May 5, 2014

Amy Goldman Fowler, Trustee

Ms. Krista Mathews Dean
Director of Corporate Philanthropy
Children's Hospital of Wisconsin Foundation, Inc.
MS-3050
P.O. Box 1997
Milwaukee, WI 53201

Dear Ms. Dean:

On behalf of the Trustees (the "Trustees") of the Lillian Goldman Charitable Trust, a private foundation (the "Foundation"), I am pleased to extend a grant (the "Grant") to the Children's Hospital of Wisconsin Foundation, Inc. (the "Grantee") in the amount of Six Hundred Thousand Dollars ($600,000) (the "Grant Funds"), payable as hereinafter provided, subject to the terms and conditions below. The Grant Funds shall be payable in three installments of Two Hundred Thousand Dollars ($200,000) each. The first such installment shall be payable upon the Trustees' receipt of a copy of this Grant Agreement executed on behalf of the Grantee, together with a copy of the determination letter the Grantee received from the IRS confirming its tax exempt status. The second and third installments of the Grant Funds shall be payable in 2015 and 2016 on or about the anniversaries of the payment of the first installment.

The Foundation makes the Grant subject to the following terms and conditions which shall be deemed accepted in all respects by the Grantee's execution of this Grant Agreement:

1. The Grant is to be used exclusively to support the basic research of Dr. Ellis D. Avner (or his designees) focused on Autosomal Dominant Polycystic Kidney Disease ("ADPKD"). The specific activities to be undertaken are described in more detail in Grantee's proposal dated February 10, 2014 annexed hereto, which is hereby incorporated by reference.

2. The Grant Funds may not be used for any other purpose or program without the prior written approval of the Trustees, on behalf of the Foundation. The Grantee confirms that no goods or services were provided by the Grantee to the Trustees or the Foundation in consideration for the Grant. In addition, the Grantee

agrees that no portion of the Grant Funds will be used to support the carrying on of propaganda or otherwise attempting to influence legislation (within the meaning of Code Section 4911(d)(1)), or to support the participation in, or intervention in (including the publication or distribution of statements), any political campaign on behalf of (or in opposition to) any candidate for public office.

3. In any statement, campaign reports or materials, press release or announcement, the Grantee will refer to the donor as the "Lillian Goldman Charitable Trust", and the Grantee will request advance approval from the Trustees of the text of any such statement, campaign reports or materials, press release or announcement, if the Grant or the Foundation will be mentioned therein.

4. The Grantee represents and warrants (a) that it is an organization described in Section 501(c)(3) of the Internal Revenue Code of 1986, as amended (the "Code"), and is classified as a public charity within the meaning of Section 170 (b)(1)(A)(vi) of the Code, and (b) there is no issue presently pending before any office of the Internal Revenue Service that could result in any change to the Grantee's status under said Sections of the Code. The Grantee agrees to notify the Trust immediately in writing of any changes to its status as a public charity under Sections 501(c)(3) and 170 (b)(1)(A)(vi) of the Code.

5. The Grantee agrees that commencing on the date the Grant is received by it and continuing until the date when the Grant Funds are fully expended in accordance with this Agreement, the Grantee shall provide written reports to the Trustees describing the expenditures made by the Grantee from the Grant Funds. Said reports shall be provided at least annually. Upon expenditure of all of the Grant Funds, the Grantee shall provide the Trustees with a final report which shall contain a detailed accounting of the uses or expenditures of the Grant Funds and a description of the objectives achieved as a result of the expenditure of the Grant Funds.

6. The Grantee agrees to keep a record of all expenditures relating to the Grant, with appropriate supporting documentation, for at least three years following the year in which the Grant Funds are fully expended or the termination of the Grant for any other reason. The Grantee further agrees to permit the Trustees or the Trustees' authorized representative reasonable access during regular business hours to such financial records for the purpose of making such financial audits, verifications or other program evaluations as the Trustees deem necessary or appropriate concerning the Grant.

7. If any of the following circumstances occur, the Foundation may, in its discretion, in addition to any other remedies available to it, require that the Grantee

immediately repay the full amount of any Grant Funds which are unspent as of the date of the occurrence:

(a) The purpose of the Grant has been fully completed.

(b) The Grantee is no longer a public charity exempt from federal income taxation under Sections 501(c)(3) and 170 of the Code.

(c) The Grantee for any reason becomes unable to carry out the purpose of the Grant.

(d) The Grantee uses Grant funds for a purpose other than those set forth in this Agreement, unless the Trustees shall have consented in writing to such modification.

The Grantee shall notify the Trustees immediately in writing upon the occurrence of any of the circumstances mentioned above.

8. The Grantee may not assign or otherwise transfer any of its rights or delegate any of its obligations under this Agreement without the prior written consent of the Foundation.

9. Notwithstanding any provision of law or regulations to the contrary, the Grantee expressly agrees that the Trustees of the Foundation and their successors and assigns (and any person or entity authorized by the Foundation to enforce the terms of this Grant Agreement specifically or in general to succeed to its rights to enforce obligations of grantees (herein referred to as the Foundation's "Designee")) shall have the right and judicial standing to enforce any and all provisions of this Grant Agreement in any court or relevant forum and further agrees to oppose any person or party which asserts a contrary position, irrespective and separate and apart from any rights which the Attorney General of the State of New York may possess under law. The Grantee agrees not to contest the commencement of any such action by the Foundation, its successors and assigns or its Designee on any grounds other than that the Grantee has complied with its obligations hereunder. In furtherance thereof, the Grantee and the Foundation agree that the rights and obligations of the parties hereunder shall have the force and effect of a contract, rather than a property transfer.

10. Any term or provision of this Agreement that is invalid or unenforceable in any situation in any jurisdiction shall not affect the validity or enforceability of the remaining terms and provisions hereof or the validity or enforceability of the problematic term or provision in any other situation or in any other jurisdiction.

11. This Agreement constitutes the entire understanding between the parties and shall be governed by the laws of New York. This Agreement may be amended only by a written instrument signed by the authorized representatives of the Foundation and the Grantee.

12. All notices, requests, demands, or other communications permitted or required to be given under this letter agreement shall be in writing and shall be deemed given or made when sent by United States certified or registered mail, return receipt requested and postage prepaid, or by a nationally recognized overnight courier, delivery fee prepaid, and in either case to the persons and at the addresses specified below:

If to the Foundation:

Amy Goldman Fowler, Trustee
164 Mountain View Road
Rhinebeck, NY 12572

Copy to:

Donald A. Goldsmith, Esq.
Holland & Knight LLP
31 West 52nd Street
New York, NY 10019

If to the Children's Hospital of Wisconsin Foundation, Inc.:

Ms. Krista Mathews Dean
Director of Corporate Philanthropy
Children's Hospital of Wisconsin Foundation, Inc.
MS-3050
P.O. Box 1997
Milwaukee, WI 53201

The persons and addresses set forth above, from time to time, may be changed by written notice sent as aforesaid to the other party.

Please acknowledge acceptance of the terms of this letter agreement by signing and returning one copy this letter to the Trustees addressed as follows:

Lillian Goldman Charitable Trust
c/o Holland & Knight LLP
31 West 52nd Street
New York, NY 10019
Attn: Ms. Mary Jane Marchut

The Foundation is pleased that it can be of assistance to the Children's Hospital of Wisconsin Foundation, Inc. and Dr. Avner's ADPKD research. We look forward to hearing from you.

Sincerely,

LILLIAN GOLDMAN
CHARITABLE TRUST

By: Amy Goldman Fowler
Amy Goldman Fowler, Trustee

Agreed to and Accepted by
the Children's Hospital of Wisconsin Foundation, Inc.
on this 8th day of May, 2014.

By: _____

Name: Jeffrey Stewart

Title: C.O.O.

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Foundation Proposal from Medical College of Wisconsin (Avner/Sweeney) 2/10/14

Introduction

The Comprehensive Childhood Center for Polycystic Kidney Disease (CCC-PKD) was established at the Medical College of Wisconsin and the Children's Hospital of Wisconsin in 2004. Its goal was to expand 20+ years of NIH–funded basic research focused on the pathophysiology of PKD into an integrated translational program. This program incorporated: 1) teams of basic researchers from multiple departments; with 2) a dynamic clinical research/clinical trials infrastructure, and 3) a unique clinical program to provide specialized, comprehensive care for children and adolescents with ADPKD and ARPKD referred from all major medical centers. **This Proposal is focused on increasing basic research in ADPKD in this context.** Our CCC-PKD is uniquely positioned to accomplish this goal, as adolescents with ADPKD in our Program are the primary target group for therapeutic intervention to prevent progression of the morbidity and mortality of ADPKD. Further, we have developed a collaborative partnership of interdisciplinary researchers, as well as unique models and reagents to study the molecular and cellular pathophysiology of ADPKD. Our CCC-PKD is particularly relevant to the focus of the Arno Foundation, given the increasing data from many laboratories that as "multimeric protein complex diseases", the basic mechanisms causing disease development and progression in both ADPKD and ARPKD (and their future therapies) are quite similar-they are genetically-determined pediatric diseases [1]. An ancillary objective of the CCC-PKD center is to attract new scientific expertise to the study of PKD through training initiatives; and creating scientific opportunities for scientists using complementary and unique approaches.

Background of Program Leaders:

Ellis D. Avner, MD, was appointed Founding Director of the Children's Research Institute and Associate Dean for Pediatric Research in 2004. He currently serves as Professor of Pediatrics and Physiology at the Medical College of Wisconsin, and Attending Physician and Director, Multidisciplinary Program for Childhood Polycystic Kidney Disease in the Division of Nephrology at the Children's Hospital Health System of Wisconsin.

Dr. Avner received his MD from the University of Pennsylvania, School of Medicine. He served his internship and residency at Children's Hospital, Boston, where he also completed his fellowship in pediatric nephrology. Dr. Avner's faculty career began in 1980 at the University of Pittsburgh, School of Medicine, and the Children's Hospital of Pittsburgh. In 1988 he was appointed as a tenured Professor of Pediatrics at the University of Washington, School of Medicine and Division Chief of Pediatric Nephrology at Children's Hospital and Medical Center in Seattle in 1988. Dr. Avner was appointed as the Gertrude Lee Chandler Professor and Chairman of Pediatrics at Case Western Reserve University and the Chief Medical Officer at Rainbow Babies and Children's Hospital in 1995; posts he held until his move to the Children's Research Institute and the Medical College of Wisconsin. He has held leadership positions in numerous professional organizations including the Society of Pediatric Research, the International Pediatric Nephrology Association, the American Society of Transplantation, and the Polycystic Kidney Disease Foundation. He served as President of the American Society of Pediatric Nephrology and the Council of American Kidney Societies, and served as an elected member of the Standing and Executive Committees of the International Pediatric Association. Dr. Avner has received numerous national and international awards including the Henry L. Barnett Lifetime Achievement Award from the American Academy of Pediatrics in recognition of his outstanding teaching and research contributions to the field of Pediatric Nephrology.

Dr. Avner has served on the editorial boards of 15 key journals in the areas of nephrology and developmental biology. He is the senior editor of the standard global textbook of his subspecialty, *Pediatric Nephrology, 6th edition, 2009.(7th edition pending;2015)* He has authored more than 330 original articles, invited reviews, chapters, and books in the area of renal developmental biology, polycystic kidney disease and pediatric nephrology. Dr. Avner has served multiple roles in NIH-based peer review, including a regular appointment to the General Medicine B Study Section, which he chaired from 1993-1995. He also has chaired 13 other ad-hoc NIH review groups which have focused on genetic kidney disease. Dr. Avner has directed two NIH funded Research Centers of Excellence in Pediatric Nephrology/Polycystic Kidney Disease, as well as 62 individual research or training awards from the NIH, the March of Dimes and other Foundations, and Industry. Such awards have funded Dr. Avner's research, training, and mentoring programs continuously since 1982. In the last 32 years, Dr. Avner has generated over $44 million of extramural support for his programs. Through his research and training programs, Dr. Avner has trained over 28 pre- and post-doctoral fellows, many of whom now lead Children's Nephrology Programs in major academic centers in the United States, Europe and Asia.

William E Sweeney, Jr., Assistant Professor of Pediatrics, MCW; Operations Manager of the Children's Research Institute of Children's Hospital Health System of Wisconsin; and Co-administrator and Laboratory Director of the PKD Center joined Dr. Avner in 1981. He has been an essential partner in the development of our Comprehensive PKD Center. He has been responsible for the development and refinement of unique techniques and reagents which have become standard for PKD investigators. These include the development of pre-clinical animal models, experimental model systems and techniques, and **many of the reagents to be specifically utilized in this Proposal.** He, in collaboration with Dr. Avner, developed much of the research infrastructure of the Children's Research Institute, which he now manages in the context of all the scientific research cores of MCW. He has, co-authored many of the aforementioned papers and grants, as well as co-directed the PKD overall Laboratory and training initiatives as well as faculty mentoring programs.

The Avner-Sweeney lab research focuses on key mediators in the molecular and cellular pathophysiology of polycystic kidney diseases. Recently, unique alterations in normal developmental and injury-induced signaling pathways have been identified following mutations in cystic kidney disease genes. These seminal findings identify specific pathways that are responsible for the initiation and progression of disease in patients with both ADPKD and ARPKD. Such alterations provide key targets for PKD-specific therapy. Accordingly, the CCC-PKD team, in collaboration with industry, the NIH, and other CRI Investigators are planning the first clinical trials for adolescents and children with ADPKD and ARPKD in the near future.

Experimental Background for this Proposal

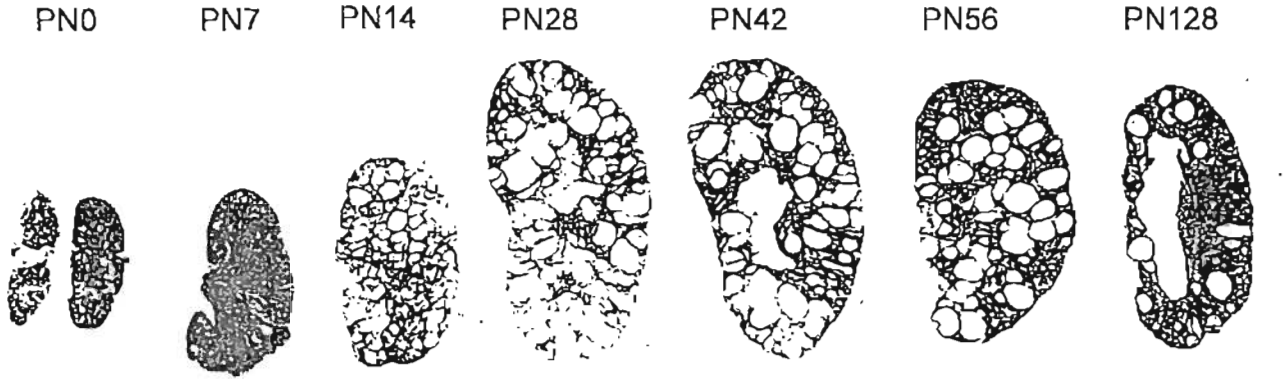
Pediatric nephrologists have long recognized the clinical similarities and challenges of differential diagnosis between ADPKD and ARPKD when neonates present with large renal masses. As recently as 1980 these diseases were named adult PKD and infantile PKD based on age of presentation. As the science of PKD progressed, the genes for ADPKD (*PKD1* and *PKD2*) and ARPKD (*PKHD1*) were identified and the protein products of these genes (PC1, PC2 for ADPKD) and (fibrocystin or polyductin) for ARPKD were predicted from the DNA sequence (in part by the CCC-PKD) [2]. These discoveries led to the development of essential tools necessary to study the cellular and molecular pathophysiology of PKD. These tools led to fundamental discoveries that guide current CCC-PKD research efforts. These include: 1) the ability to genetically diagnose PKD which led to the recognition that the historical disease classifications were inaccurate. ADPKD can present as early as the third trimester of pregnancy and as late as the fifth decade of life, or be asymptomatic. The clinical presentation of ARPKD ranges from the third trimester of pregnancy to the second decade of life; 2) in situ RNA and sequence specific antibodies revealed that ADPKD and ARPKD protein products are co-expressed in multimeric protein complexes at specific locations within cells, explaining the similarity and overlap of symptoms between ADPKD and ARPKD; 3) complex interactions between PKD genes and their protein products occur at a molecular level and the dosage of gene product, especially PC1, plays a role in disease severity; and 4) renal injury such as ischemia or abnormal metabolism can occur when a cyst outgrows its blood supply. These features demonstrate that appropriate models that faithfully recapitulate the disease are essential for future research progress and that ADPKD or ARPKD cannot be adequately studied in isolation (cells at a single stage of disease, or animal models created by conditional inactivation or "knockout" of genes). The expression of PKD proteins varies in an organ-specific, temporal and spatial manner. **Of particular importance for this proposal, human ADPKD is a hypomorphic state in which an inadequate amount of gene product is produced over a lifetime.**

A large number of signaling pathways have been implicated in the pathophysiology of PKD [3-5]., and confusing, often contradictory data has resulted due in part, to the use of inappropriate models. We were among the first to test combination therapy using multiple drugs or compounds such as multi-kinase inhibitors that target multiple pathways shown to be aberrantly active in multiple animal models of PKD [6]. We were also the first to target signaling molecules such as c-Src that activate multiple downstream pathways now uniformly accepted to be critical in disease development and progression [7]. To inform our choice of targets we created a conditionally immortalized PKD mouse where all the cells contained a temperature sensitive large T antigen [8]. This permitted selection and under permissive conditions, nearly unlimited expansion of segment specific, tubular cystic epithelial cells and interstitial cells at specific stages of disease progression. Cells were removed from permissive conditions and allowed to lose all large T antigen and differentiate before analysis. This strategy permitted extensive analysis using a variety of complimentary techniques, on the specific cells affected in kidney, liver, and vasculature at different stages of disease.

Unfortunately, attempts at developing ADPKD rodent models have been largely unsuccessful in creating valuable pre-clinical models which express "human-like" diseases for research. *Pkd1* knock out (*PKD1-/-*) animals die in utero and heterozygotes (PKD1+/-) either don't develop cysts, or develop mild disease very late in life. Conditional models that control the timing and site of *PKD1* inactivation do not accurately reflect the human disease course because these models artificially result in loss of all functional protein at one time point. Thus the rate of disease progression is dependent upon the time of inactivation and is either very fast of very slow. [9-14]. Previously described animal models designed to express less than 50% of normal PC1 (hypomorphic models) develop very rapidly progressive disease and death, making therapeutic testing impossible, and failing to reflect the gradual kidney enlargement and disease progression typical of human ADPKD [14]

Our CCC-PKD recently developed a stable hypomorphic model of *PKD1* by breeding a rapidly progressing hypomorphic model of *PKD1* on a mixed background, onto a congenic C57-BL6/J background (manuscript in preparation for publication). As shown in Figure 1 below, the (*PKD1-MCW*) mouse model of ADPKD demonstrates a consistent disease course that begins in utero with very mild tubular dilatation, progresses through a period of excessive tubular proliferation, cyst growth and renal enlargement, followed by progressive renal fibrosis resulting in reduced kidney size before end stage renal disease (ESRD) and death occur between 5 and 6 months. This model mimics the complete disease course that occurs in human ADPKD and provides an excellent model to analyze the pathophysiology of renal cyst formation and progressive enlargement as well as the development of progressive fibrosis. Initial analysis has demonstrated that the signaling abnormalities found in human ADPKD are also abnormal in this model. The length of the disease course provides a reasonable time frame for testing therapeutic interventions and permits evaluation of disease mechanisms and possible effects of intervention over the entire disease course of ADPKD.

Figure 1



As shown in Figure 1 the PKD1-MCW model of ADPKD has two phases of disease, a rapid proliferative phase (PN0-PN28) where the kidney enlarges due to cyst formation and growth and, a fibrotic, scarring phase (PN42-PN128) that results in the kidney becoming smaller.

We have also crossed the PKD1-MCW model with a BL6/J Immorto mouse which will allow the development of temperature sensitive conditionally immortalized cell lines from specific tubular segments and specific interstitial cell populations at defined stages of disease progression as we have done previously [8, 15, 16].

Proposal: The long term goal of the CCC-PKD is to develop therapies that dramatically delay or prevent symptomatic disease. We have developed a unique murine model of ADPKD that recapitulates the course of ADPKD in humans. This model will be used to delineate the molecular and cellular pathophysiology of ADPKD, in segment specific renal tubules at specific disease stages which has previously not been possible. **This will set the stage, in the context of the CCC-PKD, for development and testing of future disease-specific therapies in children and adolescents with ADPKD prior to the development of significant morbidity and mortality.**

Specific Aim 1. We hypothesize that changes in signaling activity are disease stage specific. The *PKD1-MCW* model will be used to study stage and organ-specific signaling pathways and disease mechanisms utilizing the paradigms developed in our studies of ARPKD. Temperature-sensitive conditionally immortalized cell lines will be established from specific tubular segments as well as from distinct interstitial cells at defined stages of disease progression. These cells lines will be used to examine changes in gene expression, miRNA expression, and activity of signaling pathways in cystic tubular epithelia. Co-culture and 3-dimensional culture techniques will be

used to examine critical determinants of cell communication between cystic tubular epithelial and interstitial cells. *In vitro* findings will be verified *in vivo* by western analysis, immunohistochemistry and PCR-arrays of whole kidneys at specific disease stages. Laser capture micro-dissection will be used if whole kidneys dilute out changes.

Specific Aim 2. We hypothesize that changes in signaling activity can be normalized by pharmacological intervention. We will use findings from SA1 to develop targeted therapeutic interventions at key disease stages that correspond to stages we clinically see in children and adolescents with ADPKD in the clinical component of the CCC-PKD. We have found that this model has many of the same signaling abnormalities reported in human ADPKD, but with this model we have identified critical times when signaling changes occur. Maximizing the power of our bench to bedside approach previously described, the clinical trial component of our CCC-PKD will have the potential to develop unique targeted therapies. These include developing interventions that prevent or slow the development of fibrosis, which is ultimately responsible for progressive organ dysfunction (kidney and liver) in both ADPKD and ARPKD. (Such studies might also provide insight into the poorly understood role of the vasculature in the pathophysiology of ADPKD. This poorly understood area may lead to a productive scientific interaction with the MCW/CRI vascular developmental biology program in partnership with the CCC-PKD).

Specific Aim 3. We hypothesize that ischemia that occurs around an ADPKD cyst that outgrows its vascular supply initiates a normal proliferative renal repair mechanism that abnormally continues when the level of PKD 1 gene product is below a minimum threshold. The initiation of renal repair mechanisms and inability to appropriately terminate the proliferative signal may be a key factor which contributes to the progression of PKD.
In order to address this hypothesis we will examine the extent and location of hypoxia in the *PKD1-MCW* model in relation to proliferating cells using Hypoxyprobe® to detect hypoxia and BrdU to label proliferating cells. The Hypoxyprobe system, which we were the first to use to determine tissue hypoxia in PKD, uses pimonidazole-HCL, a water soluble compound that has a wide tissue distribution after injection. Hypoxyprobe requires a ($pO2 < 10mmHg$) to become activated and form adducts. These adducts can be visualized with polyclonal or monoclonal antibodies to pimonidazole.

OTHER CONSIDERATIONS-DIRECTIONS FOR THE FUTURE

As noted, the CCC-PKD has developed additional models which can and will be used when appropriate. For example we have placed the *PKHD1* gene from the PCK rat into consomic rat strains in an effort to identify modifiers that alter disease severity in ARPKD. Placing the *PKHD1* gene onto the FHH background unexpectedly resulted in amelioration of the cystic disease [17]. Preliminary data from CCC-MCW investigators studying ischemia reperfusion injury (IRI) suggest that the FHH strain at MCW is resistant to IRI (personal communication-Professor Scott Van Why). If confirmed this would provide an excellent model to evaluate the role of ischemia in cyst progression.

SUMMARY

The CCC-PKD is a unique scientific program which has been productive for the last 10 years in Milwaukee. It serves as a paradigm for the future of individualized medicine, and has engaged basic scientists in multiple disciplines and clinicians in multiple sub-specialties to direct their work and expertise towards the study of PKD. Based on over 30 years of focused work by the Avner-Sweeney laboratory program, it is a major national referral center for science, future clinical trials, and clinical care for patients with PKD. This proposal developed for the Arno Foundation is only a small example of its potential to focus on fundamental issues, engage multidisciplinary expertise and perform vital scientific investigations which will continue to unravel the complex scientific basis and future treatment of ADPKD. We are confident that the CCC-PKD will continue to grow at our Institution as it has been accepted as a model for translational science and the future growth of our academics in a rapidly changing environment. It will continue to attract interest of scientists, the NIH, Industry, and perhaps most importantly, new trainees who will study the science of PKD. Our laboratory program continues to train US and foreign renal fellows that now lead Children's Nephrology Programs in major academic centers in the United States, Europe and Asia. The current focus on ADPKD as a "pediatric disease" is not only appropriate, but focuses resources appropriately on those who will maximally benefit from therapies developed for the future from the science of today.

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