

## Boss Donates Kidney to Employee

Chris Jernigan Went Above and Beyond the Call of Duty for Employee Lisa White; Both Are Doing Well Post-Surgery



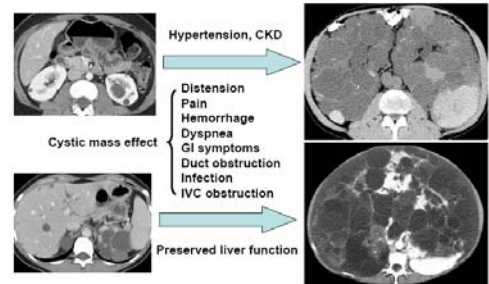
<http://www.abcnews.go.com/GMA/story?id=3297688&page=1>



## Autosomal Dominant Polycystic Kidney Disease: Membership in the Cysterhood

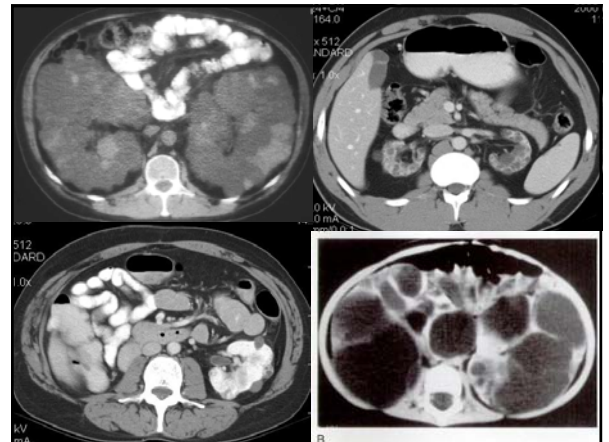
Arlene B. Chapman M.D.  
Emory University School of Medicine

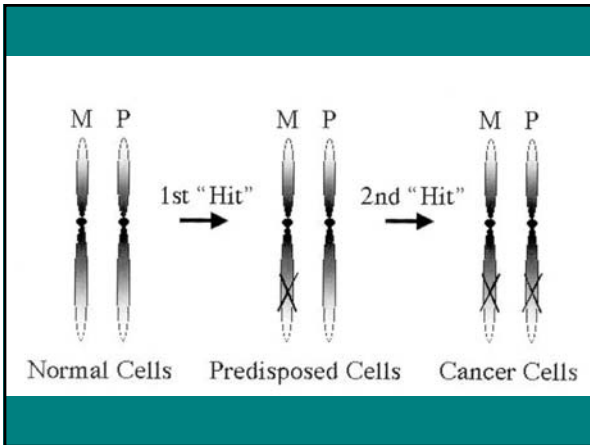
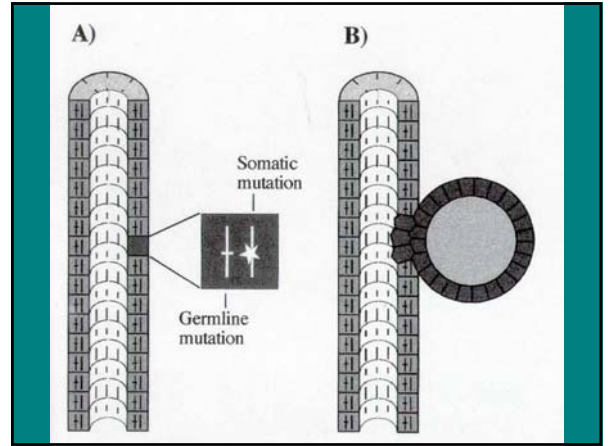
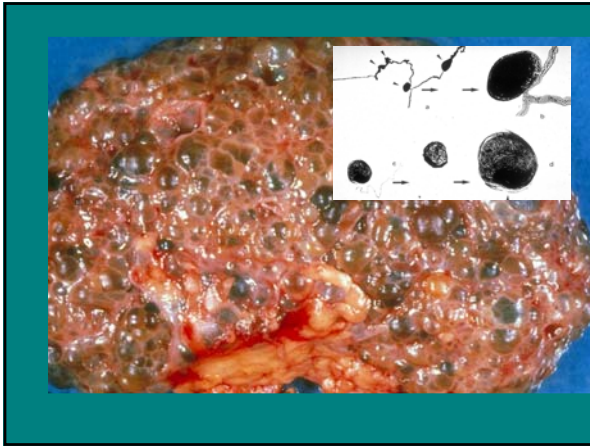
### Cysts are the disease



## CYSTIC DISEASES OF THE KIDNEY

Disease	Freq	Chrom	Gene locus	Protein	Function
ADPKD	1:1,000	16p13.3	<i>PKD1</i>	Polycystin1	Receptor?
	1:15,000	4q 21.2	<i>PKD2</i>	Polycystin2	Cation channel
ARPKD	1:20,000	6q24.2	<i>PKHD</i>	Fibrocytin/polyductin	Receptor
VHL	1:25,000	3p25	<i>VHL</i>	vhl	Tumor Suppressor
TSC	1:20,000	9q34.3	<i>TSC1</i>	hamartin	Tumor Suppressor
		16p13.3	<i>TSC2</i>	tuberin	Suppressor
MCD1	1:50,000	1q21	<i>MCKD1</i>	?	?
MCD2	1:50,000	16p13	<i>MCKD2</i>	Uromodulin, Tamm Horsfall Protein	
NPH1	1:15,000	2p13.1	<i>NPHP1</i>	Nephrocystin	Cell-cell adhesion
NPH2	1:50,000	9q22	<i>NPHP2</i>	Inversin	
NPH3	1:50,000	3q21	<i>NPHP3</i>	Nephrocystin-3	
NPH4	1:15,000	1p36	<i>NPHP4</i>	Nephrocystin-4 nephroretinin	



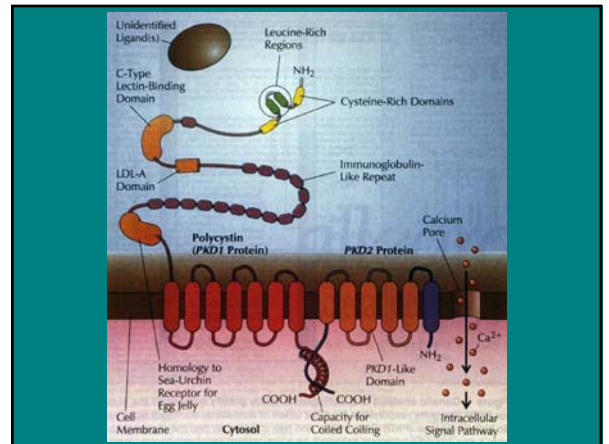
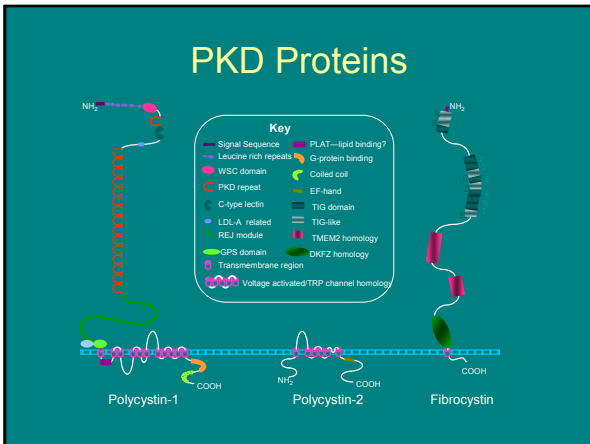


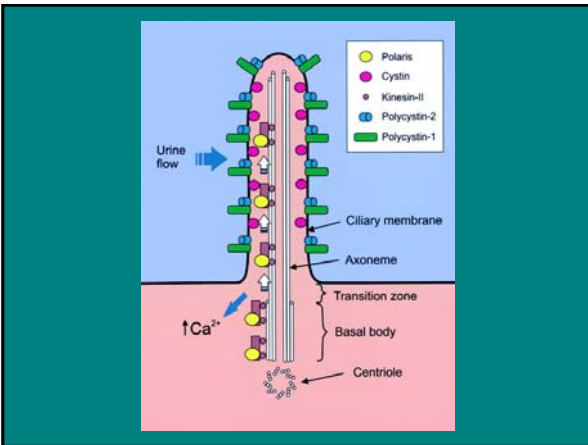
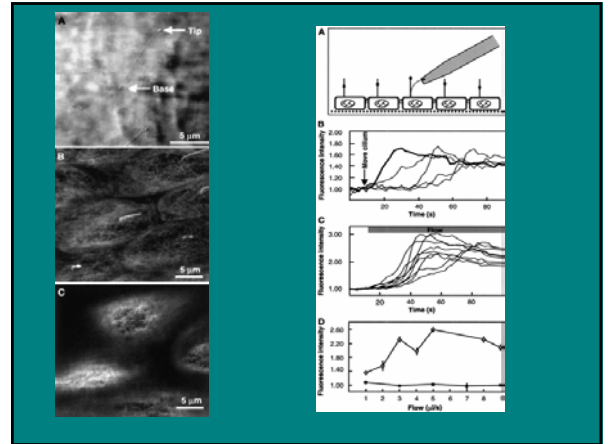
### PKD Genes and Transcripts

**1994**  
50 kb gene, 14 kb transcript  
> 275 mutations  
Missense: 28%

**1996**  
70 kb gene, 3 kb transcript  
> 75 mutations  
Missense: 11%

**2002**  
472 kb gene, 13 kb transcript  
> 275 mutations  
Missense: 60%



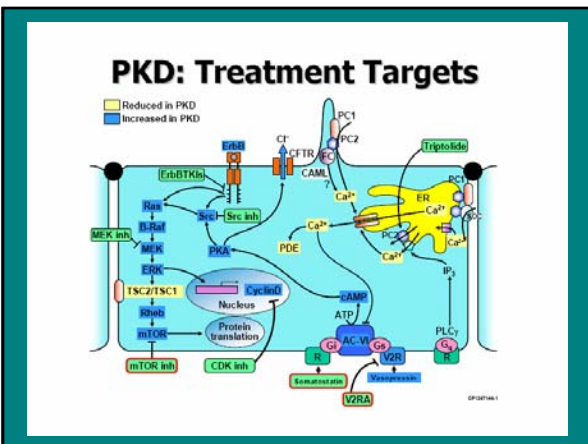


### Cystic Phenotype

- Well differentiated
- Polarized
- Normal cell-cell/matrix interactions
- Low rate of division and apoptosis
- Branching tubules in collagen gels
- Reabsorptive
- Planar polarity

- De-differentiated
- Polarization defects
- Integrin- $\alpha 3 \beta 1$ , E-cadherin
- High rate of division and apoptosis
- Cysts in collagen gel
- Secretory phenotype
- Loss of planar polarity

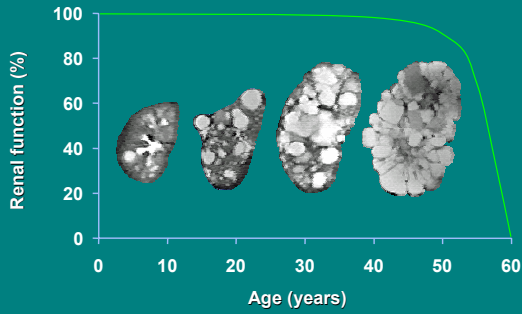
CP1102943.7



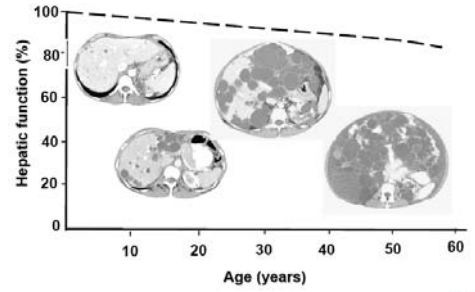
I have recommended to the Board of Trustees that Dan Larson donate both of his kidneys!

...and I will donate my kidneys when the FDA allows renal volume as an endpoint

## When to Treat and What to Measure?



## POLYCYSTIC LIVER DISEASE



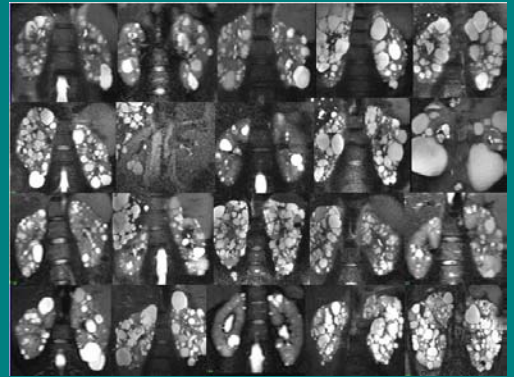
## CRISP Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

Prospective longitudinal observational study with annual protocolized visits, MRIs and GFR measurements

Age 15-45 yrs

eGFR >70 ml/min

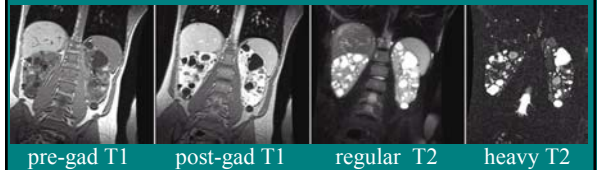
2/3 with hypertension <35 yrs or PrU >300 mg/d

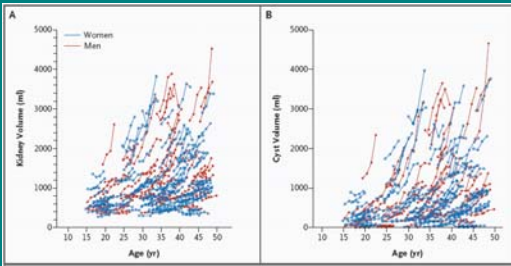


Inter-observer variability: 2.1%  
 Intra-observer variability: 2.4%  
 Day-to-day variability: 2.4%

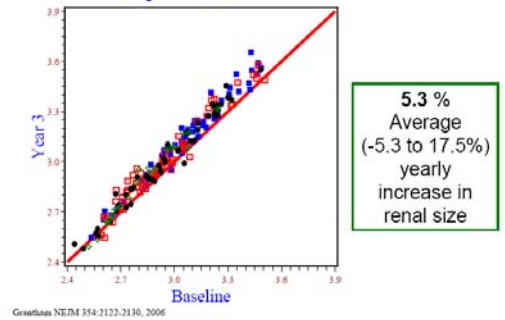
## MR protocol

Sequence	Cyst	Parenchyma
pre-gad T1	dark	gray
post-gad T1	dark	bright
regular T2	bright	gray
heavy T2	bright	dark



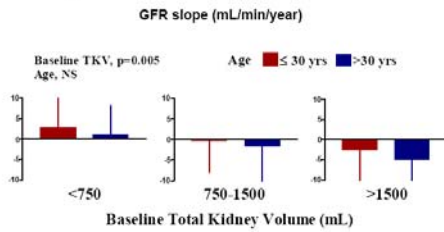


### CHANGE in TOTAL KIDNEY VOLUME, BL-YR3



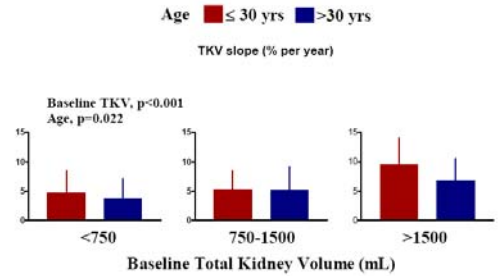
### CRISP Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

#### Change in GFR by Kidney Volume at Baseline



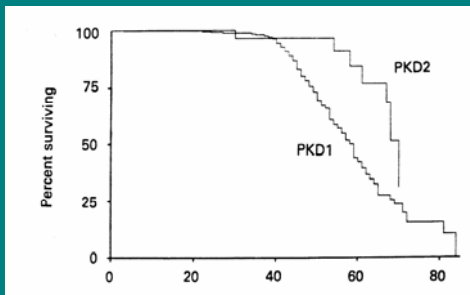
Grantham NEJM 354:2122-2130, 2006

#### Change in TKV by Kidney Volume at Baseline

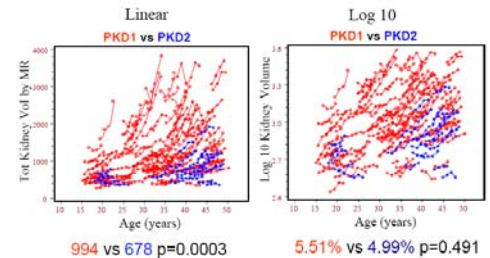


Grantham NEJM 354:2122-2130, 2006

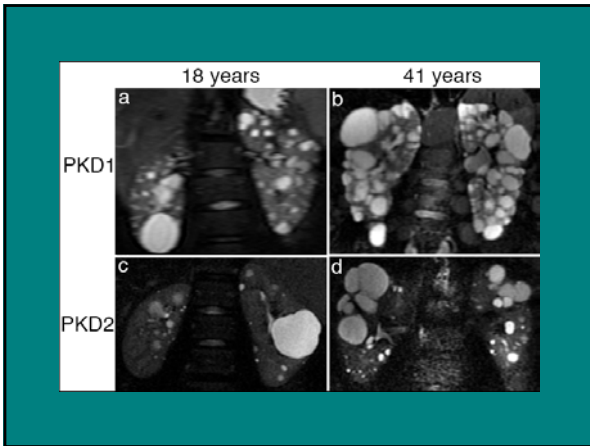
### Cumulative Survival of PKD1 vs PKD2



### CHANGES in TKV: PKD1 vs. PKD2



Harris, JASN 17:3013, 2006



### CRISP II: No more gadolinium!

- ◆ FDA warning: Nephrogenic Systemic Fibrosis
- ◆ Patients with dialysis or impaired renal function receiving Gadolinium contrast

### New T2/T1 FIESTA or FISP Image

<http://www.arpkdstudies.uab.edu>

### North American ARPKD Database

- **Eligibility criteria:**
  - compatible histopathology or
  - diffusely enlarged, echogenic kidneys and at least additional one criteria:
    - (i) biopsy-proven ARPKD in a sibling
    - (ii) clinical or radiological evidence for biliary fibrosis
    - (iii) absence of renal cysts in parental US (parents >30 yo)
    - (iv) parental consanguinity
- **Exclusion criteria:**
  - ADPKD
  - urinary tract malformations
  - major congenital anomalies of other systems

Guay-Woodford and Desmond. *Pediatrics* 111:1072-80, 2003

### ARPKD: Comparative clinical data

	No. Am. Database (N=166*)	Bergmann (2005) (N=164)
Prenatal dx	48%	23%
Hyponatremia	26%	NA
Hypertension	65%	76%
CRF	42%	86%
ESRD	13%	29%
Growth retardation	24%	16%
Chronic lung disease	12%	—
Portal hypertension	15%	44%
1-yr survival	92%	85%

TO FIND OUT IF YOU MAY BE ELIGIBLE TO PARTICIPATE IN HALT PKD ...

**If you live in one of these Eastern states -**  
 Connecticut, Delaware, District of Columbia, Florida, Georgia, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont or Virginia - please call:  
 Salt Lake Regional Medical Center, Salt Lake, UT  
 1-866-584-2735 (toll-free)

**If you live in one of these Southern states -**  
 Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Texas, Virginia, West Virginia - please call:  
 1-404-586-8260

**If you live in one of these Midwestern states -**  
 Arkansas, Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, Oklahoma, South Dakota, West Virginia, Wisconsin - please call:  
 1-800-430-2616 (toll-free)

**If you live in one of these Western states -**  
 Arizona, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Texas, Utah, Washington, or Wyoming - please call:  
 1-877-768-1297 (toll-free)

**University of Colorado Health Sciences Center  
 Denver, Colorado**



**For more information on Polycystic Kidney Disease, please contact the PKD Foundation:**  
 1-866-PKD-CURE or www.pkdfoundation.org

## HALT PKD


A Clinical Research Study

To  
**HALT Progression of Polycystic Kidney Disease**



Developed by the Polycystic Kidney Disease Treatment Network  
 www.pkdnw.edu/pkdnw

**Participating Research Institutions:**  
 Cleveland Clinic Foundation, Cleveland, OH  
 Brigham Young University, Provo, UT  
 Baylor University Medical Center, Dallas, TX  
 University of Colorado, Denver, CO  
 University of Colorado, Boulder, CO  
 University of Colorado, Aurora, CO  
 University of Colorado, Fort Collins, CO  
 University of Colorado, Greeley, CO  
 University of Colorado, Pueblo, CO  
 University of Colorado, Steamboat Springs, CO  
 University of Colorado, Grand Junction, CO  
 University of Colorado, Durango, CO  
 University of Colorado, Silverton, CO  
 University of Colorado, Vail, CO  
 University of Colorado, Aspen, CO  
 University of Colorado, Leadville, CO  
 University of Colorado, Breckenridge, CO  
 University of Colorado, Steamboat Springs, CO  
 University of Colorado, Grand Junction, CO  
 University of Colorado, Durango, CO  
 University of Colorado, Silverton, CO  
 University of Colorado, Vail, CO  
 University of Colorado, Aspen, CO  
 University of Colorado, Leadville, CO  
 University of Colorado, Breckenridge, CO



## HALT PKD

The Polycystic Kidney Disease Treatment Network (PKD-TN) will emphasize in 2011 its design clinical trials for treating hypertension that could be effective in slowing kidney growth in people who suffer from polycystic kidney disease. Working together, PKD-TN investigators from leading U.S. medical centers designed the HALT PKD trial to help slow or prevent the progression of Polycystic Kidney Disease (PKD) in a portion of the population of patients with PKD. The trial is being conducted in 12 U.S. Department of Health and Human Services. These clinical trials have been designed to investigate whether a combination of specific blood pressure medications when started with controlling blood pressure to normal targeted levels, will slow the rate of kidney growth in PKD patients, as compared to other medications currently used for treating high blood pressure. Individuals accepted to HALT PKD will participate in the study for six years.

**FACTS:**

- PKD is a disease in which cysts grow in the kidneys over time. This causes the kidneys to increase in size and eventually shut down.
- PKD affects over 600,000 Americans.
- PKD is the most common genetic, life-threatening disease.
- Autosomal Dominant PKD (ADPKD) is passed from one generation to the next by an affected parent, with each child of an ADPKD parent having a 50% chance of inheriting the disease.
- High blood pressure occurs in 40-70% of the people who have PKD.
- There is no cure for PKD. Current research focuses on slowing down progression of the disease by controlling blood pressure.

**How may one be eligible for HALT PKD?**

- You are between 18-65 years of age.
- You have a confirmed diagnosis of ADPKD.
- You will not need dialysis or transplant soon.
- Your blood pressure is at least 130/80 mm Hg.
- You do not have heart disease, heart failure, or diabetes requiring medication.
- You are not pregnant or plan to become pregnant during the next 4 years.

**What are the benefits of participation?**

- You will help advance knowledge of PKD.
- You will be closely followed by a physician for the length of the study.
- Clinical visits, lab tests, and study medications will be provided at no charge.
- Your reimbursement up to \$2000 plus travel expenses will be provided.
- A device for using blood pressure readings at home will be provided at no charge.

**If you would like a study coordinator to contact you about participating in HALT PKD, please fill out the form below and return it to the HALT PKD Project Manager, Krista Redburn.**

Yes, Please contact me about participating in HALT PKD.

Name: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 City: \_\_\_\_\_  
 State: \_\_\_\_\_ Zip Code: \_\_\_\_\_  
 Home Phone: \_\_\_\_\_  
 Work Phone: \_\_\_\_\_  
 Cell Phone: \_\_\_\_\_  
 Email: \_\_\_\_\_  
 Signature: \_\_\_\_\_

Please note that final determination of eligibility for HALT PKD requires a very specific assessment of each potential participant based on defined inclusion/exclusion criteria.

Please return this form to:  
 Ms. Krista M. Redburn  
 Project Manager for HALT PKD  
 Washington University School of Medicine  
 660 South Euclid Avenue, Suite 600 East  
 St. Louis, MO 63110  
 Phone: 314-434-0118  
 Fax: 314-434-0108  
 Email: [2008@pkdnw.edu](mailto:2008@pkdnw.edu)

## HALT Progression of Polycystic Kidney Disease (HALT PKD)

This study is currently recruiting patients.

**Sponsors and Collaborators:** [National Institute of Diabetes and Digestive and Kidney Diseases \(NIDDK\)](#)  
 Boehringer Ingelheim Pharmaceuticals  
 Merck  
 Polycystic Kidney Disease Foundation

**Information provided by:** National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

**ClinicalTrials.gov Identifier:** NCT00283686

## Purpose of HALT

- The efficacy of interruption of the renin-angiotensin-aldosterone system (RAAS) on the progression of cystic disease and on the decline in renal function in autosomal dominant kidney disease (ADPKD) will be assessed in two multicenter randomized clinical trials
- 1) early disease defined by GFR >60 mL/min/1.73 m<sup>2</sup> (Study A); and 2) moderately advanced disease defined by GFR 30-60 mL/min/1.73 m<sup>2</sup> (Study B)
- Participants will be recruited and enrolled, either to Study A or B, over the first two years. Participants enrolled in Study A will be followed for a total of four years, while those enrolled in Study B will be followed for four-to-six years, with the average length of follow-up being five years
- The two concurrent randomized clinical trials differ by eligibility criteria, interventions and outcomes to be studied

## Specific Aims of Study A

- To study the efficacy of ACE-I/ARB combination therapy as compared to ACE-I monotherapy and usual vs. low blood pressure targets on the percent change in kidney volume in participants with preserved renal function (GFR >60 mL/min/1.73m<sup>2</sup>) and high-normal blood pressure or hypertension (>130/80 mm Hg).

## Specific Aims Study B

- To study the effects of ACE-I/ARB combination therapy as compared to ACE-I monotherapy in the setting of standard blood pressure control (130/80 mm Hg or below) on the time to a 50% reduction of baseline eGFR, ESRD or death, in hypertensive individuals with moderate renal insufficiency (GFR 30-60 mL/min/1.73m<sup>2</sup>).

## Inclusion Criteria for HALT PKD

Diagnosis of ADPKD.

Age 15-49 (Study A); Age 18-64 (Study B).

GFR >60 mL/min/1.73 m<sup>2</sup> (Study A); GFR

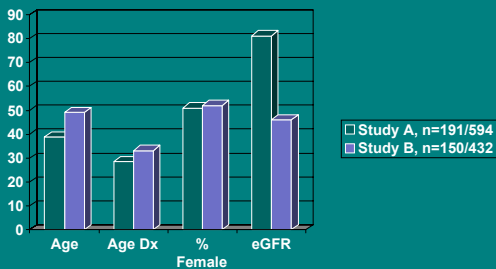
30-60 mL/min/1.73 m<sup>2</sup> (Study B).

BP ≥130/80 or receiving treatment for hypertension.

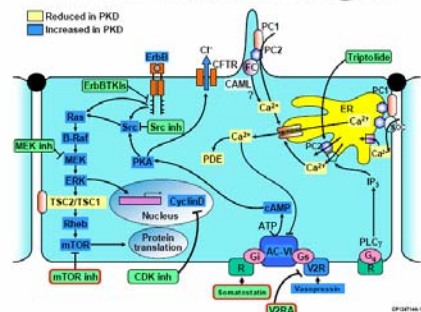
## Outcomes of HALT

- Primary Outcome Measures:
- Study A: Change in total kidney volume, as assessed by abdominal MR at baseline, 2 years, and 4 years follow-up.
- Study B: Time to 50% reduction of baseline eGFR, ESRD (initiation of dialysis or preemptive transplant), or death.  
Total Enrollment: 1018
- Study start: January 2006; Expected completion: December 2011

## Baseline Characteristics of HALT Participants



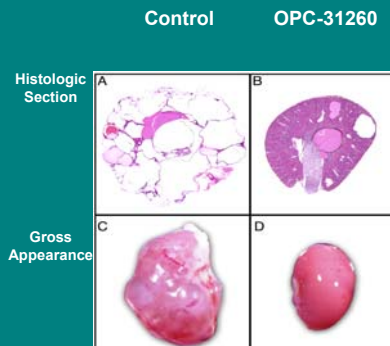
## PKD: Treatment Targets



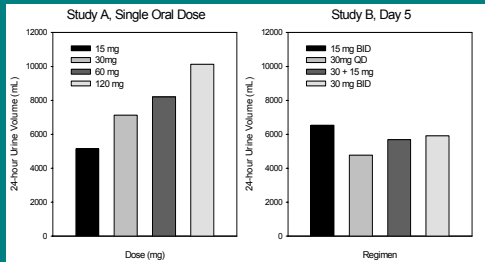
## Vasopressin/ADPKD

- ADPKD is characterized by:
  - A mild lack of urinary concentrating ability early in the course of the disease *and*
  - Higher vasopressin levels in hypertensive ADPKD individuals *and*
- Increased renal cAMP may be related to disease progression in ADPKD by promoting epithelial cell proliferation and chloride-driven fluid secretion

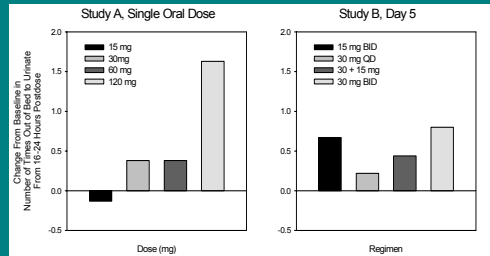
OPC-31260 Vasopressin Blockade Pkd2<sup>WS25/-</sup> mice  
Kidneys at 16 weeks (treated 13 weeks)



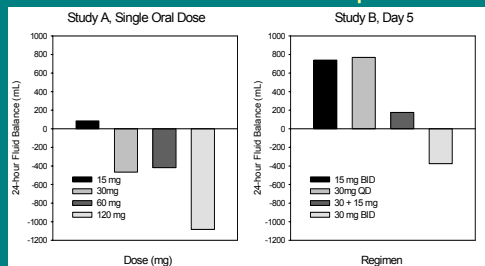
## Mean 24-Hour Urine Volume Following Single (Study A) or Multiple (Study B) Oral Doses of Tolvaptan



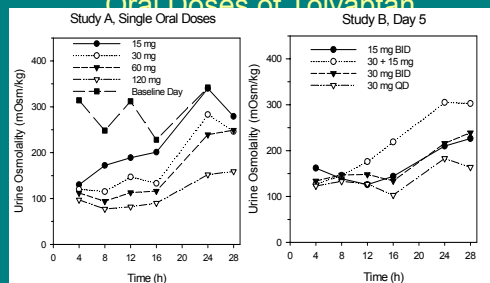
## Mean Change from Baseline in Number of Times Out of Bed to Urinate Following Single (Study A) or Multiple (Study B) Oral Doses of Tolvaptan



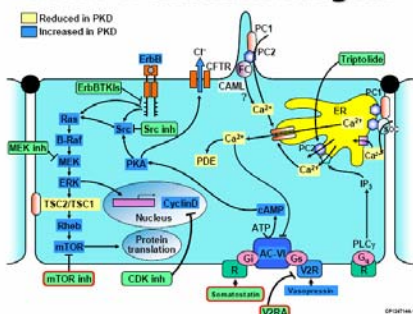
## 24-Hour Fluid Balance Following Single (Study A) or Multiple (Study B) Oral Doses of Tolvaptan



## Mean Urine Osmolality Following Single (Study A) or Multiple (Study B) Oral Doses of Tolvaptan



## PKD: Treatment Targets



Pilot Study of Rapamycin as Treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD)  
 This study is not yet open for patient recruitment.  
 Verified by The Cleveland Clinic January 2006

Sponsored by: The Cleveland Clinic  
 Information provided by: The Cleveland Clinic  
 ClinicalTrials.gov Identifier: NCT00286156

## Purpose

- This study is a prospective, randomized, placebo-controlled, clinical trial designed to compare the effects of an agent that has antiproliferative (1,2), antiangiogenesis (3), and tumor-progression blocking capabilities (4), namely, rapamycin (Rapamune®), in the treatment of autosomal-dominant polycystic kidney disease (ADPKD).

## General Procedures

- In Group I participants will have a GFR  $> 60$  ml/min/1.73 m<sup>2</sup>, and in Group II participants will have a GFR 25-59 ml/min/1.73 m<sup>2</sup>. ADPKD individuals who volunteer and qualify, will be randomly and prospectively assigned to treatment with rapamycin at either a high or low trough blood level or to standard care (each 1/3 of enrolled patients) for one year. The two treatment groups will receive rapamycin doses aimed at maintaining the 20- to 24-hour trough blood levels at either 2 to 5 ng/mL (low-dose), or greater than 5 to 8 ng/mL (high-dose). These trough levels are in the lower range of levels used when treating renal transplant recipients in whom trough levels are typically maintained between 5 and 15 ng/mL.

## Outcomes of interest

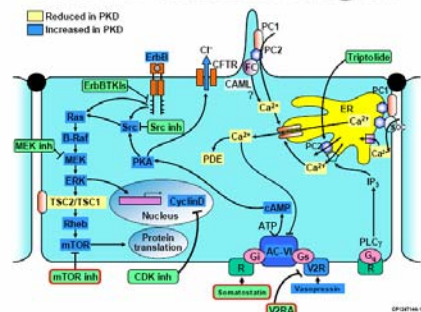
Primary Outcome Measures:

- Change in Iohalamate GFR from baseline to 12 months

Secondary Outcome Measures:

- Change in total kidney volume as measured by 3D-CT from baseline to 12 months and adverse events.
- Total Enrollment: 45

## PKD: Treatment Targets



Somatostatin in Polycystic Kidney: a Long-Term Three Year Follow up Study  
This study is currently recruiting patients.  
Verified by Mario Negri Institute for Pharmacological Research June 2007

Sponsored by: Mario Negri Institute for Pharmacological Research

Information provided by: Mario Negri Institute for Pharmacological Research

ClinicalTrials.gov Identifier: NCT00309283

Norberto Perico, MD 003903545351 [perico@marionegri.it](mailto:perico@marionegri.it)

## Purpose

- To determine if somatostatin administered monthly as an intramuscular injection will slow the rate of growth of cysts determined by MR imaging

## Outcomes of Interest

- Primary Outcome Measures:
  - Change over baseline of the total kidney volume at 1 and 3 years follow-up (estimated by gadolinium contrast enhanced and T2-weighted magnetic resonance imaging, MRI).
- Secondary Outcome Measures:
  - Absolute and percent change over baseline by MRI analysis will be compared in the two ADPKD groups at baseline, at one and three years follow-up
  - Total renal parenchymal volume
  - Residual renal volume
  - Renal parenchymal volume taken up by small cysts, < 5 mm<sup>3</sup>

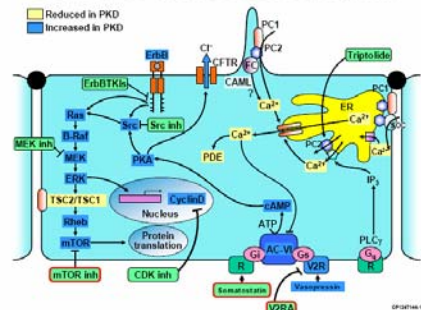
Total Enrollment: 66  
Study start: April 2006; Expected completion: April 2010

- Additional functional parameters will be compared in the two groups at baseline and at 1, 2, 3 years follow-up as follows:
  - Systolic and diastolic blood pressure
  - GFR (plasma iohexol clearance)
  - GFR (over baseline)
  - RPF (plasma PAH clearance)
  - Serum creatinine concentration
  - Diuresis
  - 24 h urinary protein excretion rate
  - 24 h urinary albumin excretion rate
  - Protein, albumin, creatinine concentrations on spot morning urine samples
  - Protein /creatinine ratio on spot morning urine samples
  - Albumin/creatinine ratio on spot morning urine samples
  - Urinary sodium, urea, glucose, phosphorus concentrations (24 hr samples)
  - Urine osmolality (calculated)

## Eligibility Criteria

- No evidence of associated systemic, renal parenchymal or urinary tract disease
- Age > 18 years
- Clinical and ultrasound diagnosis of ADPKD
- GFR > 40 ml/min/1.73 m<sup>2</sup> (estimated by the 4 variable MDRD equation)

## PKD: Treatment Targets



**Octreotide in Severe Polycystic Liver Disease**  
This study is currently recruiting patients.  
Verified by Mayo Clinic March 2007

**Sponsors and Collaborators:** Mayo Clinic  
Novartis

**Information provided by:** Mayo Clinic  
**ClinicalTrials.gov Identifier:** NCT00426153

Page J. Linda 507-255-0405 [page.linda@mayo.edu](mailto:page.linda@mayo.edu)

## Purpose

- To determine the effect of intramuscular octreotide on the progression of liver cystic disease in patients with severe polycystic liver disease who are not considered for liver surgery

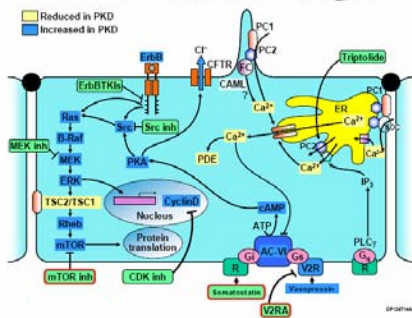
## Outcomes of Interest

- Primary Outcome Measures:
  - Percent change in liver volume as measured by MRI at baseline and 12 months.
- Secondary Outcome Measures:
  - Percent change in liver cyst volume, renal volume, and renal cyst volume as measured by MRI at baseline and 12 months.
  - Response rates, based on changes in liver and renal volume.
  - Adverse events.
  - Changes in quality of life.
- Total Enrollment: 42
- Study start: January 2007

## Inclusion Criteria

- Age - 18 years and older.
- Diagnosis of Polycystic Liver Disease (PLD) associated with ADPKD or isolated Autosomal Dominant Polycystic liver Disease (ADPLD).
- Severe PLD defined as a liver volume >4000 mL or symptomatic disease due to mass effects from hepatic cysts.
- Not a candidate for or declining surgical intervention

## PKD: Treatment Targets



The Effect of High and Low Sodium Intake on Urinary Aquaporin-2 in Autosomal Dominant Polycystic Kidney Disease  
 This study is currently recruiting patients.  
 Verified by Holstebro Hospital August 2006

Sponsored by:  
 Holstebro Hospital

Information provided by: Holstebro Hospital  
 ClinicalTrials.gov Identifier: NCT00410007

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## Study Purpose

- The aim of the study is to test the following hypotheses:
  - that the function and/or regulation of AQP2 and /or ENaC in the principal cells is abnormal in ADPKD.
  - if an abnormal function of the principal cells is present in autosomal dominant polycystic kidney disease, this will become more pronounced at high and low sodium intake

## Inclusion Criteria

- Caucasian men and women
- age 18-65 years
- BMI between 18.5-30.0 kg/m<sup>2</sup>
- ADPKD
- Kidney function: stages 1-4.

## Outcomes of Interest

- AQP-2; fractional sodium excretion, p-vasopressin; p-aldosterone.  
Secondary Outcome Measures:
- u-p-AQP-2; u-ENaC (alpha, beta, gamma); CH2O; u-cAMP; uPGE-2, GFR.
- Total Enrollment: 25
- Study start: October 2006

## Summary

- Therapies and approaches to ADPKD have put new hope on the horizon for a better life and potentially a cure for this disorder
- You, more than anyone else, particularly at this time, will make an impact on outcomes for patients with ADPKD