PKD FOUNDATION
Polycystic Kidney Disease

PKD FOUNDATION FIVE-YEAR SUMMARY

Support of Research for PKD in Children

PKDF has invested over $2 million since 2006 for research, support, education and awareness for ARPKD, ADPKD in children, and congenital hepatic fibrosis (CHF), a disease closely associated with ARPKD. The Foundation also strives to provide support through funding and collaborations in the following ways.

Representation in PKDF Scientific Advisory Committee

MADE UP OF 14 PRESTIGIOUS PKD PHYSICIANS AND SCIENTISTS, THE Scientific Advisory Committee (SAC) oversees our research and medical programs aimed at discovering and delivering treatments for PKD. The SAC meets throughout the year to discuss relevant medical issues, provide guidance to our staff and review and approve research applications for grants and fellowships in the field of PKD science. All our materials and publications are approved by SAC members, who possess the highest level of experience and knowledge in PKD clinical and scientific work. One current member in particular is a champion in the pediatric PKD space:

Erum Aftab Hartung, MD, MTR, is a pediatric nephrologist at the Children's Hospital of Philadelphia (CHOP). Her research interests include ARPKD, development of imaging biomarkers of kidney and liver disease, and neurocognitive outcomes in children with chronic kidney disease. She currently serves as chair of the Research Committee of the American Society of Pediatric Nephrology, and is the Associate Program Director for the pediatric nephrology fellowship at CHOP. Dr. Hartung's research is funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health) and the University of Pennsylvania. Dr. Hartung is on the faculty of the Perelman School of Medicine at Penn as Assistant Professor of Pediatrics. She lives in Swarthmore, PA with her husband and two children.

Past SAC members dedicated to PKD in children and ARPKD

John J. Bissler, MD served on the SAC from 2008 to 2018, and is a pediatric nephrologist in Memphis, Tennessee. He is the Director of the Tuberous Sclerosis Center of Excellence and the Director of the Division of Nephrology at St. Jude Children's Research Hospital and LeBonheur Children's Hospital. Dr. Bissler is also a Professor of Pediatrics at the University of Tennessee. He received his medical degree from Northeast Ohio Medical University and has been in practice for more than 20 years. He is Board certified in pediatrics and pediatric nephrology with expertise in angioedema, kidney disease and tuberous sclerosis.

Lisa Guay-Woodford, MD served as Chair of the SAC from 2002 to 2005. She currently serves as the Director of the Children's Research Institute's Center for Translational Science in Washington, D.C. She has become an internationally recognized pediatric nephrologist with a research program focused on identifying clinical and genetic factors involved in the pathogenesis of inherited renal disorders, most notably ARPKD. Her laboratory has identified the disease-causing genes in several experimental models of recessive polycystic kidney disease and her group participated in the identification of the human ARPKD gene as part of an international consortium. In addition, her laboratory was the first to identify a candidate modifier gene for recessive polycystic kidney disease. For her contributions to the field, she was awarded the Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease, given by the Polycystic Kidney Disease Foundation and the International Society of Nephrology.

Katherine Dell, MD served on the SAC from 2002 to 2005, joined the Board of Trustees in 2019 and is a board-certified pediatric nephrologist and Vice Chair of Research for the Pediatric Institute at Cleveland Clinic. Her research focuses on development and application of quantitative magnetic resonance imaging (MRI) techniques as biomarkers for chronic kidney disease progression, including progression of autosomal recessive polycystic kidney disease (ARPKD).

Research funding dedicated to research in pediatric PKD

OVER THE PAST FIVE YEARS, PKDF HAS AWARDED BIENNIAL research grants (transitioned to annual as of 2019) to outstanding PKD researchers to increase understanding of the genetic and pathological processes involved in PKD. Although the results of all PKDF-funded scientific projects may ultimately benefit and contribute to discoveries in PKD in children, we'd like to highlight the following projects.

2021 grants

Erum Hartung, MD CHILDREN'S HOSPITAL OF PHILADELPHIA

Intracranial aneurysms and vascular abnormalities in ARPKD

Unlike the dominant form of polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD) has historically not been thought to cause an increased risk of intracranial aneurysms (ICA; outpouchings of arteries in the brain) or other problems with blood vessels (vascular abnormalities). However, there have now been six reported cases of ICA in children and young adults with ARPKD, and another two individuals reported with aneurysms in other parts of the body. In some cases, these aneurysms caused significant complications such as bleeding in the brain or even death. Despite the potentially devastating effects of ICAs and other blood vessel problems, we do not know how commonly they occur in individuals with ARPKD and whether they can be prevented, because to our knowledge there have been no prior systematic studies to investigate this issue. Our overall objective is to determine how common ICA and blood vessel abnormalities are in individuals with ARPKD, and to study potential risk factors for these problems, such as high blood pressure, abnormal function of the cells lining the blood vessels (endothelial dysfunction), and increased stiffness of the blood vessels. This study will yield important information to guide the care of individuals with ARPKD by helping to inform whether screening for ICA and other blood vessel problems is indicated, and by identifying potentially treatable risk factors to prevent vascular complications.

Melissa Little, PhD MURDOCH CHILDREN'S RESEARCH INSTITUTE

In vitro modelling of autosomal recessive polycystic kidney disease

Autosomal recessive polycystic kidney disease (ARPKD), caused by mutations in the *PKHD1* gene, is a devastating kidney and liver disease affecting babies and children. Most babies are born unable to produce any urine which also affects lung development. These babies require prolonged intensive care, breathing support and dialysis from birth. They often remain in hospital for the first four to six months of life and remain on dialysis until kidney transplantation. Milder cases can present later but ultimately require dialysis and transplantation in childhood or young adulthood. Furthermore, 10 to 20% of patients will also require liver transplantation in childhood. Little is understood about how *PKHD1* functions within the kidney and how *PKHD1* mutation leads to cysts. Consequently, there are no established treatments for ARPKD.

Researchers often study genetic diseases in animals as a surrogate model for human disease. However, animals with *PKHD1* mutations don't develop kidney cysts like human ARPKD patients. *PKHD1* therefore has unique functions in humans and needs to be studied using human kidney cells. Obtaining kidney cells from paediatric ARPKD patients by kidney biopsy is impractical and unethical.

Our laboratory is one of few in the world generating stem cells from patients with kidney disease and turning them into 3D mini-kidneys in a dish (called organoids). We have developed a new method to grow collecting duct (CD) cells, which are the cells that develop cysts in ARPKD. When we grow CD organoids from stem cells carrying *PKHD1* mutations, they form large cysts. This represents an opportunity to study ARPKD in a human model without having to biopsy a human kidney.

In this proposal we will compare healthy and ARPKD-patient kidney organoids to better understand how defects in *PKHD1* lead to cyst formation. In the short term, this will help us to understand the function of *PKHD1* and possibly also allow the testing of treatments to reduce cyst growth. To move towards drug screening, we will miniaturize our cultures using a robotic cell handling and imaging platform. This will allow us to create almost 400 kidney models on one plate the size of a cell phone. Showing we can test drugs in this way will provide the foundation for future work screening potentially thousands of potential therapies to see which works best at reducing cyst growth in the ARPKD organoids. As such, this may lead to the development of the first treatments for ARPKD. The long term hope is to be able to grow an individual patient's kidney cells within this system and find the best treatment for their particular *PKHD1* mutation. This type of 'personalized therapeutics' would be a world first. In the long term this approach may also be applied to other diseases of the collecting duct, including ADPKD.

2019 grants

Sorin Fedeles YALE UNIVERSITY

Controlling the viability of PKD mutant cells via inactivation of XBP1 as a novel strategy to treat ADPKD

Polycystic kidney and liver diseases belong to a family of genetic fibrocystic disorders that primarily affect the kidney and liver. The current proposal focuses on a pathway, i.e., Ire1α-XBP1, that we have recently implicated in the pathogenesis of ADPKD and that we have found, to our surprise, to play an important role in controlling the viability of *PKD1* deficient cells. Genetic inhibition of this pathway in relevant mouse models of ADPKD led to a slowing down of disease progression and significantly improved kidney function. Avenues that can inhibit Ire1α-XBP1 may thus hold clear therapeutic potential for the treatment of ADPKD and potentially, ARPKD.

2019 fellowship

Rebecca Walker, PhD UNIVERSITY OF MARYLAND

Relieving the Stress of PKD: A new role of PKHD1 in detoxification mediated via differential cleavage of the intracellular domain

ARPKD is a severe disease causing cyst-development throughout the kidneys caused by mutation in the *PKHD1* gene. Our knowledge of mechanisms underlying ARPKD cyst-development is greatly lacking. Our lab has found a possible link between *PKHD1* protein and detoxification of harmful chemicals in the kidney. We believe that *PKHD1* protein is processed to produce fragments that move around inside kidney cells and activate pathways which warn the cell of toxins. Success in this investigation will transform our understanding of cyst-development in PKD and provide potential innovative targets for patient treatment.

2018 grants

Whitney Besse, MD YALE UNIVERSITY

Genetic approach to define mediators of Polycystin-1 function in PKD

We seek to learn how to compensate for the genetic defect in ADPKD by either increasing the functional amount of the missing proteins or blocking the effects resulting from loss of the mutant proteins. Besides *PKD1* and *PKD2*, many additional human genes are required for the function of the ADPKD proteins. Mutations in these gene can be rare causes of kidney/liver cysts, and study of them can shed light on the pathways we need to target for treatment. This proposal will investigate two such genes, *DNAJB11* and *PKHD1*, in which we identified mutations causing liver/kidney cysts in adults. Excitingly, *DNAJB11* is known to have chaperonea function, something that has been upregulated successfully in cystic fibrosis treatment. *PKHD1* is the disease gene for ARPKD. We will use mouse models to investigate whether the cysts we

see in some carrier parents of ARPKD children suggest that *PKHD1* also affects the ADPKD proteins.

Daria Ilatovskaya, PhD MEDICAL UNIVERSITY OF SOUTH CAROLINA

Effects of dietary salt restriction on cystogenesis in ARPKD

Autosomal recessive form of the polycystic kidney disease (ARPKD) is a genetic disorder that has an incidence of 1 in 20,000 live births; infants affected with this disorder, if they survive, develop chronic kidney failure by adolescence and eventually require kidney transplantation. ARPKD patients are advised to limit their salt intake as it is generally accepted that excessive salt consumption is harmful to people with hypertension and chronic kidney disease (CKD). However, latest data show that both excessive and insufficient salt intake might be detrimental for CKD. Currently there are no studies that would address how salt might affect ARPKD development and whether it may produce beneficial or harmful effects. This project is focused on the role of diet, and specifically its salt content, in the development of ARPKD. Anticipated results of this study will provide novel insights potentially useful for the treatment of the disease.

2016 grants

Katherine M. Dell, MD CASE WESTERN UNIVERSITY

Magnetic Resonance Fingerprinting (MRF) to Assess ARPKD Kidney and Liver Disease

Autosomal recessive polycystic kidney disease (ARPKD) is a disorder that affects both kidneys and the liver and can present life-long challenges to affected patients. Several new therapies have shown promise in ARPKD animal models. However, these therapies have not been studied in ARPKD patients because there are no clinically-available, reliable, non-invasive ways to measure the effects of treatment. We have identified two magnetic resonance imaging (MRI) measures that may provide this key missing piece. Unfortunately, MRI studies are long and require patients to sit still, which is not possible for young children. In the proposed studies, we will investigate a novel MRI method, called MR fingerprinting (MRF). MRF may allow these studies to be performed very rapidly, having the potential to allow ARPKD patients of all ages to be part of clinical trials for new therapies.

Feng Qian, PhD UNIVERSITY OF MARYLAND, SCHOOL OF MEDICINE

Role of Fibrocystin/Polyductin in Health and ARPKD

This proposal tackles a long-standing problem in the field of autosomal recessive polycystic kidney disease (ARPKD), which is caused by mutations of the *PKHD1* gene. It will identify and characterize the important cellular defects caused by mutations of the *PKHD1* gene. Insights gained will advance our fundamental understanding of the function of the *PKHD1* gene and enable us to develop effective therapies for ARPKD.

Edward Inscho, PhD UNIVERSITY OF ALABAMA AT BIRMINGHAM

Renal Vascular Function in ARPKD

This proposal tackles a long-standing problem in the field of autosomal recessive polycystic kidney disease (ARPKD), which is caused by mutations of the *PKHD1* gene. It will identify and characterize the important cellular defects caused by mutations of the *PKHD1* gene. Insights gained will advance our fundamental understanding of the function of the *PKHD1* gene and enable us to develop effective therapies for ARPKD.

Supported scientific meetings

PKDF IS DEDICATED TO FUNDING PKD-RELEVANT SCIENTIFIC AND clinical meetings that bring together PKD scientists from around the world to discuss current findings and encourage research collaborations. The following meetings have focused specifically on research related to PKD in children and ARPKD.

PKD in Children Conference

May 3–5, 2019 in Chicago, IL | April 21–23, 2017 in New York City

The PKD in Children Conference brought together parents, caregivers and clinicians to learn how managing PKD in children impacts families. This conference connected parents and caregivers with expert physicians to learn more about how to manage their child's disease providing vital knowledge about ADPKD and ARPKD. Sessions designed specifically for parents provided a unique opportunity to learn from experts in the field while connecting with others and supporting each other.

PKD Research Conference

June 29–July 1, 2018 in Kansas City, MO

A basic science symposium was held in concert with PKDF's PKD Connect Conference. The motivation for the meeting was that PKD research was rapidly progressing and opportunities to explore recent developments in a small, interactive environment promotes research collaborations and the development of novel therapeutics.

Research specific to PKD in children was presented by Dr. Daria Ilatovskaya (Medical University of South Carolina), Dr. Maria Irazabal (Mayo Clinic), Dr. Timothy Kline (Mayo Clinic) and Dr. Barbara Tschida (Recombinetics).

FASEB — PKD: Challenges, Differing Viewpoints and Ways Forward

June 25–30, 2017 in Big Sky, MT

This science research conference focused on the autosomal dominant (ADPKD) and recessive (ARPKD) forms of PKD, autosomal dominant polycystic liver diseases with mild or no kidney involvement (ADPLD) and syndromic forms of PKD caused by mutations in genes encoding for proteins in the primary cilium (ciliopathies). The specific goals were: assemble an interdisciplinary program of basic scientists and clinical researchers that are at the forefront of PKD research to provide a comprehensive update on recent advances in PKD; provide a format where trainees and junior investigators can present, network and collaborate; generate a platform for informed discussion to help resolve unanswered questions in PKD; promote the development of novel therapies for PKD.

American Society of Pediatric Nephrology

April 30–May 3, 2016 in Baltimore, MD

This meeting brought together researchers, clinicians and students to review the current research and its impact on the future of medical care. A special session on ARPKD was hosted by PKDF with the goal to discuss genetic research and understand the utility and limitations of current genetic tests for diagnosis, therapy guidance and other aspects of clinical care.