Strategic Planning Meeting for Polycystic Kidney Disease
July 10-11, 2002
Meeting Summary

The Strategic Planning Meeting on Polycystic Kidney Disease was held July 10-11, 2002, at the Natcher Conference Center, the National Institutes of Health, to discuss future research directions with the greatest promise for significant advances towards effective treatment of autosomal dominant polycystic kidney disease (ADPKD). The discussions were divided into four sessions with 21 speakers and participation of 31 scientists, physicians, and representatives from patient advocacy groups. This summary reflects the consensus view reached in these discussions.

The pace of polycystic kidney disease (PKD) research has greatly accelerated in the last decade. This research is just beginning to have an impact on the treatment of patients with PKD. Further advances with significant impact on the treatment of these patients seem extremely likely within the next decade, and optimal progress will require the coordinated efforts of scientists and physicians from nearly all the disciplines of renal science and from other disciplines.

Goal

Improve the quality and duration of life for patients with dominant and recessive forms of PKD within the next 10 years

General Objectives

- Ascertain the potential value and feasibility of disease registries for PKD
- Define the function of molecules and pathways that cause, affect, or aggravate PKD
- Outline future directions for genetic research in PKD
- Develop treatments that improve the quality of life and longevity of patients with PKD

Specific Objectives

Specific objectives are presented separately, as discussed during the four sessions of the meeting. They are as follows:

Disease Registry Issues Session

This session discussed the objectives and logistics of developing a registry for PKD and reviewed the existing patient databases. Attendees agreed that PKD registries would be of great potential value if the objectives could clearly be defined and the logistic problems solved.

Registry Objectives

1. The short-term and long-term objectives should be clearly identified
2. The goals of autosomal recessive polycystic kidney disease (ARPKD) and ADPKD registries may be very different; therefore, two registries are recommended:
    - ARPKD registry potentially for all patients, for more basic characterization of the disease, including natural history, prognostic markers, etc.
    - ADPKD registry for more selected, extensively characterized cohorts for genotype/phenotype correlations and other studies of sources of disease variability

Registry Logistics

1. Challenges in multi-site collaborations
    - Need for advisory/oversight committee
    - Clear definition of specific collaborative efforts, acceptance of competing efforts
    - Ownership: Who will own the data?
    - Access: Who will have access to the data and how will access be regulated?
    - Provision of data: Who will report and enter the data?
    - Quality control: How will it be assured?
    - Need for broad, shared motivation and ownership (group studies usually placed last in investigators' to-do lists)
    - Patient advocacy issues
    - DNA repository issues

2. Registry institutional review board (IRB) issues
    - Approval by one IRB for the Disease Registry is easier to obtain than approval by IRBs at multiple sites
    - Appropriate and accurate informed consent necessary
    - Recontacting may not be approved unless it is integral part of initial consent
    - Security/firewalls

3. Registry funding

Existing PKD Patient Databases

1. North American ARPKD (Lisa M. Guay-Woodford, M.D.; U. of Alabama, Birmingham)
    - Designed as a longitudinal database
    - Initiated in 1998
    - 230 patients currently enrolled

2. ARPKD/CHF Alliance's Registry (Colleen B. Zak, R.N.; lay advocacy organization, Kirkwood, PA)
    - IRB-approved collection began in 2002 with 133 kits.

- Centralized repository and distribution of blood, pedigree, and clinical data for research projects demonstrating merit
- Self-administered research survey

3. PKD mutation database (David Ravine, M.D.; Cardiff, UK)
   - Locus specific mutation databases
   - No samples collected

Cell Biology/Function Session

The cell biology/function session focused on the identification of specific research priorities and methodologies with the ultimate goal of defining the function of molecules and pathways that cause, affect, or aggravate polycystic kidney disease. Attendees agreed that integrated approaches using multiple model systems would be necessary to achieve this goal.

Research Priorities

1. Protein characterization
   - Determine the sub-cellular and functional localization of the ADPKD/ARPKD gene products
   - Determine the ADPKD/ARPKD protein complexes
   - Identify the PC1 and fibrocystin/polyductin ligands/receptors
   - Characterize PC1 proteolysis (functional significance, regulation, identify proteases)
   - Determine the functional significance of *PKHD1* splicing
   - Determine the function of PC-like molecules
   - Identify factors involved in ADPKD/ARPKD cyst formation

2. Polycystin signaling pathways
   - Both normal and aberrant in cyst-lining epithelia
   - Ca^{2+} signaling
   - G protein signaling
   - Other signaling pathways
   - Life stage-specific (developing vs. mature tissue)
   - Cell type-specific (epithelial vs. non-epithelial)
   - Subcellular compartment-specific

3. Polycystin channels—properties and regulation
   - Requirement of PC1 for PC2 function
   - Location of polycystin channel function and how it gets there
   - Components/partners of polycystin channels (PC1/2 and PC1L/2L molecules)
   - Regulation/gating of polycystin channels
   - Activation and inactivation mechanisms
   - Cellular pathways modulated by polycystin channel

4. Polycystin channel—functional role *in vivo*
   - Role of polycystin channels in the kidney

- Consequences of PKD mutations on the channel function of polycystins and on cellular processes
- Mechanisms of how mutations to the polycystins lead to disease
- Define processes responsible for fluid secretion

5. Cilia and PKD
   - Determine whether the polycystins are the mechanically-sensitive cation channels in the primary cilium
   - Functional connection between the primary cilium and tubule cyst formation
   - Functional relationship between polycystins, and between polycystins and other components of the primary cilium
   - Relationship between flow, intracellular calcium, and tubular structure
   - Chemosensory functions of the primary cilium: a role in the regulation of tubule epithelial geometry and subsequent cyst formation?

Methodologies

- Continue to screen/clone novel cystic genes to determine the variety of pathways/cellular structure involved in cyst formation and define novel models for therapeutic intervention
- Develop additional cell models (primary cultures, immortalized cell lines, organ culture systems) for easy manipulation and study of PKD pathways
- Use of model systems for genetic screens (*C. elegans*, Drosophila, zebrafish, mouse), gene disruption (*C. elegans*, Drosophila, zebrafish, mouse), small molecule/drug screens (*Chlamydomonas*, *C. elegans*, zebrafish), structural studies (all species, conservation of important structures), and cell biology studies (all species, direct relevance to kidney epithelia, vertebrates)
- Develop a human PKD tissue bank to further investigate abnormalities observed in tissue derived from model systems

Genetics Session

The genetics session focused on outlining future directions for genetic research in polycystic kidney disease. The general consensus was that major advances in the genetics of polycystic kidney disease had occurred within the past few years, that these advances have, to a large extent, taken us where we now are, and that the tools for further progress are available or can readily be made.

Research Priorities

1. Gene identification
   - Map and identify other ADPKD genes—PKD3
   - Map and identify genes in rodent models of PKD
   - Map and identify PKD genes in lower organisms

2. Homologous genes
   - Define the HG region—mutational significance

- Analysis of polycystin and fibrocystin/polyductin homologs in mammals and lower model organisms structures/function)

3. Mutational mechanisms evaluation
   - Somatic mutation in ADPKD—functional significance
   - Phenotype associated with complete deletion of fibrocystin/polyductin

4. Better animal models of ADPKD/ARPKD generation
   - Knockout/transgenic models of PKHD1
   - Conditional knockouts/knockins of all genes
   - Knockdowns, RNAi in non-mammalian systems

5. Splicing/cleavage and transcriptional regulation
   - PKD1—functional significance
   - PKD2— functional significance
   - PKHD1—functional significance

6. Genomics/proteomics
   - Assay cDNA/protein changes in PKD cells/tissues

7. Genotype/phenotype studies
   - Improve mutational analysis
   - Genetic heterogeneity (non-renal disease in ADPKD; ARPKD?)
   - Allelic heterogeneity—ADPKD (specific phenotypes; larger populations)
   - Allelic heterogeneity—ARPKD (severity of phenotypes; CHF; larger populations)

9. Modifier loci mapping/identification
   - Rodent models of PKD
   - Rodent models of ADPKD/ARPKD
   - Association studies of candidate modifiers in human populations (genetically well characterized; large populations)
   - Map modifiers in human populations (concordant/discordant sib pairs; large populations; various phenotypes)
   - Map/identify modifiers in nonmammalian models of PKD

Funding and Support of Mechanisms

1. Large populations required
   - Populations for mapping/testing ADPKD modifiers
   - Populations for genotype/phenotype studies: ARPKD
   - Multicenter studies
   - Accurate clinical and mutational data

2. Supportive infrastructure
   - Extension of disease registries
   - Statistical support

- Worldwide collaboration

3. Genotyping facility to map rodent genes

Therapeutic Interventions Session

The session on therapeutic interventions focused on outlining plans that would improve the quality and longevity of patients with PKD. Attendees agreed that treatments targeting renal microvascular disease and, in particular, the renin-angiotensin system seem at the present time well founded, safe, feasible, and promising, and that networks developed for such clinical trials may serve as a model for future trials of novel therapies currently under development.

Research Models

- Various approaches are necessary (tissues, cellular models, animal models, and humans).
- Interaction between basic and physician scientists is mandatory.

Readouts to Examine Beneficial Effects of Any Therapeutic Intervention

- Early interventions more likely to prevent the progression of PKD to ESRD
- GFR decline too late to be used as an effective readout
- MR measurements of renal, cyst, and parenchymal volumes may be the best way to ascertain the effectiveness of therapeutic interventions (preliminary results of CRISP study).
- MR measurements of renal blood flow are also encouraging (fall in renal blood flow precedes the decline in GFR).
- Microalbuminuria and proteinuria as a surrogate index for progression (used in AASK study)
- Urinary cytokines deserve further study as surrogate markers of disease activity/progression.
- Effects on the heart, in particular left ventricular hypertrophy, are important (cardiovascular disease has emerged as the number one cause of death in patients with PKD).
- Effects on the liver are also important (as patients live longer, hepatic complications related to PKD are more common).

Renin-Angiotensin-Aldosterone System

- Considerable data implicate the involvement of the renin-angiotensin system in PKD.
- A number of non-PKD studies in heart and kidney (experimental urinary tract obstruction, cyclosporin toxicity, and diabetic nephropathy) have shown the beneficial effects of blocking the renin-angiotensin system.
- Previous clinical trials targeting the renin-angiotensin system in ADPKD have been inconclusive because of inadequate statistical power, late timing of the interventions, short duration of follow-ups, inadequate design, and possibly failure to achieve the desired pharmacologic effect.
- Of all the possible interventions targeting different pathogenetic mechanisms operative in PKD, a clinical trial targeting the renin-angiotensin system at multiple levels currently is most feasible, promising, and safest.

Renal Microvascular Disease as a Therapeutic Target

- Profound remodeling of the renal vasculature (arterial remodeling, rarefaction and angiogenesis) is a well-known, early, and common feature of ADPKD
- Multiple pathogenetic mechanisms probably contribute to this vascular remodeling (i.e., activation of the renin-angiotensin-aldosterone system, insulin resistance and hyperinsulinemia, sympathetic hyperactivity, impaired nitric oxide production, increased endothelin production), although this has not been well characterized in PKD.
- These pathogenetic mechanisms are common to ADPKD and other conditions (black race, obesity, aging, and diabetes mellitus) characterized by salt-sensitive hypertension and increased susceptibility to progressive renal damage.

Angiogenesis

- Angiogenesis is increased in the polycystic kidneys.
- The relationship between angiogenesis and epithelial and matrix proliferation needs study.
- Angiogenesis may influence the fluid source for secretion.
- Therapeutic interventions in this area could involve inhibitors of angiogenesis factors, including VEGF 1 and 2 and angiopoietin, although recent reports indicate that VEGF administration reduces renal fibrosis and stabilizes renal function in the remnant kidney model and in cyclosporin-induced nephropathy.
- Other drugs with anti-angiogenesis properties, such as captopril and COX2 inhibitors, are currently marketed in the United States.

Fluid Secretion into Cysts

- Fluid secretion into cysts is a fertile area for research (cysts in only 5% of nephrons; cyst enlargement involves fluid secretion).
- The effects of cyst expansion on stretch-activated ion channels and on the cystic fibrosis translocating receptor are in need of study.
- Potential inhibitors of fluid secretion in PKD, including those blocking potassium channels, as well as agents such as amiloride to block sodium channels, need to be studied.

Gene Modifiers

- Therapeutic interventions might be devised based on an analysis of phenotype/genotype correlations in large populations.
- In animal models, novel gene delivery systems (e.g., microbubble-enhanced ultrasound transfection) might allow use of the contralateral kidney as a control in gene replacement. therapies.

Speakers

David R. Beier, MD, PhD
Associate Professor of Medicine
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Arlene Chapman, MD
Associate Professor of Medicine
Emory University
Atlanta, GA

Judy Cho, MD
Assistant Professor of Medicine
Department of Medicine
University of Chicago
Chicago, IL

Garry R. Cutting, MD
Professor, Pediatrics and Medicine
Institute of Genetic Medicine
Johns Hopkins University
Baltimore, MD

Iain Drummond, PhD
Assistant Professor
Renal Unit /Mass General Hospital
Department of Medicine, Harvard Medical School
Boston, MA

Gregory Germino, MD
Associate Professor of Medicine
Department of Medicine
Johns Hopkins University School of Medicine
Baltimore, MD

Lisa Guay-Woodford, MD
Professor and Director, Genetic and Translational Medicine
Department of Medicine
University of Alabama at Birmingham
Birmingham, AL

William Guggino, PhD
Professor of Pediatrics and Physiology
Department of Physiology
Johns Hopkins University School of Medicine
Baltimore, MD

Peter Harris, PhD
Professor, Biochemistry, Molecular Biology, Medicine
Department of Nephrology
Mayo Clinic
Rochester, MN

J. Phillip Miller, AB
Professor, Biostatistics
Washington University School of Medicine
St. Louis, MO

Ronald Perrone, MD
Associate Chief, Division of Nephrology
Medical Director, Renal Transplantation
Department of Medicine
New England Medical Center
Tufts University School of Medicine
Boston, MA

David Ravine, MB, BS, DM, FRACP, MRCPa
Consultant Clinical Geneticist,
Molecular Genetic Pathologist
Medical Genetics Service for Wales
Cardiff, Wales

Richard Sandford, PhD, FRCP
Wellcome Trust Senior Fellow in Clinical Research
Department of Medical Genetics
University of Cambridge
Cambridge, England

Robert W. Schrier, MD
Professor and Chair
Department of Medicine
University of Colorado
Denver, CO

Stefan Somlo, MD
Associate Professor, Internal Medicine
Associate Professor, Genetics
Department of Medicine
Yale University School of Medicine
New Haven, CT

Kenneth R. Spring, DMD, PhD
Chief, Section of Transport Physiology
Laboratory of Kidney and Electrolyte Metabolism
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, MD

Vicente E. Torres, MD
Professor of Medicine
Department of Nephrology
Mayo Clinic
Rochester, MN

Vicky Whittmore, PhD
Senior Scientific Advisor
Tuberous Sclerosis Alliance
Crofton, MD

Colleen B. Zak, RN
ARPKD/CHF Alliance
Kirkwood, PA

Jing Zhou, MD, PhD
Associate Professor, Medicine
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Planning Meeting Attendees

Seth L. Alper, MD, PhD
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Robert Bacalla, MD
Associate Professor of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

K. Ty Bae, MD, PhD
Assistant Professor
Washington University School of Medicine
St. Louis, Missouri

John J. Bissler, MD
Assistant Professor
Children's Hospital Medical Center
Cincinnati, Ohio

Josephine Briggs, MD
Director, Division of Kidney, Urologic and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Matthew Buechner, PhD
Assistant Professor
University of Kansas
Lawrence, Kansas

Cathleen Carlin, PhD
Associate Professor
Case Western Reserve University School of Medicine
Cleveland, Ohio

Vincent Gattone, PhD
Professor of Anatomy and Cell Biology
Indiana University School of Medicine
Indianapolis, Indiana

Jared Grantham, MD
Professor of Medicine
Kansas University Medical Center
Kansas City, Kansas

Mary M. Harris
Writer/Editor
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Gladys Hirschman, MD
Director, Chronic Renal Diseases and Pediatric Nephrology
Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Daniel Larson, BS
President/CEO
PKD Foundation
Kansas City, Missouri

Josh Lipschutz, MD
Assistant Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Catherine Meyers, MD
Director, Inflammatory Renal Disease Programs, Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Dana Miskulin, MD, MS
Nephrologist and Clinical Researcher
New England Medical Center
Boston, Massachusetts

Christopher M. Palatucci, PhD
Director, Business Development
Athena Diagnostics, Inc.
Worcester, Massachusetts

Gregory J. Pazour, PhD
Assistant Professor
University of Massachusetts Medical School
Worcester, Massachusetts

Carrie Phillips, MD
Assistant Professor
Indiana University School of Medicine
Indianapolis, Indiana

Rebecca Rasooly, PhD
Director, Genomics/Proteomics
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Joel Rosenbaum, PhD
Professor of Molecular, Cellular, and Developmental Biology
Yale University
New Haven, Connecticut

Thomas Schultheiss, MD, PhD
Assistant Professor of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Christine Sorenson, PhD
Assistant Scientist
University of Wisconsin-Madison
Madison, Wisconsin

Theodore Steinman, MD
Professor of Medicine
Harvard Medical School
Director, Dialysis Unit
Beth Israel Medical Center
Boston, Massachusetts

Michael Sutters, MD
Assistant Professor of Medicine
Johns Hopkins University
Baltimore, Maryland

William E. Sweeney, MS
Operational Manager
Horuitz Pediatric Research Center
Case Western Reserve University
Cleveland Ohio

Paige Q. Szajnuk, BS, JD
Program Director
PKD Foundation
Kansas City, Missouri

Angela Wandinger-Ness, PhD
Associate Professor
University of New Mexico Health Sciences Center
Albuquerque, New Mexico

Terry Watnick, MD
Assistant Professor of Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland

Patricia D. Wilson, PhD
Professor
Mount Sinai Medical School
New York, New York

David Woo, PhD
Associate Professor
University of California, Los Angeles
Los Angeles, California

Quanding Wu, MD, PhD
Assistant Professor
Department of Cell Biology
Vanderbilt University
Nashville, Tennessee

Bradley Yoder, PhD
Assistant Professor of Cell Biology
University of Alabama at Birmingham
Birmingham, Alabama