

FINAL REPORT
FASEB SUMMER RESEARCH CONFERENCE, SNOWMASS, CO
Polycystic Kidney Diseases: Molecular Pathways, Pathogenic Mechanisms and Translational
Applications
July 27, 2008 to August 1, 2008

Organizers:
Robert Bacallao
Peter Harris

On July 27th to August 1, 2008 the third triennial FASEB sponsored conference on Polycystic Kidney Disease (PKD) was convened. One hundred and ten scientists at various career stages attended the meeting. The goal of the meeting was to bring together physicians and basic scientists for presentations and discussions with the goal of broadening our understanding of the basic biology of Polycystic Kidney Disease. The meeting demonstrated that the field is expanding dramatically in that novel roles for cilia have been uncovered; links to PKD signaling pathways with cell cycle regulation and planar polarity were explored. The conference facilities provided an exceptional environment for interactions between meeting participants through formal presentations, a lively poster session and meals. The format of the meeting which brought together post-doctoral fellows, graduate students, junior and senior career scientists, allowed for frequent and enlivening discussions between all participants.

Highlights of sessions and topics discussed

There were 10 scientific sessions and one poster session scheduled in the meeting. The scientific presentations were scheduled for 35 minute talks followed by 10 minute question and answer sessions. The meeting started with a remarkable presentation by Dr. Helen McNeil from the Samuel Lumenfeld Institute. She set the tone of the meeting in her talk describing her work on planar polarity in drosophila and then identifying homologs of drosophila planar polarity genes in mouse and finally showed that knocking out one mouse homolog, fat4 leads to polycystic kidney disease. Session one focused on cellular changes associated with mutations in polycystins. Alterations in intracellular calcium handling were discussed by Darren Wallace (University of Kansas, Kansas City) and were followed on with a lecture of the regulation of polycystin-1 biogenesis and signaling presented by Mike Caplan (Yale University, New Haven, CT). The morning session was completed with a presentation on the PACS proteins in secretory pathways and disease offered by Gary Thomas (Oregon Health Sciences, Portland, OR) and Dr. Zhou's (Harvard University, Boston, MA) work on Nek 8 kinase and polycystins. Session 2 was devoted to functional analysis of PKD proteins. Seth Alper (Harvard University, Boston, MA) discussed his findings on changes in purinergic mediated flow-regulated Ca²⁺ signaling in cell lines with mutations in polycystin-1. Feng Qian (Johns Hopkins University, Baltimore, MD) spoke on processing and function of ADPKD and ARPKD proteins. This lecture was followed by Leo Tsiokas (University of Oklahoma, Oklahoma City, OK) who spoke on activation mechanisms of TRPP2 (polycystin-2) channels and then Tatyana Masyuk (Mayo Clinic, Rochester, MN) discussed here work examining the role of small RNA's, specifically miR-15a in cholangiocyte proliferation and its potential role in hepatic cystogenesis. Session 4 was designed to explore the insights garnered on PKD proteins by examining model systems. Zhaoxia Sun (Yale University, New Haven, CT) discussed her work on the Zebrafish gene,

seahorse and its role in linking the Wnt pathway with cilia function. Joel Rosenbaum (Yale University, New Haven, CT) gave a seminal talk on analysis of cilia function in the *Chlamydomonas* model. Maureen Barr (Rutgers University, New Brunswick, NJ) discussed polycystin ciliary targeting and function in *C. elegans* and her talk was followed by Lynne Quarmby, (Simon Fraser University, British Columbia, CA) who discussed her work on cystic proteins in the *Chlamydomonas* model system. A unique feature of the meeting was a session devoted to the scientific tools available to PKD investigators. The session was started by a talk from Brad Yoder (University of Alabama, Birmingham, AL) describing the resources available at the NIH sponsored P30 site at UAB. Dr. Yoder described the transgenic mouse facility, Immunohistochemical core and genomics cores available to researchers. Peter Harris (Mayo Clinic, Rochester, MN) described the ADPKD computer database which correlates genomic data with patient data. Vincent Gattone (Indiana University, Indianapolis, IN) showed work done by the electron microscopy core facility sponsored by the PKD Foundation. Finally Ron Perrone (Tufts University, Boston, MA) provided an update on the NIH sponsored HALT study.

Session 5 continued the thematic goal of linking cilia function to polycystin proteins. Michel Leroux (Simon Frazier University, British Columbia, CA) discussed the work coming from *C. elegans* in the Meckel syndrome related proteins. Wallace Marshal (University of California, San Francisco, San Francisco, CA) talked about the role of centriole, basal body in cell division and cilia-related disease. Jeremy Reiter (University of California, San Francisco, San Francisco, CA) talked about the role of cilia in Hedgehog-mediated tumorigenesis. Finally Marco Pontoglio (Institute Pasteur, Paris, FR) discussed his work on planar cell polarity defects in PKD. Session 6 was devoted to syndromic forms of PKD. Nick Katsanis (Johns Hopkins, Baltimore, MA) discussed his work on Bardet-Biedl syndrome. Vince Gattone (Indiana University, Indianapolis, IN) gave a lecture on a animal model of Meckle Gruber Syndrome, this talk was followed by a lecture given by Friedhelm Hildebrandt (University of Michigan, Ann Arbor, MI) on nephronophthisis and related disorders. The session was wrapped up with a talk by Brunella Franco (Naples, IT) on the Oral-facial-digital syndrome. There was a short session later that day that was used to highlight recent advances, one talk by Darwin Bell (Medical University of South Carolina, Charleston, SC) on his recent work characterizing TRP channels in cystic epithelia and a second talk by Dinesh Yernool (Purdue University, Lafayette, IN) on work characterizing structures of the c-terminal regulatory domains of polycystin channels.

Session 7 was centered on insights into PKD from animal models. Marie Trudel (IRCM, Montreal, CA) discussed results of studies from her PKD1 knock in mouse. Stephan Somolo (Yale University, New Haven, CT) talked about conditional knockout mouse models that he has created. Dorien Peters (LUMC, Leiden, The Netherlands) discussed her work on disrupting the PKD1 gene in transgenic models. Lastly, Oliver Wessely (Louisiana State University, Baton Rouge, LA) was chosen from his abstract to give an oral presentation of this work on Bicaudal C in the *Xenopus* model system. Session 8 was devoted to understanding PKD related proteins and discussion of their functional activity in the cell. Harvey Florman (University of Massachusetts, Worcester, MA) discussed his work on polycystins in sperm. Angela Wandinger-Ness (University of New Mexico, Albuquerque, NM) talked on polycystin-1 targeting in renal epithelial cells. Christopher Ward (Mayo Clinic, Rochester, MN) discussed the role of exosomes in polycystin mediated, cilia based signaling. Lastly Xiangyi Lu (Wayne State University, Detroit, MI) discussed her work on genetic analysis of *drosophila* PKD2 signaling pathways.

Session 9 marked the transition from basic and translational science to more clinically derived topics. Arlene Chapman (Emory University, Atlanta, GA) discussed insights into ADPKD disease course based on results from the CRISP study. Meral Guanay-Aygun (NHGRI, Bethesda, MD) talked about the natural history of ARPKD and congenital hepatic fibrosis (CHF). Lisa Guay-Woodford (University of Alabama, Birmingham, AL) discussed her work on modifying genes in PKD while Klaus Zerres (RWTH Aachen University, Institute for Human Genetics, Aachen, FRG) discussed his work on molecular diagnostics in ARPKD.

The final session looked forward to therapeutics and ongoing clinical trials in PKD. Perico Norberto (Mario Negri Institute for Pharmacological Research, Bergamo, IT) talked about Somatostatin treatment in ADPKD. His work was followed by a lecture by Ellis Avner (Medical College of Wisconsin, Milwaukee, WI) on therapeutic efficacy of Src inhibitors in ARPKD and animal models of PKD. Vicente Torres (Mayo Clinic, Rochester, MN) discussed the current status of the Tolvaptan trial in the United States and Oxana Ibraghimov-Beskrovnya (Genzyme, Framingham, MA) discussed screening strategies for therapies in PKD.

Overview of funding outcome

Overall the funding environment was very tough. The organizers were successful in garnering support from NIDDK to help with travel grants for young investigators. These monies were used to give travel stipends to all attendees that presented posters (there were 35 posters presented). The Office of Childhood Disease also contributed to the R13 budget to the amount of \$25,000. The R13 grant represented a helpful collaboration between administrators in the renal program of the NIDDK and the Office of Childhood Diseases. Additional funds were successfully obtained from the Polycystic Kidney Disease Foundation (PKDF). The PKD Foundation contributed the largest sum of money to support the meeting, \$50,000. Commercial funding support was obtained by generous contributions from Otsuka Pharmaceuticals, Merck and personal contributions by research scientists from Genzyme. Funding requests were sent out to over 20 different pharmaceutical companies without success, nevertheless the organizers were successful in covering all travel and registration fees for all the speakers and session chairs.

Overview of attendees

The meeting brought together 110 researchers with an interest in basic, translational and clinical science related to PKD. Of the 43 presenters, 10 were from international institutions, 15 were women and two were early career investigators. Each session had chairs who were relatively senior scientists and there were 18 session chairs for the 9 presentations. Of the 18 session chairs, 5 were women. Overall the attendees represented an excellent mix of young investigators with senior scientists, many of whom are considered thought leaders in the PDK field.

Summary of the business meeting

As per FASEB guidelines a business meeting was held on the evening of the fourth day of the meeting. The majority of attendees attended the business meeting and it was determined by unanimous vote that another meeting on Polycystic Kidney Disease should be held by FASEB in three years. Dr. Peter Harris was elected to serve as the meeting organizer. Two co-organizers

were elected, Jim Calvett and Dorien Peters. Next the potential meeting sites were debated, and by majority vote the Saxon Woods, Vt site was chosen for the next meeting site to be held in 2011. Additional issues discussed in the business meeting were what programmatic initiatives would the scientists like to see come from the NIH and how can the scientific community help the PKD Foundation achieve their aims. Additionally what further changes to the reagents available to researchers are needed? The community suggested that NIDDK hold a meeting that included Pharmaceutical companies, patient stakeholders, researchers and government officials from the NIH and the FDA to discuss research issues, drug development and patient concerns in a single meeting. The NIH official in attendance agreed to work on this project.

Attendees mentioned that it is still difficult to acquire critical reagents in the field. Dr. Guay-Woodford agreed to garner emails from researchers to compile a list of transgenic mouse lines that are difficult to obtain. Her goal is to make the NIH core site sponsored at her center at University of Alabama, Birmingham to be a repository for transgenic models.

Finally attendees agreed to help the PKD Foundation with fundraising efforts and communicating with the public on issues of scientific concern to stakeholders in the

Proposed future of the topic

One exceptional point brought out by the Snowmass meeting is that research into PKD has ramifications for a wide variety of diseases which include diabetes, genetic diseases of children, retinitis pigmentosa, and cancer. The cell biology of this disease spans areas of planar polarity, epithelial cell polarity, cell cycle regulation, cilia biogenesis and function, cell-extra cellular matrix interactions and protein sorting. There is a large and vibrant research community and this disease (PKD) is an area of emphasis for NIDDK. In my opinion this area of research will be an important subject for future FASEB meetings. Lastly it should be pointed out that response to this meeting by all attendees has been overwhelmingly positive. A frequent comment offered has been that the FASEB sponsored meeting on PKD held at Snowmass was the best scientific meeting they ever attended. This outpouring of unanimous response from the attendees gives credit to the FASEB staff that helped organize the meeting and provide the essential logistical support to make the meeting a success.