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

1. Eugene E Lin, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. RBP-J in Foxd1+ renal stromal progenitors is crucial for the proper development and assembly of the kidney vasculature and glomerular mesangial cells. Am J Physiol-Renal 2014 Jan; 306(2):F249-58 PMCID:PMC3920017 [Available on 2015/1/15]
2. Sequeira-Lopez MLS, Lin EE, Li M, Hu Y, Sigmund CD, **Gomez RA**. The earliest metanephric arteriolar progenitors and their role in kidney vascular development. Am J Physiol Regul Integr Comp Physiol. 2015 Jan 15; 308(2):R138-49
3. Lin EE , Pentz ES, Sequeira-Lopez MLS, **Gomez RA**. Aldo-keto reductase 1b7, a novel marker for renin cells, is regulated by cyclic AMP signaling. Am J Physiol Regul Integr Comp Physiol. 2015 Sep;309(5):R576-84. PubMed PMID: 26180185; PubMed Central PMCID: PMC4591380.
4. Belyea BC, Xu F, Sequeira-Lopez MLS, **Gomez RA**. Loss of Jagged1 in Renin Progenitors Leads to Focal Kidney Fibrosis. Physiol Rep. 2015 Nov; 3(11). pii: e12544. doi: 10.14814/phy2.12544.
5. Lu KT, Keen HL, Weatherford ET, Sequeira-Lopez ML, **Gomez RA**, Sigmund CD. Estrogen Receptor α Is Required for Maintaining Baseline Renin Expression. Hypertension. 2016 May; 67(5):992-9. PubMed PMID: 26928806; PubMed Central PMCID: PMC4833511.
6. **Gomez RA**, Sequeira-Lopez ML. Novel Functions of Renin Precursors in Homeostasis and Disease. Physiology (Bethesda). 2016 Jan; 31(1):25-33. PubMed PMID: 26661526; PubMed Central PMCID: PMC4698453.
7. Hu Y, Li M, Göthert JR, **Gomez RA**, Sequeira-Lopez ML. Hemovascular Progenitors in the Kidney Require Sphingosine-1-Phosphate Receptor 1 for Vascular Development. J Am Soc Nephrol. 2016 Jul; 27(7):1984-95. PubMed PMID: 26534925. (Epub ahead of print) [PMCID In Progress]
8. Sequeira-Lopez ML, Nagalakshmi VK, Li M, Sigmund CD, **Gomez RA**. Vascular versus tubular renin: role in kidney development. Am J Physiol Regul Integr Comp Physiol. 2015 Sep 15; 309(6):R650-7. PubMed PMID: 26246508; PubMed Central PMCID: PMC4591368.

Abstracts

1. Eugene E Lin, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. RBP-J controls the fate of the kidney vasculature. Poster presented at High Blood Pressure Research 2012 Scientific Sessions, September, 2012, Washington, DC, USA.
2. Eugene E Lin, Maria Luisa S. Sequeira-Lopez and R. **Ariel Gomez**. Foxd1+ stromal cells, the required progenitor for renal vascular development. Oral presentation at High Blood Pressure Research 2013 Scientific Sessions, September, 2013, New Orleans, LA, USA.
3. Eugene E Lin, Ellen S Pentz, Minghong Li, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. The Notch signaling pathway regulates the fate of renal FOXD1+ stromal cells and their descendants. Accepted for a poster presentation at High Blood Pressure Research 2014 Scientific Sessions, September, 2014, San Francisco, CA, USA.
4. Lin EE , Sequeira-Lopez MLS, **Gomez RA**. The Notch signaling pathway regulates the fate of renal FOXD1+ stromal cells and their descendants. Poster presentation at High Blood Pressure Research 2014 Scientific Sessions, September, 2014, San Francisco, CA, USA.

5. Belyea BC, Xu F, Sequeira-Lopez MLS, **Gomez RA**. Jagged1 and Morphological Integrity of the Kidney. September 2014. High Blood Pressure Research Conference. San Francisco, California. Poster presentation.
6. Lin EE , Pentz ES, Sequeira-Lopez MLS, **Gomez RA**. Foxd1+ stromal cells: the progenitors for kidney vascular development. Oral presentation at the National Kidney Foundation's Spring Clinical Meetings, 2015.
7. Lin EE , Pentz ES, Sequeira-Lopez MLS, **Gomez RA**. Foxd1+ stromal cells: the progenitors for kidney vascular development. Oral presentation at the Nephrology Young Investigator's Forum, Mid-Atlantic Regional, 2015.
8. Belyea BC, Xu F, Sequeira-Lopez MLS, **Gomez RA**. Loss of Jagged1 in Renin Progenitors Leads to Focal Kidney Fibrosis. July 2015. International Workshop on Developmental Nephrology. Snowbird, Utah. Poster Presentation.
9. Maria Florencia Martinez, Ellen Pentz, Silvia Medrano, Masafumi Oka, Mazhar Adli, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. Super-Enhancers in the renin cell. Oral presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.
10. Evan Brown, Stephen Turner, Alex Koppel, Maria Luisa S. Sequeira-Lopez, **R. Ariel Gomez**. Use of single cell RNA-sequencing for characterizing renin cell populations. Poster presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.
11. Silvia Medrano, Evan Brown, Maria Florencia Martinez, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. Use of a CRISPR/Cas9 system for renin cell lineage specification. Poster presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.
12. Masafumi Oka, Maria Luisa S. Sequeira-Lopez, **R. Ariel Gomez**. Renin cells contribute to vascular pathology in renin deficient mice. Poster presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.
13. Maria F Martinez, Silvia Medrano, Masafumi Oka, Ellen S Pentz, Allan W Dickerman, Mazhar Adli, Maria Luisa S. Sequeira-Lopez and **R. Ariel Gomez**. Enhancer Repertoires that Define Renin Cell Identity. Oral presentation, Council on Hypertension, AHA Meeting 2016.
14. Masafumi Oka, Silvia Medrano, Maria Luisa Sequeira-Lopez, **R. Ariel Gomez**. Cells Programmed For The Renin Phenotype Contribute To Vascular Pathology In Renin Deficient Mice. Oral presentation, Council on Hypertension, AHA Meeting 2016.
15. Silvia Medrano, Evan Brown, Maria F Martinez, Maria Luisa S Sequeira-Lopez, **R Ariel Gomez**. Use of a CRISPR/Cas9 System for Specification of the Renin Cell Phenotype. Poster presentation, Council on Hypertension, AHA Meeting 2016.
16. Maria Luisa S. Sequeira Lopez, Brian C. Belyea, Rajwinderjit Kaur, Silvia Medrano and **R. Ariel Gomez**.
17. 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 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

1. McLaughlin N, Yao X, Li Y, Saifudeen Z, and **El-Dahr SS**. Histone signature of metanephric mesenchyme cell lines. *Epigenetics* 8(9):970-8, 2013. PMCID:PMC3883774[Available on 2014/9/1]
2. McLaughlin N, Wang F, Saifudeen Z, and **El-Dahr SS**. In situ histone landscape of nephrogenesis. *Epigenetics* 9(2):222-35, 2014. PMCID:PMC3962532
3. Chen S, Yao X, Bachvarov D, and **El-Dahr SS**. Histone deacetylases 1 and 2 regulate Wnt and p53 signaling in the ureteric bud epithelium. *Development* 2015 Mar 15;142(6):1180-92. doi: 10.1242/dev.113506.
4. Adli M, Parlak M, Li Y, **El-Dahr SS**. J Epigenetic States of nephron progenitors and epithelial differentiation. *Cell Biochem*. 2015 Jun;116(6):893-902. PMID: 255604333.

5. Hilliard S, and **El-Dahr SS**. Epigenetic mechanisms in renal development. Pediatr. Nephrol. 2015 Oct 22. [Epub ahead of print]. PMID 26493068

Abstracts

1. '*Chromatin-based mechanisms of nephron progenitor cell renewal and fate'* presented at the International Workshop in Developmental Nephrology (IWDN-2013) in Edinburgh, Scotland, June 24-26, 2013.
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.
3. Hilliard S, El-Dahr SS. The Mdm2-p53 pathway is required for nephron progenitor cell renewal. Oral presentation, Society for Pediatric Research Meeting, Washington DC, May 4-7, 2013.
4. Wang F, Yao X, Saifudeen ZR, and El-Dahr SS. The histone H3K79 methyltransferase, Dot1l, regulates the fate of ureteric bud tip cells. Poster presentation. The American Society of Nephrology Meeting, Atlanta, GA, November 7, 2013.
5. Li Y, Ngo J, Saifudeen Z, and El-Dahr SS. Genetic deletion of the H3K79 methyltranferase, Dot1L, in mice causes renal hypo-dysplasia. The Society for Pediatric Research, San Diego, CA, April 26, 2015.
6. Li Y, Saifudeen Z, and El-Dahr SS. ΔNp63 cells pattern the ureteric bud stem cell niche and give rise to β-intercalated cells. Platform presentation – American Society of Nephrology, San Diego, CA, November 2015.

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

1. Forbes MS, Thornhill BA, Galarreta CI, Minor JJ, Gordon KA, **Chevalier RL**. Chronic unilateral ureteral obstruction in the neonatal mouse delays maturation of both kidneys and leads to late formation of atubular glomeruli. Am J Physiol Renal Physiol 305:F1736-F1746, 2013 PMCID 3882445 [Available on 2014/12/15].
2. **Chevalier RL**, Forbes MS, Galarreta CI, Thornhill BA. Responses of proximal tubular cells to injury in congenital renal disease: Fight or flight. Pediatr Nephrol 29:537-541, 2013 PMCID:PMC3925758 [Available on 2015/4/1].
3. Galarreta CI, Grantham JJ, Forbes MS, Maser RL, Wallace DP, **Chevalier RL**. Tubular obstruction leads to progressive proximal tubular injury and atubular glomeruli in polycystic kidney disease. *Am J Pathol*. 2014 Jul;184(7):1957-66. doi: 10.1016/j.ajpath.2014.03.007. Epub 2014 May 9.
4. **Chevalier RL**. Congenital urinary tract obstruction: The long view. Adv Chronic Kidney Dis. 2015 Jul;22(4):312-9. doi: 10.1053/j.ackd.2015.01.012.
5. Sergio M, Galarreta CI, Thornhill BA, Forbes MS, **Chevalier RL**. The fate of nephrons in congenital obstructive nephropathy: Adult recovery is limited by nephron number despite early release of obstruction. J Urol. 2015 Nov; 194(5):1463-72. doi: 10.1016/j.juro.2015.04.078. Epub 2015 Apr 23.
6. **Sequeira Lopez MLS**, Lin EE, Li M, Hu Y, Sigmund CD, Gomez RA. The earliest metanephric arteriolar progenitors and their role in kidney vascular development. Am J Physiol Regul Integr Comp Physiol. 2015; 308(2):R138-49. PMCID: PMC429786.
7. **Sequeira-Lopez MLS,** Torban E. New insights into precursors of the renal endothelium. *Kidney Int* (In press) 2016. [PMCID In Progress].
8. Lu K-T, Keen HL, Weatherford ET, **Sequeira-Lopez MLS,** Gomez RA, Sigmund CD. Estrogen receptor alpha is required for maintaining baseline renin expression. *Hypertension* 2016 (Epub ahead of print). PMCID: PMC4833511.
9. Gomez RA* and **Sequeira Lopez MLS***. Novel functions of renin precursors in homeostasis and disease. ***Co-corresponding author.** *Physiology.* 31(1):25-33, 2016 PMCID: PMC4698453.

10. Hu Y, Li M, Göthert JR, Gomez RA, **Sequeira-Lopez MLS**. Hemo-vascular progenitors in the kidney require S1P1 for vascular development. *J Am Soc Nephrol.* 2015; (Epub ahead of print) [PMCID In Progress].
11. Belyea B, Xu F, **Sequeira-Lopez MLS,** Gomez RA. Loss of jagged1 in renin progenitors leads to focal kidney fibrosis. *Physiological Reports*. pii: e12544. 2015. PMCID: PMC4673620.
12. **Sequeira Lopez MLS***, Nagalakshmi VK, Li M, Sigmund CD, Gomez RA. Vascular versus tubular *renin: role in kidney development. Am J Physiol Regul Integr Comp Physiol*. 309(6):R650-7, 2015; PMCID: PMC4591368.
13. Lin EE, Pentz ESP, **Sequeira Lopez MLS**, Gomez RA*. Aldo-keto reductase 1b7, a novel marker for renin cells, is regulated by cyclic AMP signaling. *Am J Physiol Regul Integr Comp Physiol.* 309(5):R576-84, 2015

Category	Saifudeen	Belyea	Medrano	Adli	Liu	Charlton	Total
Publications	3	2	2	2		6	**13***
Abstracts	2	9	7			5	**23**
Awards		3			2	2	**7**
Grants	2	1		2	2	2	**9**

PMCID: PMC4591380.

Abstracts

1. **Sequeira-Lopez MLS**, Vidya K. Nagalakshmi, Li M, Gomez RA "Vascular versus tubular renin: role in kidney development." Poster presentation at the University of Virginia, Children's hospital 27th annual research symposium, Charlottesville, VA, May 2015.
2. Vidya K. Nagalakshmi, **Maria Luisa S.Sequeira-Lopez** and R. Ariel Gomez. Membrane Immunoassay for Detecting Single cell Renin Secretion. Poster presentation at the University of Virginia, Children's hospital 28th annual research symposium, Charlottesville, VA, May 2016.
3. Vidya K. Nagalakshmi, Minghong Li, R. Ariel Gomez, **Maria Luisa S. Sequeira-Lopez "**Partial unilateral ureteral obstruction: Analyzing cell fate changes during damage and recovery in the neonatal mouse kidney". Poster presentation at the University of Virginia, Children's hospital 28th annual research symposium, Charlottesville, VA, May 2016.
4. Vidya K. Nagalakshmi, Minghong Li, R. Ariel Gomez, **Maria Luisa S. Sequeira-Lopez**. **"**Cell fate changes during tubular damage and regeneration in the mouse kidney." Oral presentation at AHA-Council of Hypertension 2016, Orlando, Florida, Sep2016.
5. **Maria Luisa S. Sequeira Lopez**, Brian C. Belyea, Rajwinderjit Kaur, Silvia Medrano and R. Ariel Gomez.
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 2012-12016. *Belyea and Medrano shared two publications

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

Publications

1. Li Y, Liu J, McLaughlin N, Bachvarov D, ***Saifudeen Z** and El-Dahr SS. Genome-wide Analysis of the p53 Gene Regulatory Network in the Developing Mouse Kidney. *Physiol Genomics*. 2013 Sep 3. PMCID: PMC3798767 [Available on 2014/10/15]
2. El-Dahr SS, Hilliard S, Aboudehen K, **Saifudeen Z**. The MDM2-p53 pathway: multiple roles in kidney development. *Pediatr Nephrol*. 2013 Sep 28. PMCID: PMC3969418 [Available on 2015/4/1]
3. Li Y, Liu J, Li W, Feng Y, Li M, El-Dahr S and ***Saifudeen Z**. p53 Enables Metabolic Fitness and Self-Renewal of Nephron Progenitor Cells. *Development 2015 Apr 1;142(7):1228-41. doi: 10.1242/dev.111617.*

Abstracts

1. **Zubaida Saifudeen**, Jiao Liu, Yuwen Li, Thomas Carroll1 and Samir S. El-Dahr. P53 Regulates Progenitor Cell Renewal in the Nephrogenic Niche of the Developing Kidney. Poster presentation, American Society of Nephrology, San Diego, Nov. 2012.
2. **Zubaida Saifudeen** Invited Speaker. Talk title: p53 in Nephron Differentiation.American Society of Nephrology, Atlanta, Nov. 2013.

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

1. **Belyea B**, Xu F, Sequeira-Lopez MLS, Gomez RA. Loss of jagged1 in renin progenitors leads to focal kidney fibrosis. *Physiological Reports*. pii: e12544. 2015. PMCID: PMC4673620 **Belyea BC**, Xu F, Sequeira-Lopez MLS, Gomez RA. Loss of Jagged1 in Renin Progenitors Leads to Focal Kidney Fibrosis. *Physiological Reports. 2015;3:e12544*
   **Selected as Editor's Choice (article of particular interest chosen by Editor-in-Chief)*
   Cited: 0 Impact Factor: Not yet determined Rank: Not available
2. **Belyea BC**, Xu F, Pentz ES, Medrano S, Li M, Hu Y, Turner S, Legallo R, Jones CA, Tario JD, Liang P, Gross KW, Sequeira-Lopez MLS, Gomez RA. Identification of renin progenitors in the mouse bone marrow that give rise to B-cell leukemia. *Nature Communications*. 2014;5:3273. PMCID: PMC3929784
   Cited: 2 Impact Factor: 11.47 Rank: 3 of 46 Multidisciplinary Sciences journals
3. Gomez RA, **Belyea B**, Medrano S, Pentz ES, and Sequeira-Lopez MLS. Fate and plasticity of renin precursors in development and disease. *Pediatric Nephrology*. 2014;4:721-6. PMCID: PMC3999616
   Cited: 4Impact Factor: 2.856 Rank: 17 of 119 Pediatric journals

Abstracts

1. **Belyea BC**, Xu F, Mehalic T, Sequeira-Lopez MLS, Gomez RA. "Yolk sac-derived renin progenitors contribute to primitive B lymphopoiesis and are at risk for neoplastic transformation." Children's Hospital Research Symposium. University of Virginia, School of Medicine. Charlottesville, VA. May 2016. Poster Presentation. *
2. **Belyea BC**, Sequeira-Lopez MLS, Gomez RA. "Yolk sac-derived renin progenitors contribute to primitive B lymphopoiesis and are at risk for neoplastic transformation." American Society for Clinical Investigation. Chicago, Illinois. April 2016. Poster Presentation.*
3. **Belyea BC**, Yu F, Sequeira-Lopez MLS, Gomez RA. "Loss of Jagged1 in Renin Progenitors Leads to Focal Kidney Fibrosis." International Workshop on Developmental Nephrology. Snowbird, Utah. July 2015. Poster Presentation. *
4. **Belyea BC**, Mehalic T, Xu F, Sequeira-Lopez MLS, Gomez RA. "Renin Progenitors and Primitive B-1 Cell Development." Department of Pediatrics Research Day. University of Virginia, School of Medicine. Charlottesville, VA. May 2015. Poster Presentation. *

5. Kaur R, **Belyea BC**, Xu F, Mehalic T, Gomez RA, Sequeira-Lopez MLS. "The Role of Renin Progenitors Within Hematopoietic Development." Department of Pediatrics Research Day. University of Virginia, School of Medicine. Charlottesville, VA. May 2015. Poster Presentation.
6. **Belyea BC**, Sequeira-Lopez MLS, Gomez RA. "Pursuing the Origins of Childhood B Cell Leukemia." University of Virginia, Cancer Center Science Fair. Charlottesville, Virginia. March 2015. Poster Presentation. *
7. **Belyea BC**, Mehalic TC, Gomez RA, Sequeira-Lopez MLS. "Cells of the Renin Lineage in the Peritoneal Cavity." High Blood Pressure Research Conference. San Francisco, California. September 2014. Platform Presentation. * *Top scored abstract*
8. **Belyea BC**, Yu F, Sequeira-Lopez MLS, Gomez RA. "Jagged1 and Morphological Integrity of the Kidney." High Blood Pressure Research Conference. San Francisco, California. September 2014. Poster Presentation. *
9. **Belyea BC**, Mehalic T, Gomez RA, Sequeira-Lopez MLS. "Cells of the Renin Lineage in the Peritoneal Cavity." Merinoff World Congress: B-1 Cell Development and Function. Tarrytown, New York. June 2014. Poster Presentation. *

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

1. Belyea BC, Xu F, Pentz ES, **Medrano S**, Li M, Hu Y, Turner S, Legallo R, Jones CA, Tario JD, Liang P, Gross KW, Sequeira-Lopez MLS, Gomez RA. Identification of renin progenitors in the mouse bone marrow that give rise to B-cell leukemia. *Nature Communications*. 2014;5:3273. PMCID: PMC3929784
   Cited: 2 Impact Factor: 11.47 Rank: 3 of 46 Multidisciplinary Sciences journals
2. Gomez RA, Belyea B, **Medrano S**, Pentz ES, and Sequeira-Lopez MLS. Fate and plasticity of renin precursors in development and disease. *Pediatric Nephrology*. 2014;4:721-6. PMCID: PMC3999616
   Cited: 4 Impact Factor: 2.856 Rank: 17 of 119 Pediatric journals

Abstracts

1. **Silvia Medrano**, Maria Luisa S. Sequeira-Lopez and R. Ariel Gomez. Hypoxia and kidney vascular pathology. Poster presentation at the 27th Annual Children's Hospital Research Symposium, University of Virginia, Charlottesville, VA, USA. May 28, 2015.
2. Maria Florencia Martinez, Ellen Pentz, **Silvia Medrano**, Masafumi Oka, Mazhar Adli, Maria Luisa S. Sequeira-Lopez and R. Ariel Gomez. Super-Enhancers in the renin cell. Oral presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.
3. **Silvia Medrano**, Evan Brown, Maria Florencia Martinez, Maria Luisa S. Sequeira-Lopez and R. Ariel Gomez. Use of a CRISPR/Cas9 system for renin cell lineage specification. Poster presentation at the 28TH Annual Research Symposium, CHRC, UVA. May 2016.

4. Maria F Martinez, **Silvia Medrano**, Masafumi Oka, Ellen S Pentz, Allan W Dickerman, Mazhar Adli, Maria Luisa S. Sequeira-Lopez and R. Ariel Gomez. Enhancer Repertoires that Define Renin Cell Identity. Oral presentation, Council on Hypertension, AHA Meeting 2016.
5. Masafumi Oka, **Silvia Medrano**, Maria Luisa Sequeira-Lopez, R. Ariel Gomez. Cells Programmed For The Renin Phenotype Contribute To Vascular Pathology In Renin Deficient Mice. Oral presentation, Council on Hypertension, AHA Meeting 2016.
6. **Silvia Medrano**, Evan Brown, Maria F Martinez, Maria Luisa S Sequeira-Lopez, R Ariel Gomez. Use of a CRISPR/Cas9 System for Specification of the Renin Cell Phenotype. Poster presentation, Council on Hypertension, AHA Meeting 2016.
7. Maria Luisa S. Sequeira Lopez, Brian C. Belyea, Rajwinderjit Kaur, **Silvia Medrano** and R. Ariel Gomez. 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 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

1. **Adli M**, Parlak M, Li Y, El-Dahr SS. Epigenetic states of nephron progenitors and epithelial differentiation. *Cell Biochem*. 2015 Jun;116(6):893-902. PMID: 255604333.
2. Singh R, Kuscu C, Quinlan A, Qi Y, **Adli M**. Cas9-chromatin binding information enables more accurate CRISPR off-target prediction *Nucleic Acids Res.* 2015 Jun 1. pii: gkv575. [Epub ahead of print]

Submitted Articles

1. Kuscu, C, Mammeadov R, Fisher N, Arslan S, Parlak M, Lee I, Kanemaki M, Bekiranov S, Adli M. Temporal and spatial epigenome editing allows precise gene regulation in mammalian cells
   Submitted to Molecular Cell, August, 2016
2. Parlak M, Peiwu Q, Kuscu C, Bandaria J, Singh R, Yildiz A* & Adli M*. Multicolor labeling and imaging nuclear organization of native chromatin loci with type II CRISPR/Cas9 system in living cells.
   In revision at Nature Communication, June 17, 2016

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 inxenograft 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 resitance in PDAC.

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

Publications
Liu, H, Chen S, Yao X, Li Y, Saifudeen Z, , El-Dahr SS. Histone Deacetylases 1 and 2 balance nephron progenitor renewal and differentiation during kidney organogenesis. In preparation.

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 poject2: 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; Guillet, 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*.
2. Lee AM, **Charlton JR**, Carmody JB, Gurka MJ, DeBoer MD. Metabolic Risk Factors in Non-Diabetic Adolescents with Glomerular Hyperfiltration. *Nephrology Dialysis Transplantation* (in press, 2016).
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.
5. Carmody, JB; Harer, MW; Denotti, AR; Swanson, JR; **Charlton, JR**. Caffeine Exposure and Risk of Acute Kidney Injury in a Retrospective cohort of Very Low Birth Weight Infants. *J Pediatr*. 2016 May;172:63-68.
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

1. **Charlton, JR**; Laws, J; Abate, HM; Pearl, VM; Sequeira-Lopez, ML. Early Cessation of Nephrogenesis in a Mouse Model of Premaurity. American Society of Nephrology Annual Meeting. November 2016. Chicago, IL. Abstract #3917.
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 7/1/16-6/30/18
   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 projectsand 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

Gomez RA, El-Dahr S, Chevalier R, Pentz ES, Sequeira Lopez MLS. Pediatric Center of Excellence in Nephrology. "Opportunities to learn methods in epigenetics, cell fate analysis and kidney injury/repair." Poster Presentation at the 47th Annual Meeting of the American Society of Nephrology, Philadelphia, PA, USA, 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