution and Function –*
June 27, 2016
Grant proposal review series. A meeting to discuss grant proposals by faculty within the department of Pediatrics and the CHRC at UVA.

- **Jennifer Charlton, M.D.,** UVA Department of Pediatrics
  *Noninvasive MRI Techniques To Detect Pathology in Murine Models of Renal Disease.* September 18, 2015.

- **Lisa Palmer, Ph.D.** Associate Professor of Pediatrics and Anesthesiology. *GSNOR/S-nitrosothiol Regulation of Vesicular Transport.* September 25, 2015.

**Public Engagement and Education**

The activities of the PCEN at UVA have been publicized through a poster presentation at the American Society of Nephrology meeting in November, 2014


In addition, the PCEN website is updated regularly to include the new pilot project and list the publications resulting from the Center research projects.

**Assessment of Progress**

**Report by External Reviewer**

Patricio Ray, M.D.
Robert Parrott Professor of Pediatrics
Children’s National Health System and the George Washington University School of Medicine Adjunct Professor of Pediatrics at Georgetown University School of Medicine