To support work being done to find treatments and a cure, we have awarded 15 research grants to PKD researchers. The Foundation will spend nearly $2.4 million over the next two years on these grants. The awardees represent top researchers and physician scientists throughout the United States, as well as Canada and Italy.

Five of the research grants focus on the development of a treatment for PKD so our patients have something that will slow the progression of the disease. The remaining ten are discovery research, which focuses on understanding the way in which cysts develop or enlarge in PKD. This must be conducted in order to identify cell compounds and pathways before therapy development can be done.

Read project details on the following pages and visit pkdcure.org/researchgrants for more.
THE REVIEWERS

Review Process
The Review Committee was comprised of ten PKD Foundation Scientific Advisory Committee (SAC) members and seven additional PKD scientists. The PKD Foundation SAC oversees PKD Foundation research and medical programs aimed at developing treatments for PKD.

SAC Members – Review Committee
Terry Watnick, M.D., SAC Chair
University of Maryland School of Medicine
Stefan Somlo, M.D., SAC Vice Chair
Yale University School of Medicine
Benjamin Cowley, Jr., M.D.
University of Oklahoma Health Sciences Center
Richard Sandford, Ph.D., FRCP
University of Cambridge
Cambridge Institute of Medical Research
John Bissler, M.D.
University of Tennessee Health Sciences Center
Angela Wandinger-Ness, Ph.D.
University of New Mexico Health Sciences Center
Iain Drummond, Ph.D.
Massachusetts General Hospital
Harvard Medical School
Ronald Perrone, M.D.
Tufts Medical Center
Darren Wallace, Ph.D.
University of Kansas Medical Center
York Pei, M.D.
Toronto General Hospital
University Health Network
Greg Pazour, Ph.D.
University of Massachusetts Medical School
Jen Pluznick, M.D.
The Johns Hopkins University School of Medicine
Norann Zahgloul, Ph.D.
University of Maryland School of Medicine
Maureen Barr, Ph.D.
Rutgers University
Peter Igarashi, M.D.
University of Texas Southwestern Health Sciences Center

Additional PKD Experts – Review Committee
Michael Köttgen, M.D., Ph.D.
University of Freiburg
Michal Mrug, M.D.
University of Alabama at Birmingham
School of Medicine

THE PROCESS
Each grant has two reviewers
Each reviewer receives six grants to review

3 primary
3 secondary
Grants ranked from 1-9 (one being strongest)

Rankings based on:
• Significance: Request for Applications specifically solicited proposals with obvious or direct potential to accelerate the development of potential therapies. Proposals focusing on childhood PKD were also encouraged.
• Innovation
• Investigator
• Environment
• Approach

OVERALL SCORE
The PKD Foundation grant review process is modeled on the NIH peer-reviewed paradigm.
# The Recipients

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<tr>
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<th>Research Grant Title</th>
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<td>Erica Golemis, Ph.D.</td>
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### International Awardees

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<td>The Eileen Creamer O’Neill Award</td>
<td>Targeting Glucose Metabolism in PKD: A Preclinical Proof-of-Concept Study*</td>
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<td>Marie Trudel, Ph.D.</td>
<td>Effects of Genetic and Pharmacological Ablation of KCNN4 on Disease Progression in Two Orthologous Mouse Models of PKD</td>
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### Research Grant Project Summaries

**Dr. Vincent H. Gattone Research Award for the Top-Rated Grant Proposal Funded by The Carlo and Micol Schejola Foundation**

**Advancing HSP90 Inhibitors Towards Clinical Trials for ADPKD**

Erica Golemis, Ph.D.
The Research Institute of Fox Chase Cancer Center
(Therapy Development)

Heat shock protein 90 (HSP90) has emerged as an important target for drug development for cancer, and HSP90 inhibitors are being tested in clinical trials for cancer. In preliminary studies, an HSP90 inhibitor was very effective in stabilizing kidney function and limiting cyst growth in a mouse model for ADPKD with a mutated PKD1 gene. In this project, mouse models will be used to extend this work in three ways: (1) evaluating whether HSP90 inhibition blocks the growth of ADPKD with a mutated PKD2 gene, (2) determining the effect of long-term dosing of an HSP90 inhibitor on kidney function and (3) determining whether the combination of an HSP90 inhibitor with another promising inhibitor, 2-deoxy-D-Glucose (2DG), further improves effectiveness in stabilizing kidney function and limiting cyst growth.

### Key Facts and Definitions:

- In PKD, fluid-filled cysts develop and enlarge in both kidneys, eventually leading to kidney failure.
- ADPKD can be inherited in a dominant way from mutations in the PKD1 or PKD2 genes.
- ARPKD can be inherited in a recessive way from mutations in the PKDH1 gene.
- A channel is a way for charged particles to move across the membranes of cells.
- A cell pathway is a biochemical pathway through which cells signal each other.
- Rodent models include rats and mice with PKD.
- A drug target is a naturally existing compound in the cell the drug is meant to act on.
- It is important to note that discovery research that focuses on understanding the way in which cysts develop or enlarge in PKD must be conducted in order to identify cell compounds and pathways before therapy development can be done.
International Awardees

The Eileen Creamer O’Neill Award
Targeting Glucose Metabolism in PKD: A Preclinical Proof-of-Concept Study*

Alessandra Boletta, Ph.D.
Fondazione Centro San Raffaele
Milan, Italy
(Therapy Development)

ADPKD cells are highly dependent on glucose, a simple sugar, for their energy production. 2-deoxy-D-Glucose (2DG) is a simple molecule resembling glucose that was found to slow down cyst growth in rodent models of PKD. This project will test whether or not 2DG improves the outcome in mouse models of late-onset and slowly progressive PKD that more closely resemble the human version of the disease. Furthermore, the project will look for additional changes in metabolism in the body of PKD patients.

Health Care Utilization and Costs of ADPKD

York Pei, M.D.
University of Toronto General Hospital
Toronto, Canada

Recent advances have led to the identification of multiple classes of drugs that have the potential to modify kidney disease progression in ADPKD. Looking forward, multiple classes of drugs have the potential to become available for treatment of ADPKD in the coming decade. However, long-term use of these medications is expected to be expensive, which poses a challenge for health care policy decision makers. This project will define the health care use and cost of ADPKD using several unique research databases that track health care use and costs in Ontario, Canada. It will also perform health economic analyses to identify the circumstances where new disease-modifying treatments offset the health care costs associated with kidney disease progression in ADPKD. This knowledge will be useful to inform health care policymakers how best to provide coverage and reimbursement for a treatment for ADPKD.

Effects of Genetic and Pharmacological Ablation (Deletion) of KCNN4 on Disease Progression in Two Orthologous Mouse Models of PKD

Marie Trudel, Ph.D.
Institut de Recherches Cliniques de Montreal
Montreal, Canada
(Therapy Development)

Senicapoc, a non-toxic inhibitor of the potassium channel KCNN4, will be tested as a new oral drug treatment for ADPKD. Experiments in cells show that KCNN4 function drives the renal cyst expansion believed to cause the progression of ADPKD towards renal failure. Preliminary results indicate two genetically engineered mouse models of ADPKD lacking KCNN4 show slower disease progression, and one model resembles the natural history of human PKD. The project will therefore test senicapoc’s ability to slow progression of PKD in both mouse models with intact KCNN4 genes. If senicapoc slows disease progression in these mice, then senicapoc tests in ADPKD patients can be initiated promptly, since senicapoc is known to have a lasting effect and to be non-toxic in human subjects without kidney disease.

*related to polycystic liver disease
United States Awardees

Role of CFTR and NKCC1 in PKD
James Calvet, Ph.D.
University of Kansas Medical Center
(Discovery Research)

The cyst-filling fluid secretion process, which is critical to the cyst growth of ADPKD, is dependent on two channels, CFTR and NKCC1. This project will determine how essential these channels are for cyst growth and overall kidney enlargement in mouse models of ADPKD. This project will also test (1) the effectiveness of a potential new treatment for PKD that targets cyst-filling fluid secretion processes and (2) whether decreased calcium in kidney cells results in increased CFTR and NKCC1 protein levels.

Preclinical Assessment of MCP-1/CCR2 Inhibition as Treatment for ADPKD
Timothy Fields, M.D., Ph.D., and Katherine Swenson-Fields, Ph.D.
University of Kansas Medical Center
(Therapy Development)

White blood cells called macrophages promote cyst growth and disease progression in PKD mouse models. Cyst cells attract macrophages primarily by making a protein called monocyte chemotactic protein-1 (MCP-1). Compelling preliminary results suggest that deleting the MCP-1 gene or blocking the macrophage infiltration with a drug (CCR2A) can slow PKD progression. This project will extend these studies in mice. Treatment to block the infiltration with CCR2A alone or in combination with tolvaptan, a drug that has shown clinical promise for PKD, will be tested. A successful outcome in these studies could facilitate the repurposing of CCR2As, alone or in combination with tolvaptan, for PKD treatment. The goal of this work is to establish new therapies for PKD that slow disease progression and relieve associated suffering.

How You Can Help Fund Research

The PKD Foundation will spend nearly $2.4 million over the next two years on these grants through the Research Grants Program.

The cost per day to fund one research grant is $350, or $45 an hour. This allows the principal investigator of the lab to hire staff, such as research assistants or fellows, who are instrumental in conducting the research. The funds can also help buy supplies, biochemicals and assist with travel costs.

If you would like to learn more about fully funding a grant (which can be named after you or a loved one), please contact Michelle Davis, Chief Development Officer, at michelled@pkdcure.org or 816.268.8477.
**Investigation of the Biological Basis and Therapeutic Effect of Anti-tumor Drug 11beta-dichloro on PKD**
Anna Rachel Gallagher, Ph.D.
Yale University
(Therapy Development)

Preliminary evidence that suggests the cells without the PKD1 gene can be treated with an anti-tumor drug, 11beta-dichloro, to cause cell death which would result in slower-growing cysts. This project will study the effect of this drug on (1) cysts from a mouse model of PKD1 and (2) cysts derived from cells that lack PKDH1 (ARPKD). The goal is providing a new treatment for PKD.

**Role of Tulp3 and the Hedgehog Pathway in PKD**
Karel Liem, Jr., M.D., Ph.D.
Yale University
(Discovery Research)

A new mouse model has been created that develops polycystic kidney disease at birth. Studies have shown that a particular pathway is overactive in these mice. When the overactivity of the pathway is decreased, this lessens the cystic kidney disease. The project will test the role of the pathway in the new mouse model and an ADPKD-1 animal model system with both young and adult animals. Identifying the pathway and a target for drugs to treat PKD will be greatly informative to treat PKD in children and adults.

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The PKD Foundation will spend nearly **$2.4 million** over the next two years.

**The Role of Beta-catenin as Signal Integrator in PKD**
Jordan Kreidberg, M.D., Ph.D.
Boston Children's Hospital
(Discovery Research)

The exact cause of the cysts in ADPKD is not completely understood. Over the past five years, the Kreidberg laboratory at Boston Children's Hospital has studied kidneys of mice with mutations in the same PKD genes that cause ADPKD in humans and found abnormalities in several cell pathways. Many pharmaceutical companies are developing drugs that target these same pathways, but drugs will not be developed for use in ADPKD in humans without more clarity of the abnormalities. This project will further study these pathways to more clearly define and understand the cause of the cysts.

**The Effects of Genetic Reactivation of Functional Polycystins on Progression of PKD**
Ming Ma, Ph.D.
Yale University
(Discovery Research)

Recently, polycystins, important proteins in ADPKD, were shown to block signals in kidney cells that cause cyst growth. The next step is to think about reintroducing normal PKD1 or PKD2 genes back to cystic tissue and, therefore, block cyst growth. ADPKD mouse models have been made that allow us to do exactly that—re-activate normal, silenced PKD1 or PKD2 genes. This project will use these models to determine whether cyst growth can be slowed or perhaps even reversed and when is the best stage in the disease to start this intervention. It will also examine the effects of altering PKD1 expression in ARPKD models. This study serves as a proof of principle (an early stage of clinical drug development when a compound has shown potential in animal models and early safety testing) for what the expectations and goals of therapy in ADPKD may be.

**related to ARPKD and ADPKD**
The grants support projects that will inform therapy development in the future and move PKD science forward to accelerate treatments to patients.

Role of miR-17–92 in the Pathogenesis of PKD
Vishal Patel, M.D.
University of Texas Southwestern Medical Center
(Discovery Research)

MicroRNAs (miRNAs) inhibit the function of genes. Abnormal levels of miRNA expression are observed in numerous diseases, including PKD. Drugs designed to correct miRNA levels are emerging as promising new ways to treat diseases. A family of miRNAs called miR-17–92 have been identified, which promotes kidney cyst growth in mice. In this application, the aim is to determine whether miR-17–92 promotes cyst growth in mouse models of ADPKD. If successful, the study will identify miR-17–92 as a new drug target for the treatment of ADPKD.

Unifying Cystogenic Mechanism of ADPKD and ARPKD**
Feng Qian, Ph.D.
University of Maryland Medical Center: Division of Nephrology
(Discovery Research)

This project tackles the fundamental question as to how the two genes, PKD1 and PKDH1 (ARPKD), work together to ensure normal kidney development and to protect the kidney from cyst formation. Recently, it was discovered that PKDH1 mutation causes kidney disease likely by damaging the PKD1 gene function. This project will investigate how the PKDH1 gene controls PKD1 gene function during development using a mouse model. The hypothesis is that the two forms of PKD have the same disease-causing process and it is expected that this work will open new ways to identify new drug targets for therapies for both ADPKD and ARPKD.

HDAC Inhibitor Mediated Kidney Cyst Reduction
Zhaoxia Sun, Ph.D.
Yale University
(Discovery Research)

In preliminary studies, histone deacetylase (HDAC) inhibitors have been found to reduce the defects seen in ADPKD in cystic animal models. Interestingly, HDAC inhibitors (HDACIs) are already being used to treat epilepsy and cancer. Although well tolerated, they do have side effects. Tissue-specific HDACIs will be more potent, have fewer side effects and are in active development for cancer treatment, providing a rich source of candidate drugs for repurposing for PKD. This project will determine which HDACIs are most relevant to ADPKD, critical information for selecting and testing type-specific HDACIs as candidate drugs for ADPKD. It will also investigate the impact of HDACIs on other forms of PKD.

The Rosemary M. Peppet Award
Phosphodiesterase/cAMP Signaling in Renal Cystogenesis (Cyst Formation) in Zebrafish
Caroline Sussman, Ph.D.
Mayo Clinic
(Discovery Research)

NOTE: This proposal uses zebrafish to screen compounds that might slow cyst development and enlargement in PKD. The zebrafish is a simple model for studying vertebrate development and genetics and is a means of understanding how not only fish, but all vertebrates including humans, develop from the moment that sperm fertilizes an egg.

**related to ARPKD and ADPKD
Research has shown that increased levels of a compound called cAMP in kidney cells are an important change that occurs in ADPKD. For example, clinical trials have shown that treatments that decrease the formation of cAMP slow disease progression. Therefore, therapies decreasing cAMP formation are promising, but they do not offer a cure, nor are they well-tolerated by many patients. Phosphodiesterases are proteins that lower cAMP levels by breaking-down cAMP, so they may also affect PKD progression. This study is testing whether altering phosphodiesterase activity affects renal cyst formation using zebrafish as a model. Information gained from this research will indicate whether drugs targeting phosphodiesterases might be effective in treating PKD.

In Vivo Analysis of Cilia Mechanosensation in the Kidney
Bradley Yoder, Ph.D.
University of Alabama at Birmingham
(Discovery Research)

The objective of this proposal is to analyze the role of cilia (short, hairlike organelles on the surface of cells) and the cystic kidney disease protein, polycystin-2, based on a mouse model. For this, a mouse model was generated in which green fluorescent cilia can be seen in a living animal. This study will determine whether bending of the cilia by urine flow through a small tube of the kidney in normal and cystic conditions results in events involving PKD2. It will also assess whether bending of the cilia results in changes in gene expression. The current models in which the cilia is studied with its relation to cystic kidney disease are based on cells grown on petri dishes. This study is one of the initial works to explore what cilia are doing while in a living kidney.