ADULT POLYCYSTIC KIDNEY DISEASE AND THE TOLVAPTAN STUDY

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APCKD

- **GENETICS**
- SCREENING AND DIAGNOSIS
- MECHANISM OF CYST GROWTH
- RENAL MANIFESTATIONS
- EXTRARENAL MANIFESTATIONS
- COURSE AND TREATMENT
- FUTURE

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (APCKD)

- INHERITANCE AS AUTOSOMAL DOMINANT TRAIT
  - AT LEAST 2 LOCI IDENTIFIED
    - 85% WITH CHROMSOME 16 (PKD1 LOCUS); MOST OTHERS WITH CHROMOSOME 4 (PKD2 LOCUS)
  - GENE PRODUCTS IDENTIFIED:
    - POLYCYSTIN 1 - PKD1: 46 EXONS CODING FOR 4000 AA PROTEIN
    - POLYCYSTIN 2 - PKD2: 15 EXONS CODING FOR 1000 AA PROTEIN
- 1 IN 400-1000 LIVE BIRTHS
- PHENOTYPIC EXPRESSION: KIDNEYS WITH EXTENSIVE CYST FORMATION AND OFTEN EXTRARENAL MANIFESTATIONS
  - 50% DETECTION RATE DURING LIFETIME

CHARACTERISTICS OF POLYCYTIN-1

- LOCATED IN RENAL TUBULAR EPITHEIAL CILIA AND PLASMA MEMBRANE
  - ALSO LOCATED IN HEPATIC AND PANCREATIC DUCTS
- LOCALIZED TO THE LATERAL CELL MEMBRANE – ALLOWING CELL-CELL AND CELL MATRIX INTERACTION AFFECTING GROWTH AND SURVIVAL OF CELLS
- IN MOUSE MODEL, EARLY PKD-1 INACTIVATION (WITHIN 13 POSTNATAL DAYS) RESULTS IN SEVERE CYST FORMATION
- PART OF THE STRUCTURE OF CILIA: SENSING FLOW IN TUBULAR LUMEN AND IN THE CENTROSOME

CHARACTERISTICS OF POLYCYSTIN-2

- SERVES A ROLE IN CALCIUM SIGNALING
- FOUND IN PLASMA MEMBRANE, ENDOPLASMIC RETICULUM AND PRIMARY CILIUM
- INTERACTS WITH POLYCYSTIN-1

INTERACTIONS BETWEEN THE POLYCYSTINS

- BOTH LOCALIZE TO CILIA
- BOTH ARE FOUND IN THE CELL MEMBRANE AND IN INTRACELLULAR LOCATIONS
- BOTH ARE FOUND IN BLOOD VESSELS AND HEPATIC DUCTS
- BOTH REGULATE G PROTEIN SIGNALING
- BOTH PROTIENS INTERACT AT THE CELL MEMBRANE
- BOTH PROTEINS CREATE A NON-SELECTIVE CALCIUM PERMEABLE CATION CHANNEL
- MECHANICAL STIMULI LEADS TO POLYCSTIN-2 MEDIATED TRANSLOCATION OF A POLYCYSTIN-1 FRAGMENT TO THE NUCLEI LEADING TO AK-1 TRANSCRIPTION

SECOND HIT HYPOTHESIS

- ONLY SEVERAL HUNDRED TO A THOUSAND NEPHRONS HAVE TO DEVELOP CYSTS TO RESULT IN RENAL FAILURE
- CYSTIC DILATATION IS FOCAL
- CYSTS MAY FORM ONLY WHEN THERE IS LOSS OF THE NORMAL HAPLOTYPE ***IN ADDITION TO*** THE INHERITED ABNORMAL GENE

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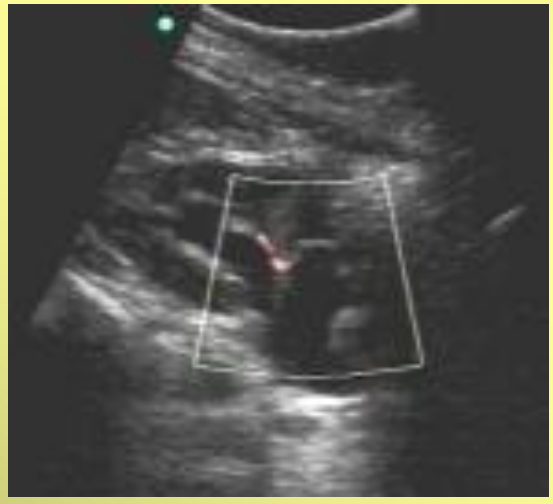
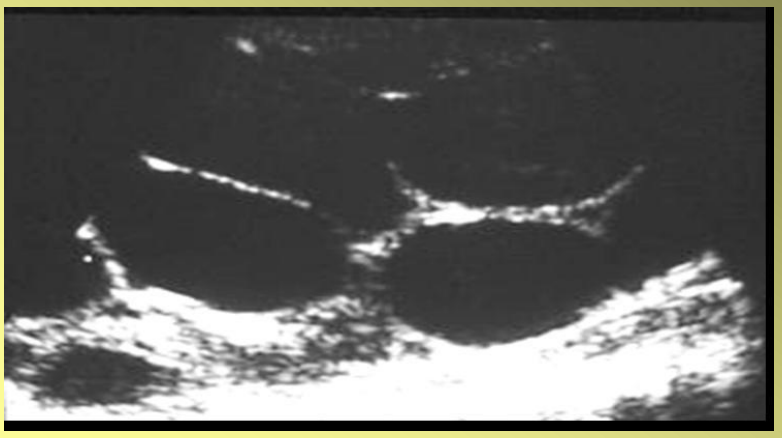
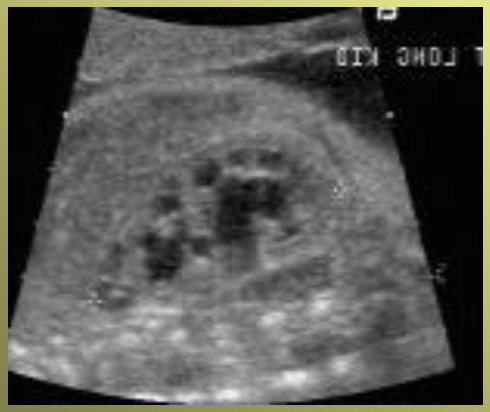
SCREENING

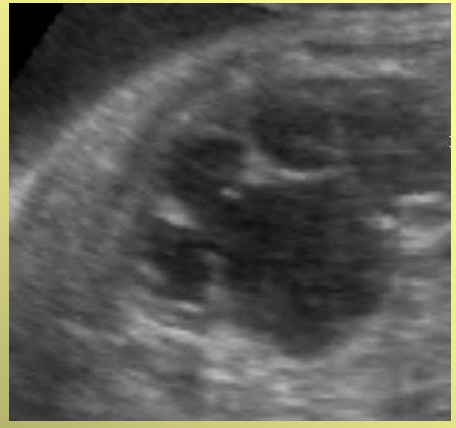
- RENAL ULTRASOUND IS USUAL INITIAL MODALITY; CT AND MRI MAY BE MORE SENSITIVE
- PATIENT AT RISK/UNKNOWN GENOTYPE
  - 15-39 YEARS: $\geq$ 3 UNILATERAL OR BILATERAL CYSTS; SENS 82-96%/SPEC 100%
  - 40-59 YEARS: 2 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 98%
  - 60 + YEARS: 4 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 100%
  - NO CYSTS AT AGE 30 RULES OUT APCKD-1
  - DETECTION OF HEPATIC OR PANCREATIC CYSTS
- PATIENT WITH NEGATIVE FAMILY HISTORY
  - 10 OR MORE CYSTS IN EACH KIDNEY
- GENETIC TESTING
  - LINKAGE ANALYSIS- REQUIRES 4 RELATIVES

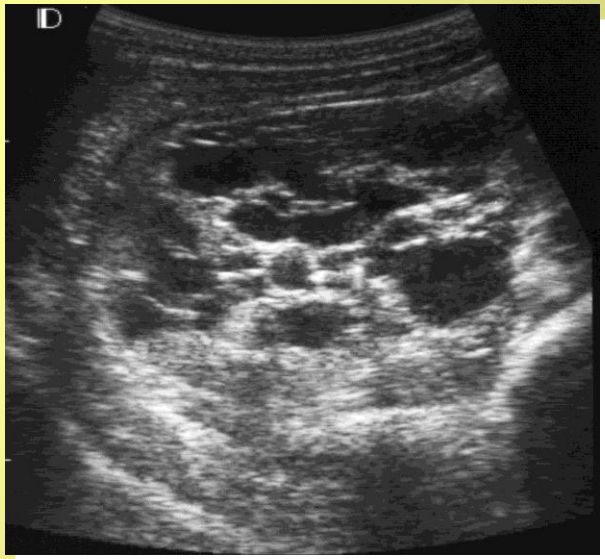
ULTRASOUND PITFALLS



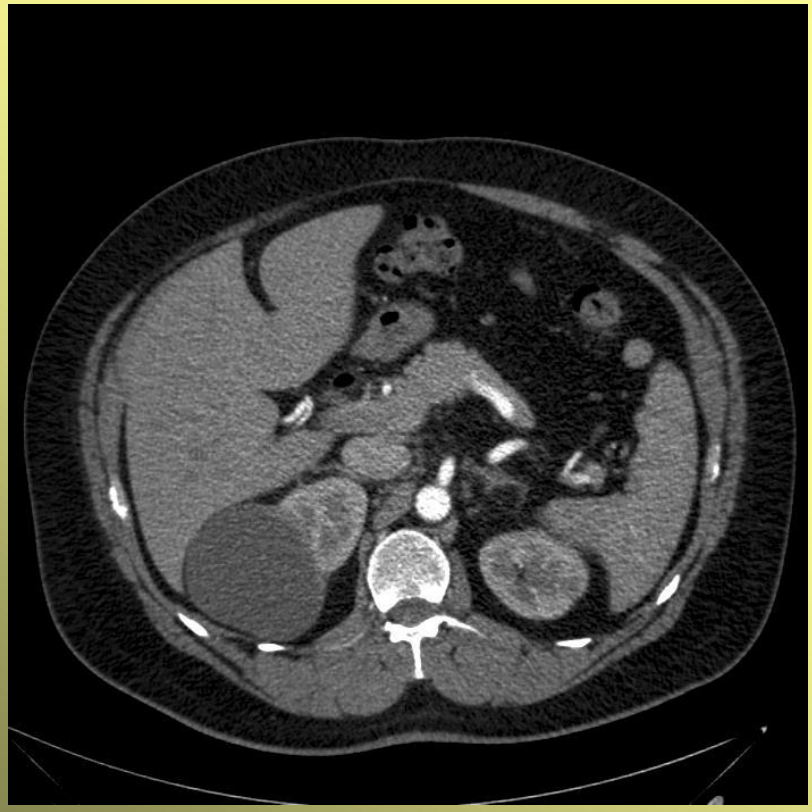


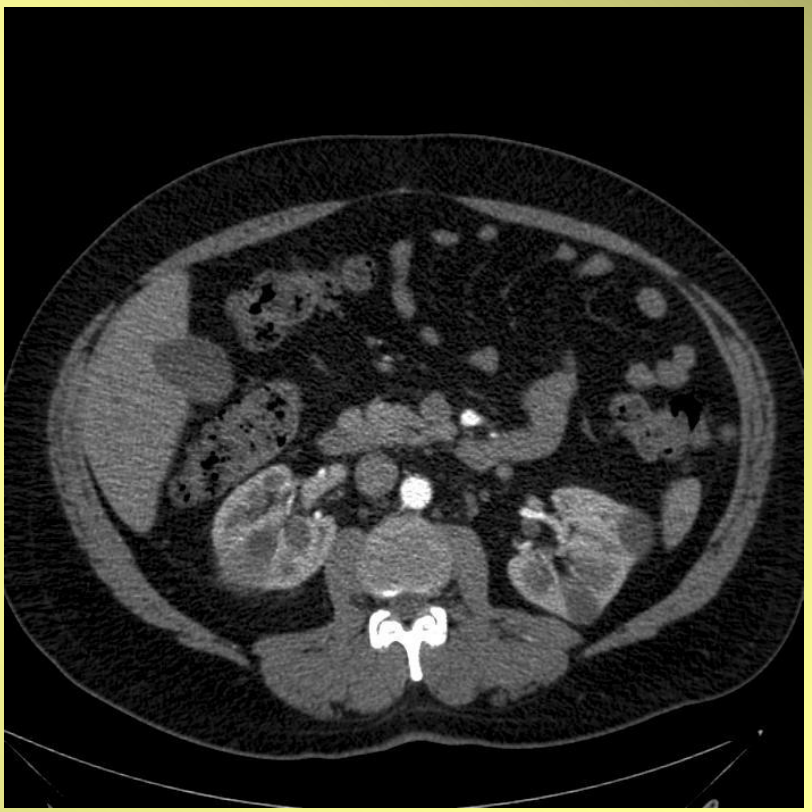




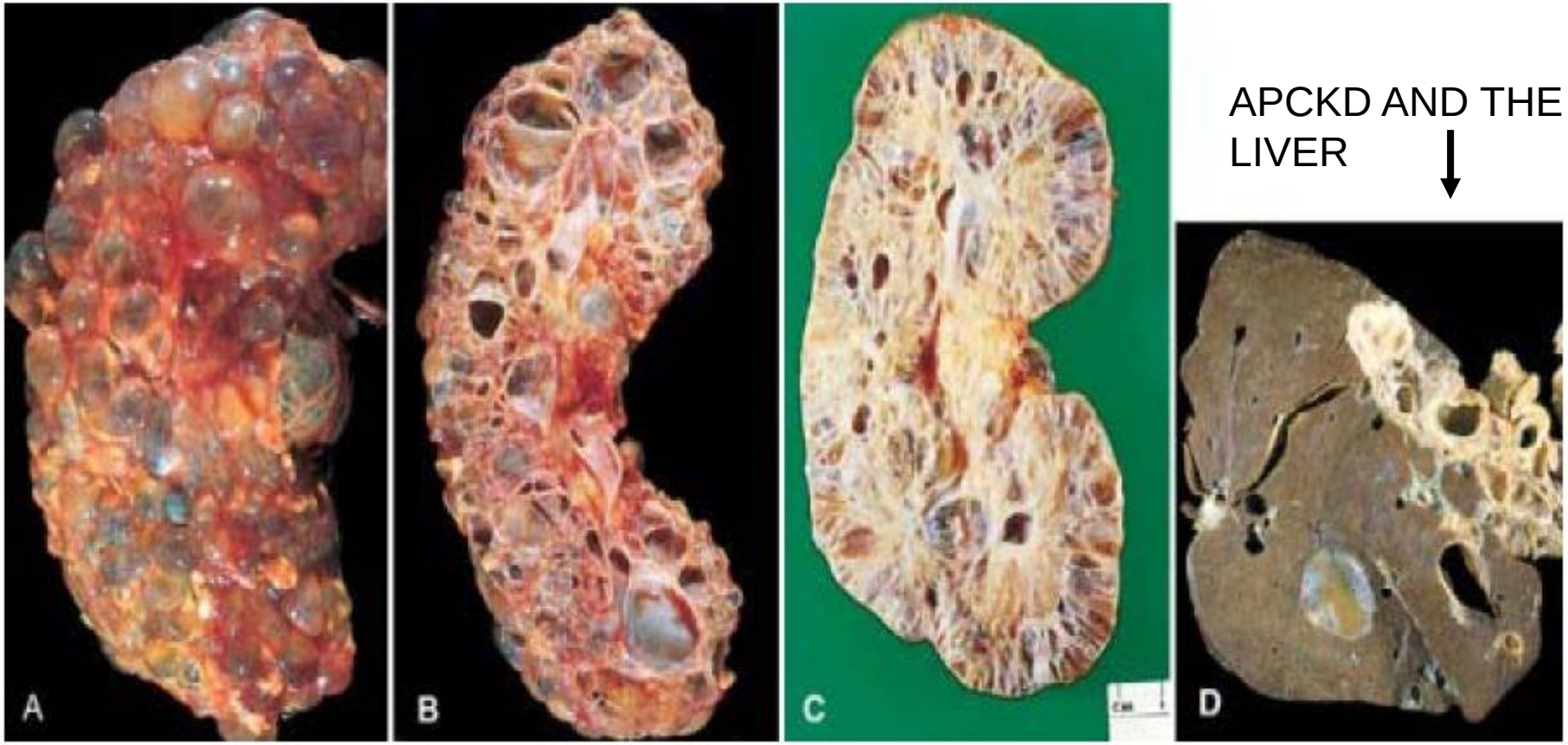


APCKD: COMPUTERIZED TOMOGRAPHY





CYCTIC KIDNEY DISEASE



APCKD AND THE LIVER

APCKD

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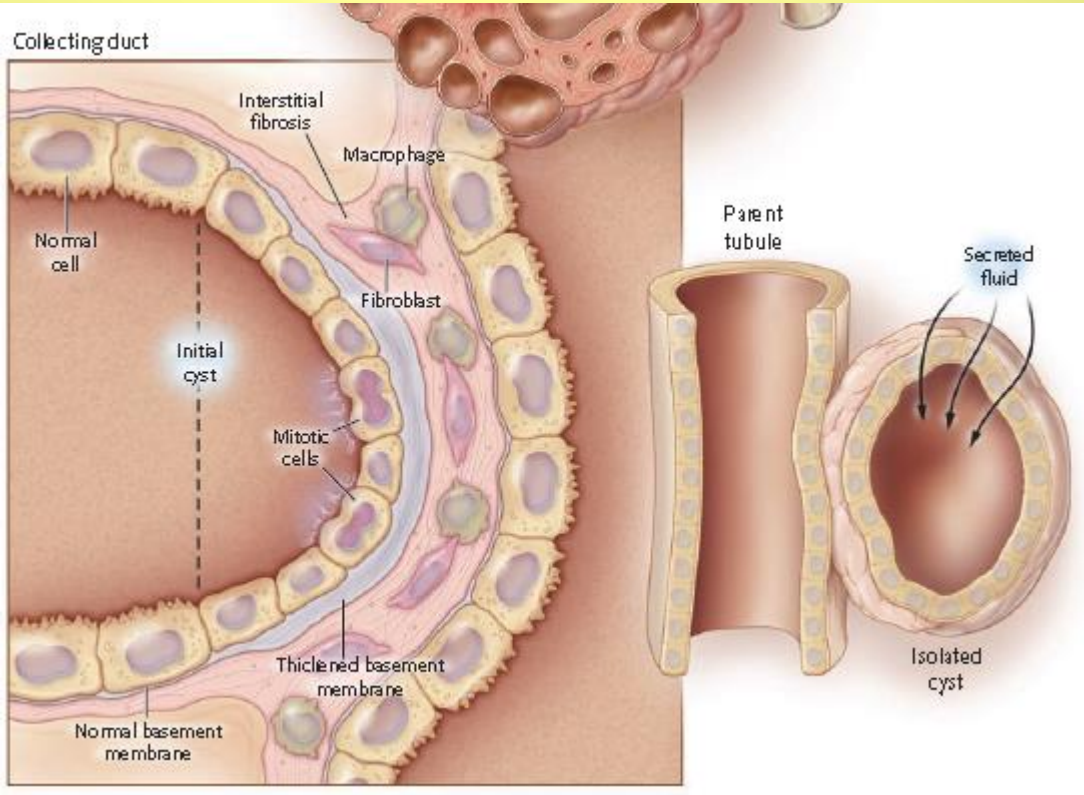
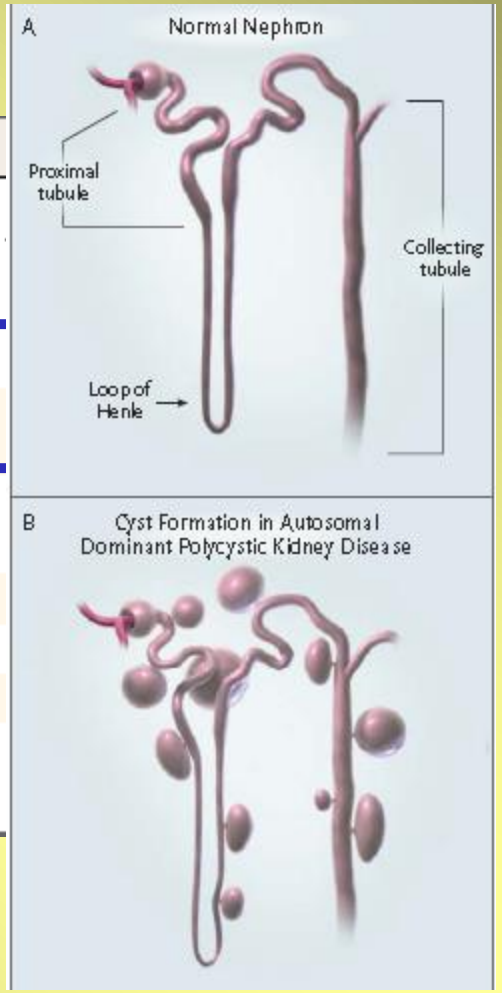
REQUIREMENTS FOR CYST FORMATION AND GROWTH

- EPITHELIAL PROLIFERATION
- FLUID SECRETION
- MATRIX REMODELING
- FIBROSIS

CYST DEVELOPMENT

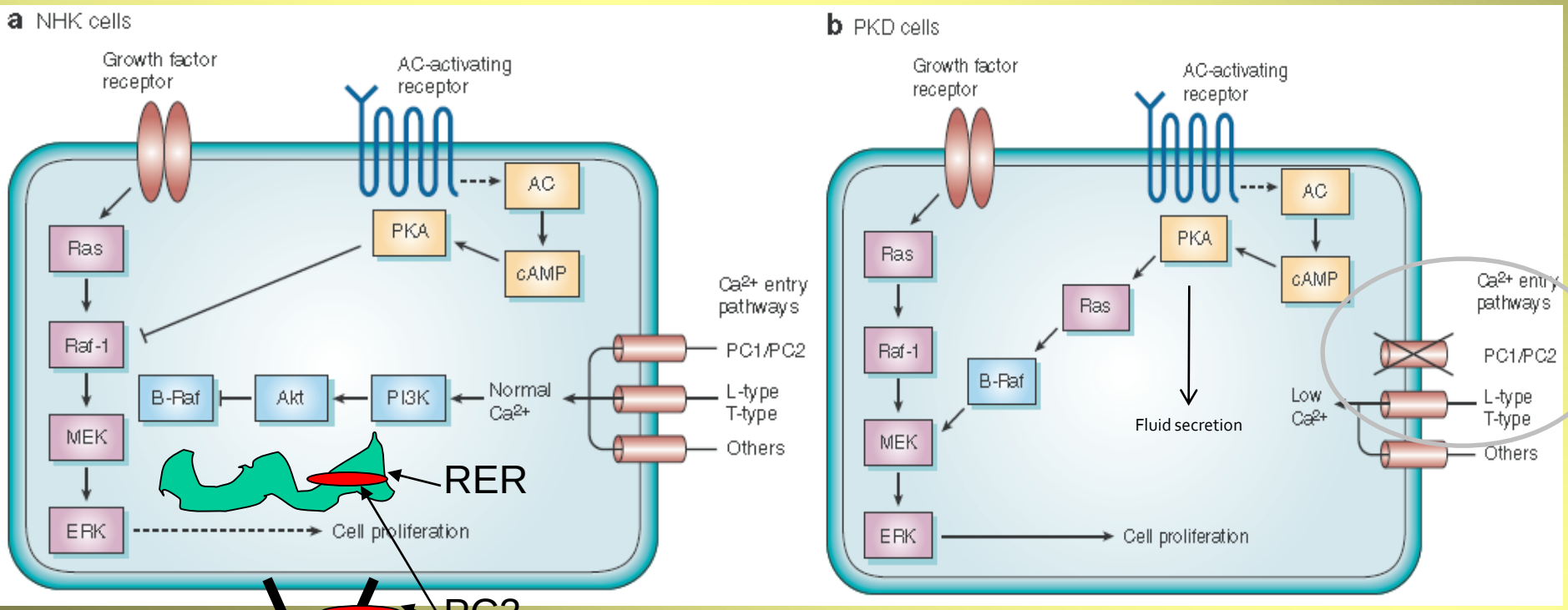


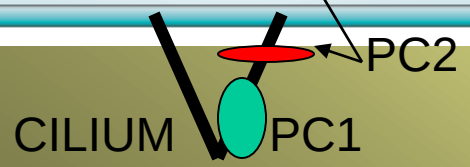


N ENGL J MED 350;14 www.NEJM.ORG OCTOBER 2, 2008

N ENGL J MED 350;2 WWW.NEJM.ORG JANUARY 8, 2004

MAP KINASE CASCADE IN NORMAL AND PCKD CELLS





Kidney International (2008) 73, 251–253

CYST GROWTH

- INITIALLY EXPANDED BY GFR
- FIBROSIS OCCURS LEADING TO LOSS OF CONNECTION TO FUNCTIONING NEPHRONS
- CYST FLUID CONTAINS GROWTH FACTORS AND STIMULATES SECRETION
  - Na-K ATPase FOUND IN APICAL MEMBRANE OF APCKD CELLS
  - CFTR: CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR A C-AMP-DEPENDENT CHLORIDE CHANNEL,IS IN THE APICAL MEMBRANE OF APCKD CELLS
  - CYST FLUID CAUSES RENAL EPITEILIUM IN CULTURE TO FORM CYSTS
- CYTIC FLUID ACCUMULATION ESTIMATED AT 26-475 mL/year
- SODIUM CONTENT OF CYSTS IS VARIABLE:
  - High Gradient Cysts (cells with tight junctions-collecting duct) and Low Gradient Cysts (proximal tubule)

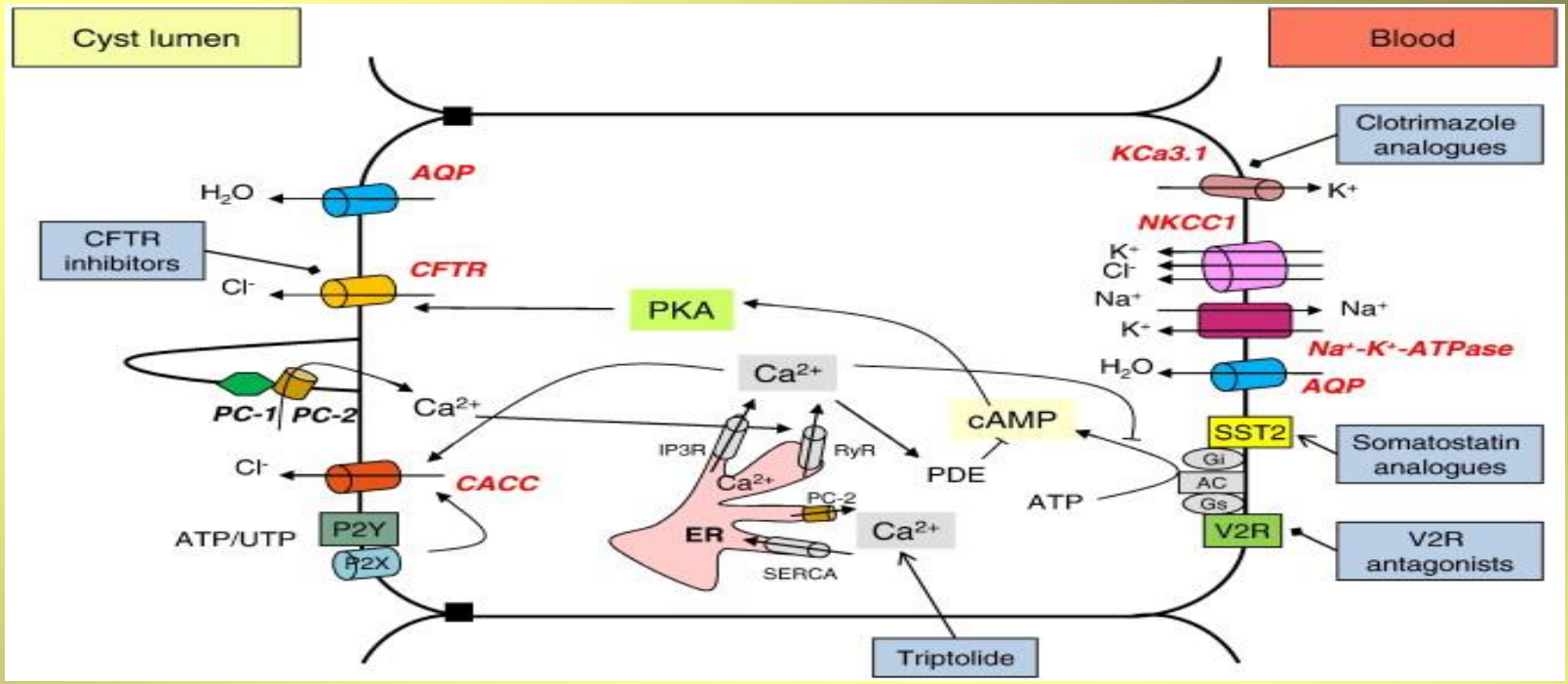


Fig. 1 Mechanisms of fluid secretion in ADPKD cyst-lining epithelial cells. Model of the transporters and channels involved in fluid accumulation in the lumen of ADPKD cysts. The apical and basolateral poles of the cell are delineated by tight junctions. T...

Sara Terryn , Anh Ho , Renaud Beauwens , Olivier Devuyst

Fluid transport and cystogenesis in autosomal dominant polycystic kidney disease

Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease Volume 1812, Issue 10 2011 1314 - 1321

http://dx.doi.org/10.1016/j.bbadis.2011.01.011

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RENAL EFFECTS OF APCKD

- CYST GROWTH AND RENAL FAILURE
- HYPERTENSION
- HEMATURIA
  - CYST RUPTURE
- PROTEINURIA
  - 300MG – 1 GRAM /24 HOURS
- RENAL CALCULI
  - MOST OFTEN URIC ACID
- LOSS OF CONCENTRATNG ABILITY
- INFECTION
- PAIN SYNDROMES
- POLYCYTHEMIA

APCKD

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EXTRARENAL EFECTS OF APCKD

- CEREBRAL ANEURYSMS
- HEPATIC CYSTS
- CARDIAC VALVE DISEASE
- COLONIC DIVERTICULI
- HERNIAS

ANEURYSMS

- INTRACEREBRAL HEMORRHAGE/SAH
  - 4%-10% INCIDENCE
  - 22% IF A RELATIVE SUFFERED A BLEED
  - 50% DEATH OR DISABILITY
- INITIAL SCREENING
  - PATIENTS WITH BLEED, POSITIVE FAMILY HISTORY, WARNING SYMPTOMS, HIGH-RISK OCCUPATION, HYPERTENSION, NEED FOR ANTICOAGULATION
- RE-SCREENING
  - HIGH-RISK PATIENTS
    - IF INITIAL STUDY IS NEGATIVE THE IS A 2.6% INCIDENCE OF AN ANEURSM AFTER 10 YEARS OF FOLLOW-UP
    - RE-SCREEN EVERY FIVE YEARS IF INITIAL STUDY IS NEGATIVE; EVERY 2-3 YEARS IF ANEURYSM IS SMALL ~ 7-10M
  - LOW-RISK PATIENTS (- FAMILY HISTORY) ?

OTHER ORGANS

- HEPATIC CYSTS
  - UP TO 80% OF PATIENTS WILL HAVE CYSTS
  - EQUAL MALE/FEMALE INCIDENCE BUT MORE SEVERE IN FEMALES AND ASSOCIATED WITH ORAL CONTRACEPTIVES USE
  - RARELY TRANSPLANTATION IS REQUIRED; RAPAMYCIN REDUCES HEPATIC CYSTS
- CARDIAC
  - MITRAL VALVE PROLAPSE AND AI
  - INCIDENCE 20%
- COLONIC DISEASE
  - DIVERTICULI

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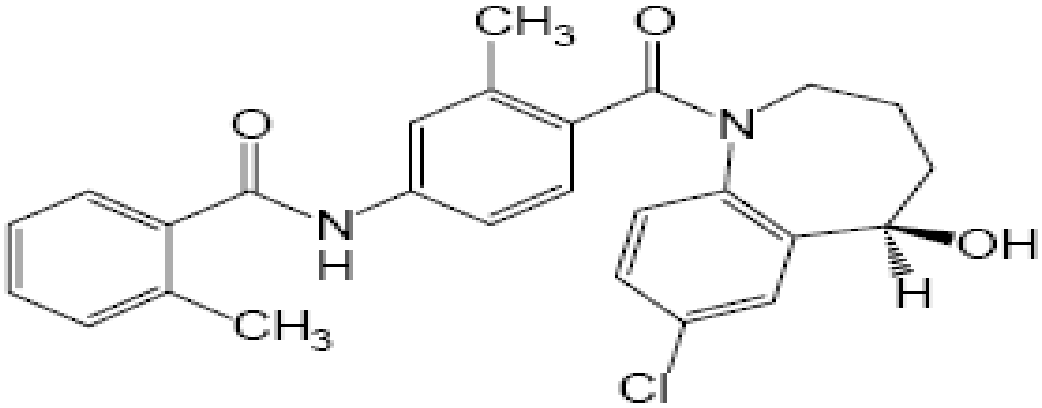
TREATMENT STRATEGIES

- PREVENTION OF CYST GROWTH
  - INIBITION OF TRANSPORT
    - VASOPRESSIN ANTAGONISTS
    - REDUCED CAFFEINE INTAKE
    - SOMATOSTATIN
  - INHIBITION OF CELL PROLIFERATION
    - VASOPRESSIN, STEROIDS, RAPAMYCIN
  - INHIBITION OF FIBROSIS
    - RAAS BLOCKADE, PROTEIN RESTRICTION
  - CYST REDUCTION
  - CONTROL OF HYPERTENSION

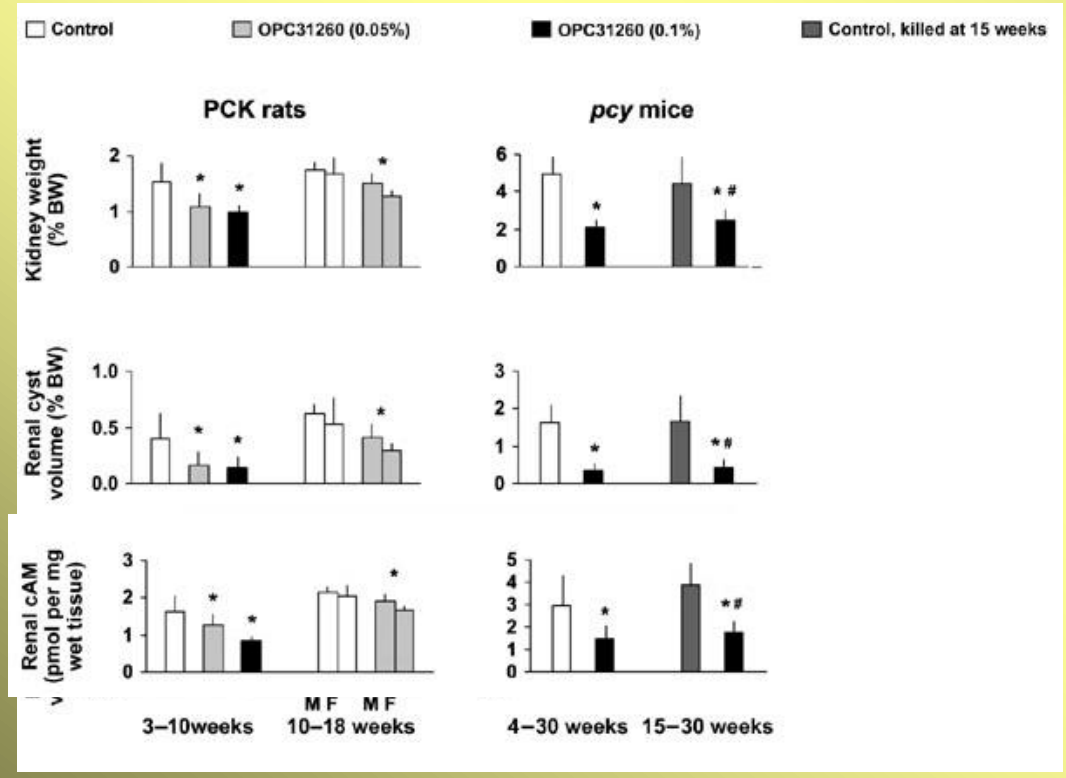
TOLVAPTAN

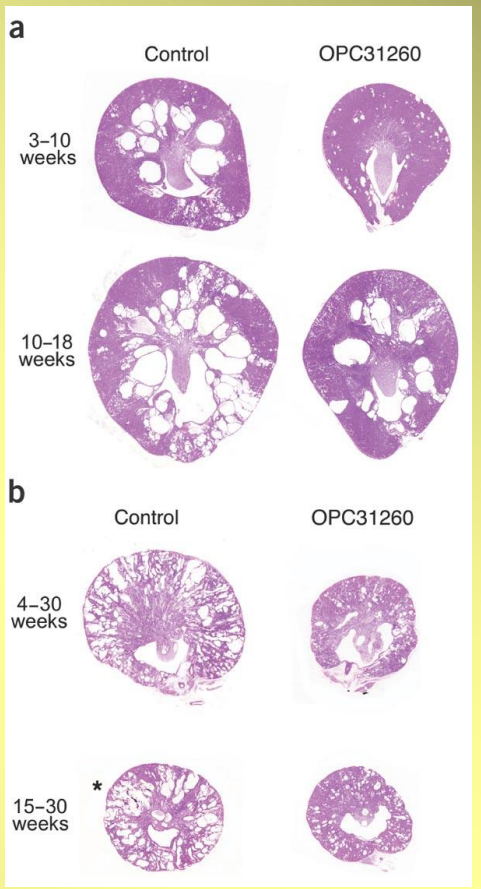
Chemical structure:



Other name:	OPC-156
INN, USAN:	Tolvaptan
Molecular formula:	$C_{26}H_{25}ClN_2O_3$
Molecular weight:	448.94
Appearance:	OPC-41061 is a white crystalline powder.

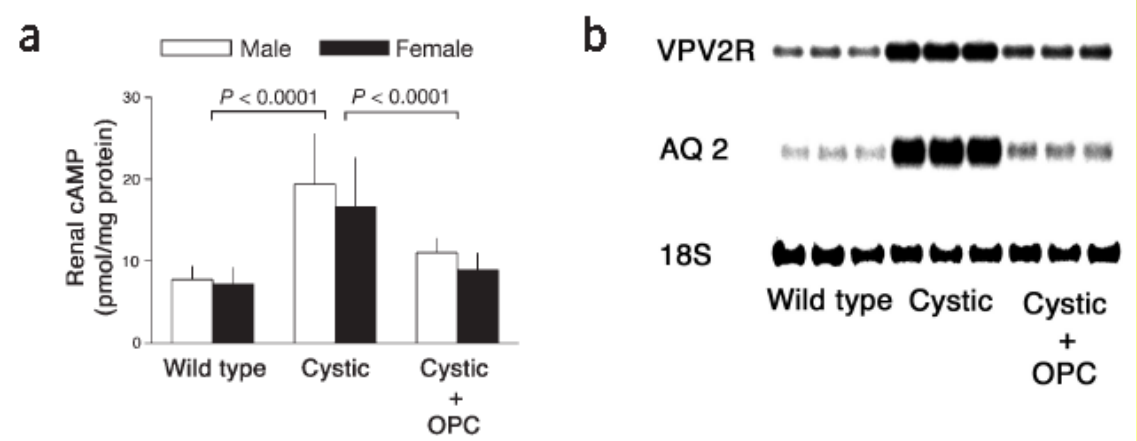
V_2 RECEPTOR ANTAGONISM

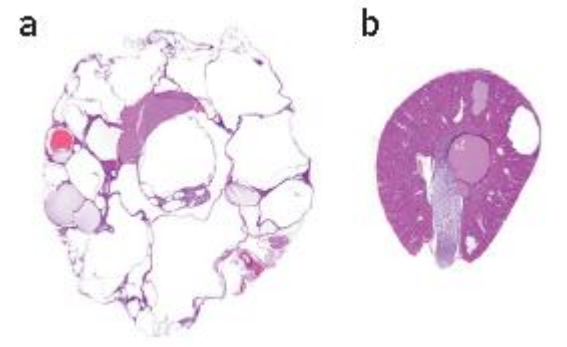


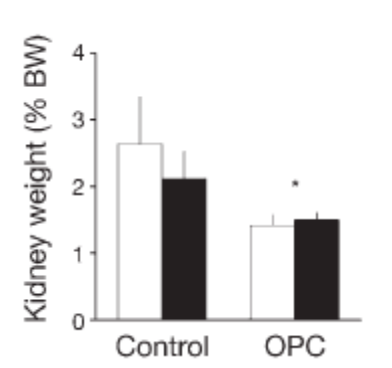


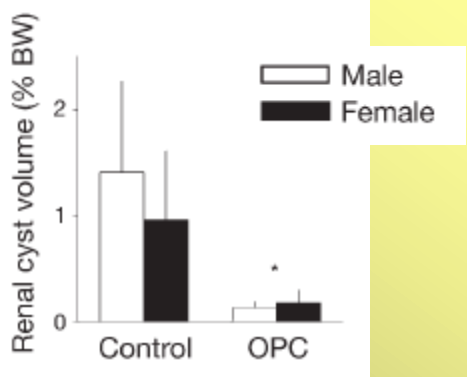
Nature Medicine **9,** 1323 - 1326 (2003)

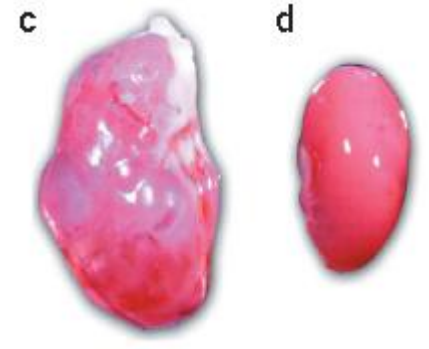
V_2 RECEPTOR ANTAGONISM



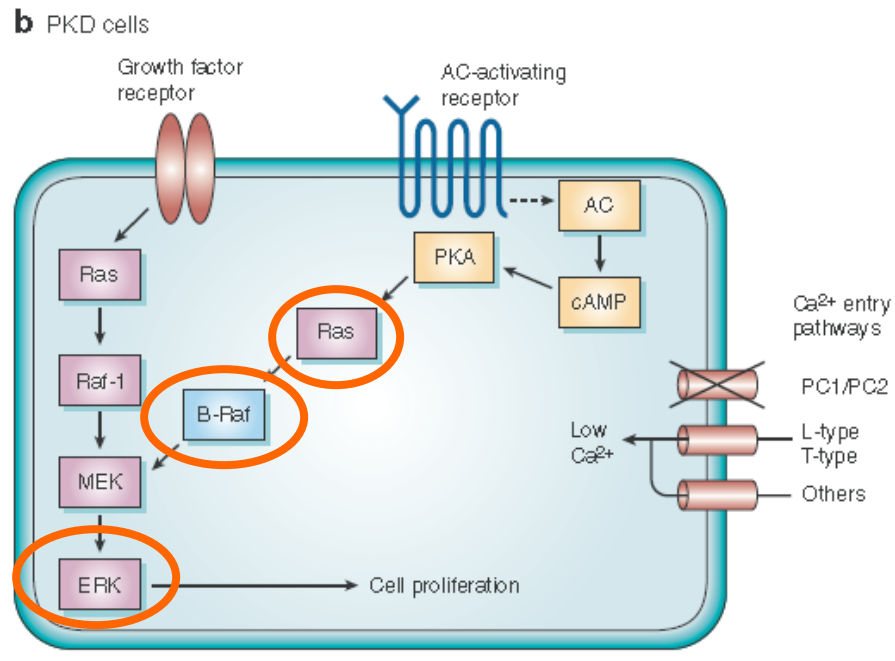


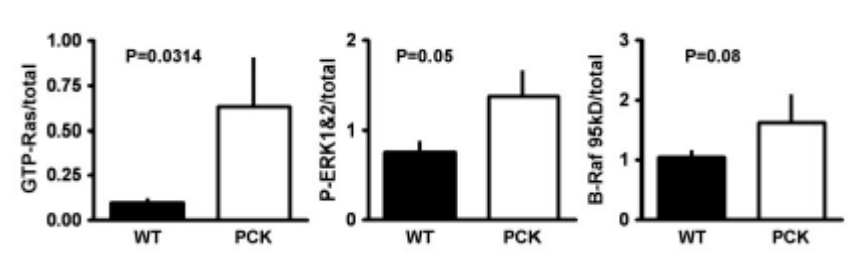


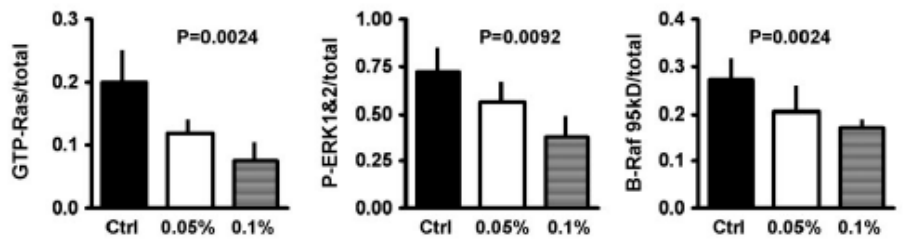


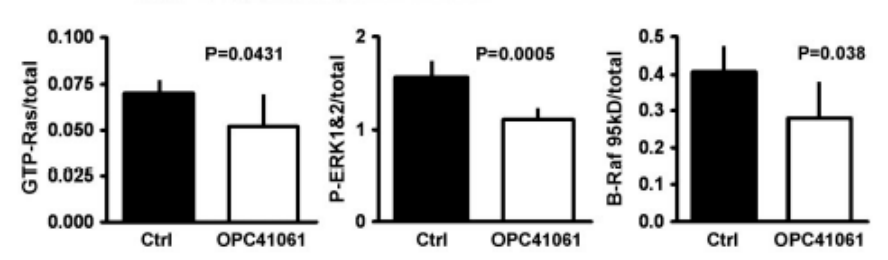


MAP KINASE CASCADE AND V_2-RECEPTOR ANTAGONIST









J Am Soc Nephrol 16: 846-851, 2005

CONCLUSIONS

- ENDOTHELIAL CELL PROLIFERATION AND FLUID SECRETION NECESSARY FOR RENAL CYST FORMATION IN HERITABLE CYSTIC KIDNEY DISEASE RESULTS FROM ALTERED CA HOMEOSTASIS AND INCREASED CAMP SIGNALING
- V2 RECEPTOR ANTAGONISTS DECREASE INTRACELLULAR CAMP
- V2 RECEPTOR ANTAGONISTS ARE ATTRACTIVE AS THERAPY BECAUSE OF THEIR RENAL SELECTIVITY
- V2 RECEPTOR ANTAGONISTS CAN BE SAFELY ADMINISTERED BASED ON PRECLINICAL AND CLINCAL DATA IN OTHER DISEASES (CHF, CIRRHOSIS)

TOLVAPTAN INTERACTION WTH V_1 & V_2 RECEPTORS

- ANTAGONISM TO AVP BINDING:
  - UP TO 300-FOLD INCREASE CONCENTRATION FOR V_1 RECEPTORS
- PLATELET AGGREGATION (MEDIATED BY V_{1a})
  - INHIBITS AVP-INDUCED AGGREGATION BUT NOT ADP-INDUCED AGGREGATION
  - TOLVAPTAN DOES NOT INDUCE AGGREGATION
- DOSE DEPENDENT INCREASE IN URINE VOLUME AND DECREASE IN URINE OSM
  - NO TOLERANCE
  - PARTIAL AGONISTIC WAS NOT DEMONSTATED
- CORRECTS HYPONATREMIA IN MODELS OF CIRRHOSIS, CHF, HYPONATREMIA

TOLVAPTAN STUDY

Primary Objective:

- Evaluate long-term efficacy of tolvaptan in ADPKD through rate of renal volume change (%) for tolvaptan-treated compared to placebo-treated subjects

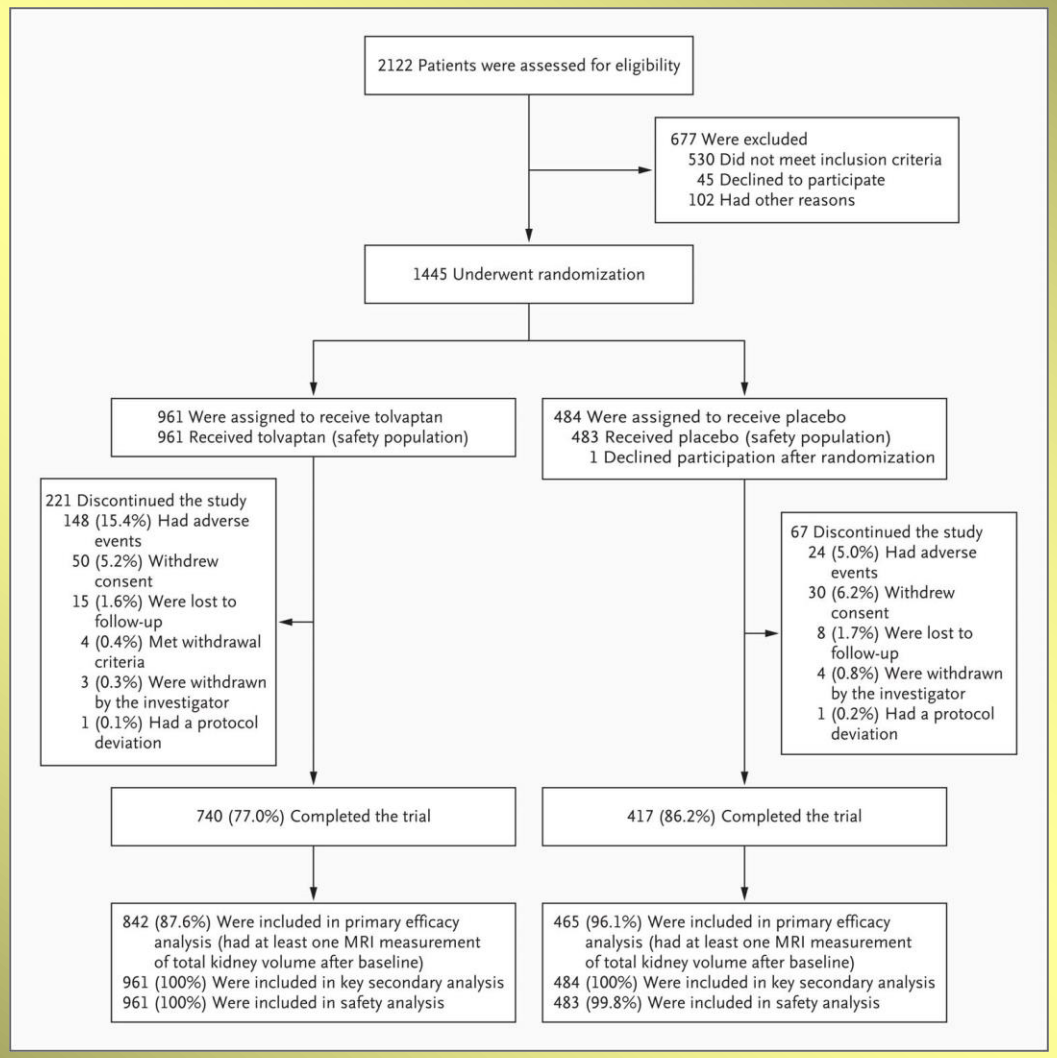
Secondary Objectives:

- Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (ie, hypertension, renal pain, albuminuria and renal function)
- Evaluate long-term efficacy of tolvaptan in ADPKD using single clinical markers of ADPKD progression
- Evaluate long-term safety of tolvaptan through standard clinical measures
- Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD

TOLVAPTAN STUDY

- PHASE 3 TRIAL
- PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM TRIAL IN PATIENTS WITH APCKD
- 1200-1500 SUBJECTS STUDIED FOR UP TO 36 MONTHS
- SUBJECTS STRATIFIED FOR GFR, RENAL SIZE AND HYPERTENSION

Patient Enrollment and Outcomes.



Torres VE et al. N Engl J Med 2012;367:2407-2418

Demographic and Clinical Characteristics of the Patients at Baseline.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

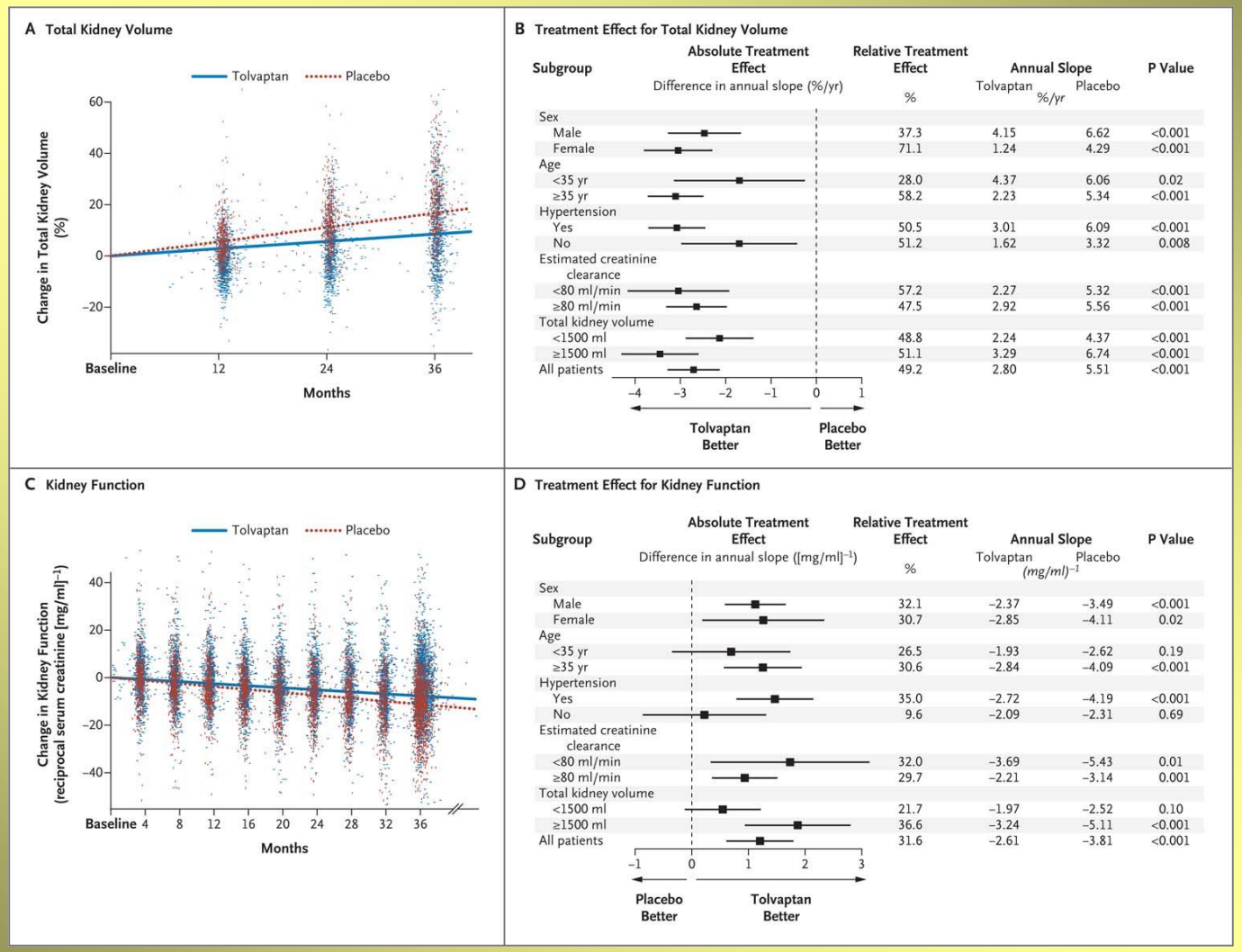
Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)
Male sex — no. (%)	495 (51.5)	251 (51.9)
Age — yr	39±7	39±7
Race — no. (%)†		
White	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Stratification factor — no. (%)		
Hypertension	765 (79.6)	382 (78.9)
Estimated creatinine clearance <80 ml/min	242 (25.2)	130 (26.9)
Total kidney volume <1000 ml	197 (20.5)	101 (20.9)
Medical history — no. (%)		
Hematuria	338 (35.2)	164 (33.9)
Kidney pain	496 (51.6)	239 (49.4)
Nephrolithiasis	187 (19.5)	109 (22.5)
Urinary tract infection	290 (30.2)	164 (33.9)
Anemia	105 (10.9)	48 (9.9)
Proteinuria	233 (24.2)	116 (24.0)
Current medication — no. (%)		
Angiotensin-converting–enzyme inhibitor	419 (43.6)	199 (41.1)
Angiotensin-receptor blocker	307 (31.9)	165 (34.1)
Angiotensin-converting–enzyme inhibitor, angiotensin-receptor blocker, or both	683 (71.1)	350 (72.3)
Beta-blocker	171 (17.8)	94 (19.4)
Calcium-channel blocker	180 (18.7)	104 (21.5)
Diuretic	32 (3.3)	14 (2.9)
Height — cm	173.5±10.4	173.6±7.8
Weight — kg	79±18	79±18
Blood pressure — mm Hg		
Systolic	128.6±13.5	128.3±13.5
Diastolic	82.5±9.9	82.5±9.3
Total kidney volume — ml	1705±921	1668±873
Height-adjusted total kidney volume — ml/m	979±515	958±483
Serum creatinine — mg/dl‡	1.05±0.30	1.04±0.32
Reciprocal of serum creatinine — $(mg/ml)^{-1}$	102.27±27.21	104.30±35.60
Estimated creatinine clearance — ml/min§	104.08±32.76	103.80±35.60
Estimated GFR — ml/min/1.73 m^2¶	81.35±21.02	82.14±22.73
Urinary albumin-to-creatinine ratio‖	7.2±14.3	8.6±21.7

* Plus–minus values are means ±SD. No significant between-group differences were found for any of the baseline characteristics. GFR denotes glomerular filtration rate.
† Race was self-reported.
‡ To convert values for creatinine to micromoles per liter, multiply by 88.4.
§ The estimated creatinine clearance was measured with the use of the Cockcroft–Gault formula.
¶ Estimated GFR was measured with the use of the Chronic Kidney Disease Epidemiology Collaboration equation adjusted for race.
‖ For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams per deciliter and creatinine in millimoles per deciliter.

Torres VE et al. N Engl J Med 2012;367:2407-2418

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume and Kidney Function.

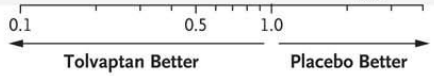


Torres VE et al. N Engl J Med 2012;367:2407-2418

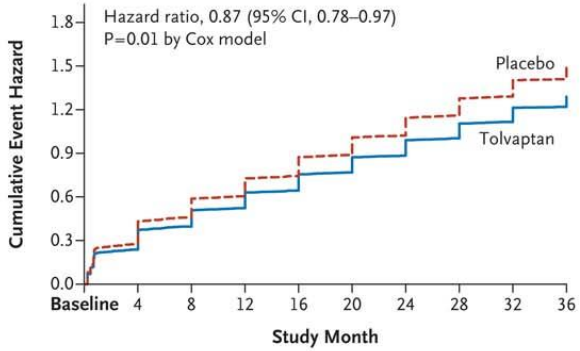
Effect of Tolvaptan on the Time to Multiple Events Associated with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

A Effects of Tolvaptan

End Point	Hazard Ratio (95% CI)	No. of Subjects	No. of Total Events	Events/100 Person-Yr	P Value
ADPKD-related composite					0.01
Tolvaptan group		961	1049	44	
Placebo group		483	665	50	
Worsening hypertension					0.42
Tolvaptan group		961	734	31	
Placebo group		483	426	32	
Worsening albuminuria					0.74
Tolvaptan group		961	195	8	
Placebo group		483	103	8	
Clinically significant kidney pain					0.007
Tolvaptan group		961	113	5	
Placebo group		483	97	7	
Worsening kidney function					<0.001
Tolvaptan group		918	44	2	
Placebo group		476	64	5	

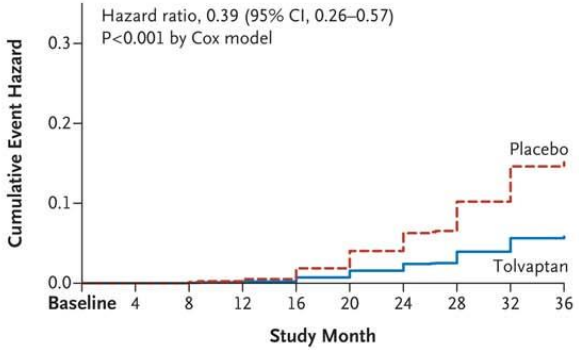


B Risk of ADPKD-Related Composite Events



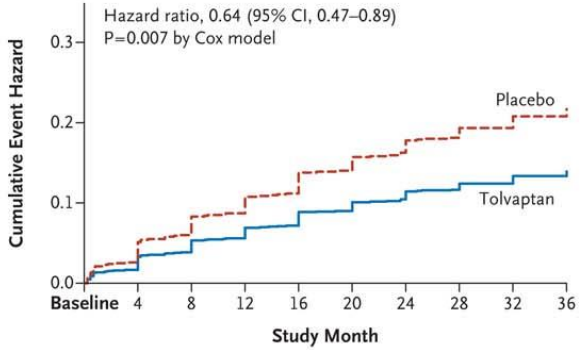
No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

C Risk of Worsening Kidney Function



No. at Risk										
Tolvaptan	918	868	833	809	791	775	762	751	743	641
Placebo	476	470	461	452	444	436	426	420	416	357

D Risk of Clinically Significant Kidney Pain



No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

Torres VE et al. N Engl J Med 2012;367:2407-2418

Most Common Adverse Events and Serious Adverse Events.

Table 2. Most Common Adverse Events and Serious Adverse Events.*

Event	Tolvaptan (N = 961)	Placebo (N = 483)
	no. of patients with event (%)	
Adverse events more common in tolvaptan group		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Diarrhea	128 (13.3)	53 (11.0)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)†	17 (3.5)
Adverse events more common in placebo group		
Hypertension	309 (32.2)	174 (36.0)
Renal pain	259 (27.0)§	169 (35.0)
Nasopharyngitis	210 (21.9)	111 (23.0)
Back pain	132 (13.7)	88 (18.2)
Increased creatinine level	135 (14.0)	71 (14.7)
Hematuria	75 (7.8)†	68 (14.1)
Urinary tract infection	80 (8.3)§	61 (12.6)
Nausea	98 (10.2)	57 (11.8)
Serious adverse events more common in tolvaptan group		
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
Serious adverse events more common in placebo group		
Pyelonephritis	5 (0.5)	5 (1.0)
Renal-cyst infection	6 (0.6)	4 (0.8)
Renal-cyst hemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Appendicitis	1 (0.1)	4 (0.8)
Nephrolithiasis	2 (0.2)	3 (0.6)
Urinary tract infection	1 (0.1)	3 (0.6)
Hypertension	1 (0.1)	3 (0.6)

* Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
† P<0.001 by Fisher's exact test, as compared with the placebo group.
‡ Pollakiuria is more commonly called urinary frequency.
§ P<0.05 by Fisher's exact test, as compared with the placebo group.

Torres VE et al. N Engl J Med 2012;367:2407-2418

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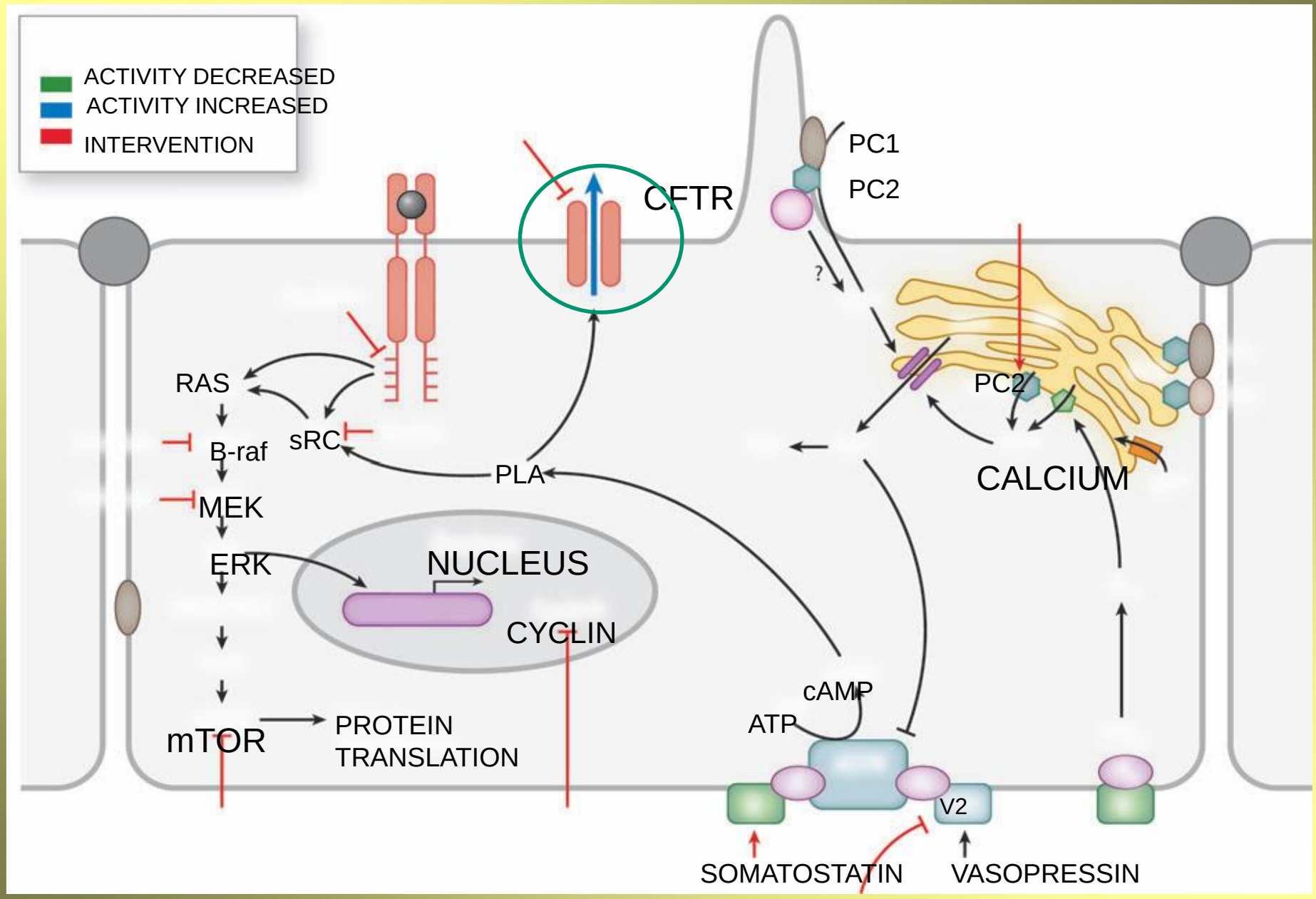
OTHER TRIALS

HALT/PKD STUDY

- TO EXAMINE THE EFFECT OF INTENSIVE RAAS BLOCKADE AND BLOOD PRESSURE CONTROL ON PROGRESSION OF APCKD
- 2 PARALLEL STUDIES:
  - A. CKD I-II DESIGN- 2X2 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL vs LOW BLOOD PRESSURE. PRIMARY OUTCOME IS CHANGE IN KIDNY SIZE OVER 5 YEARS
  - B. CKD III DESIGN- 2X1 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL. PRIMARY OUTCOME IS RATE OF PROGRESSION OF RENAL FAILURE (50% REDUCTION IN MDRD eGRF, DDT) OVER 5 YEARS
- STUDY A: n = 550; STUDY B: n = 470


ACTIVITY DECREASED
ACTIVITY INCREASED
INTERVENTION
CFTR
PC1
PC2
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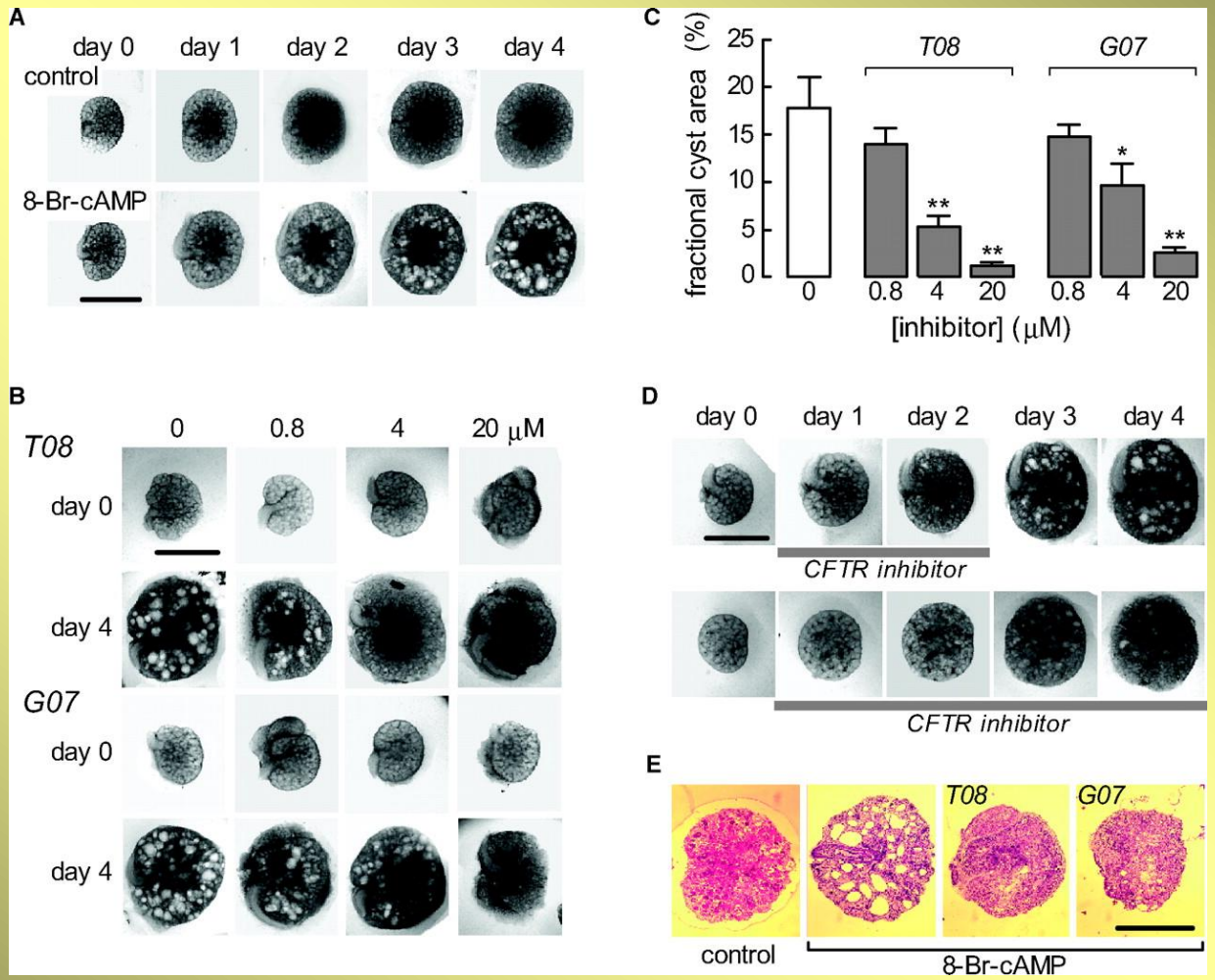
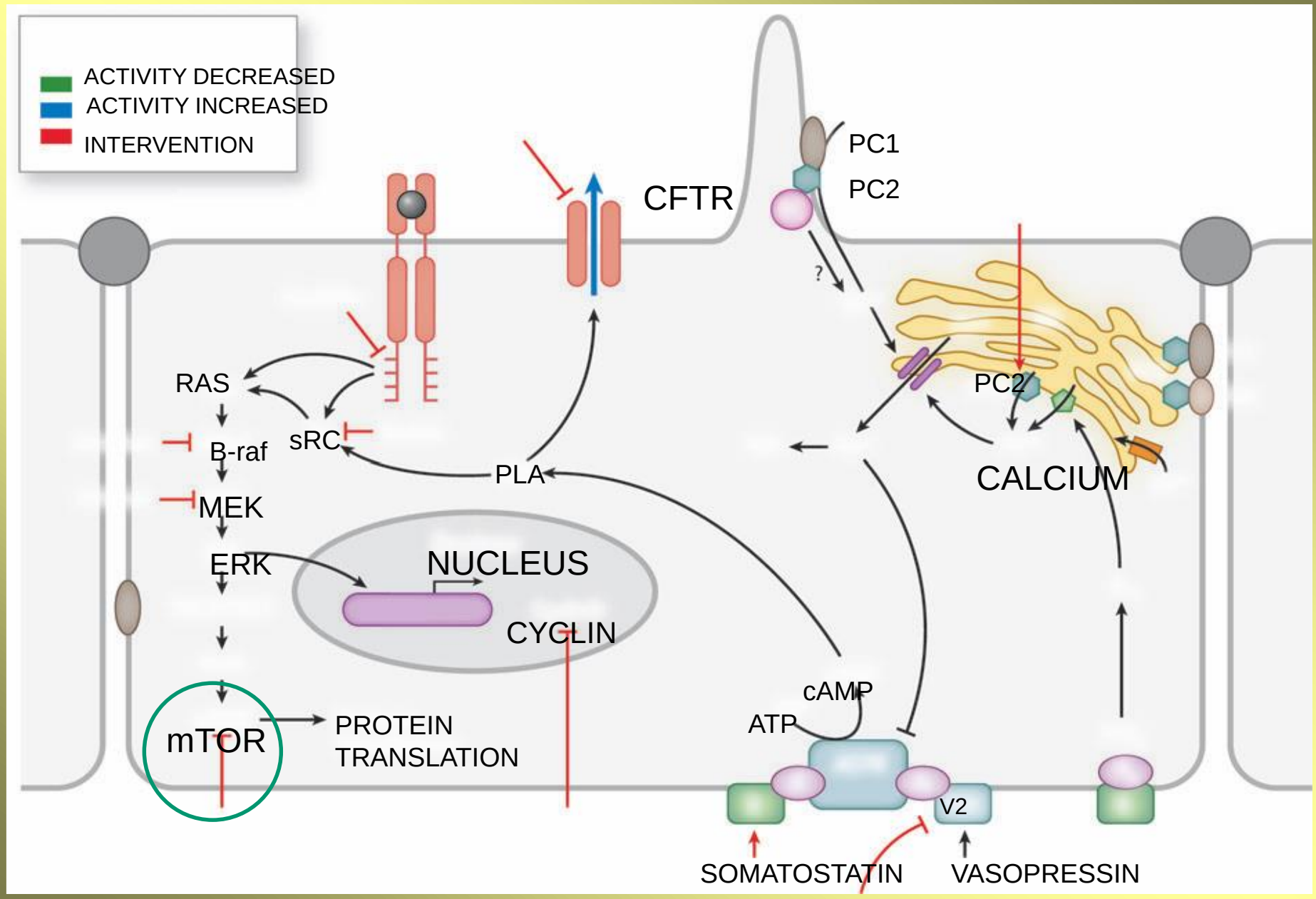
PC2
CALCIUM
RAS
B-raf
sRC
MEK
ERK
PLA
NUCLEUS
CYCLIN
mTOR
PROTEIN
TRANSLATION
cAMP
ATP
V2
SOMATOSTATIN
VASOPRESSIN

Figure 5. CFTR inhibitors slow cyst growth in embryonic kidney organ cultures



Yang, B. et al. J Am Soc Nephrol 2008;19:1300-1310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PROTEIN
TRANSLATION
cAMP
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V2
SOMATOSTATIN
VASOPRESSIN

EVEROLIMUS

WALZ ET AL NEJM 2010; 363:830-840

- 433 SUBJECTS
- EVEROLIMUS vs PLACEBO
- KIDNEY SIZE @ BASELINE, 12, 24 MONTHS
- TOTAL KIDNEY SIZE WITH EVEROLIMUS LESS THAN PLACEBO AT 12 MONTHS
- NO DIFFERENCE IN RENAL FUNCTION

SIROLIMUS

SERRA ET AL NEJM 2010; 363: 820-829

- 100 SUBJECTS
- SIROLIMUS vs STANDARD CARE
- 18 MONTHS, RANDOMIZED, OPEN LABEL
- NO DIFFERENCE IN RENAL SIZE OR RENAL FUNCTION

FOLATE-CONGUGATED RAPAMYCIN

SHILLINGFORD ET AL JASN 2010; 10:1674-81

- SIROLIMUS CONCENTRATIONS IN THE RENAL EPITHELIAL CELL MAY BE TOO LOW TO INFLUENCE PROLIFERATION
- THESE CELLS HAVE RECEPTORS FOR FOLATE
- CONGUGATING FOLATE TO THE DRUG MAY ENHANCE ITS UPTAKE BY THE CELLS

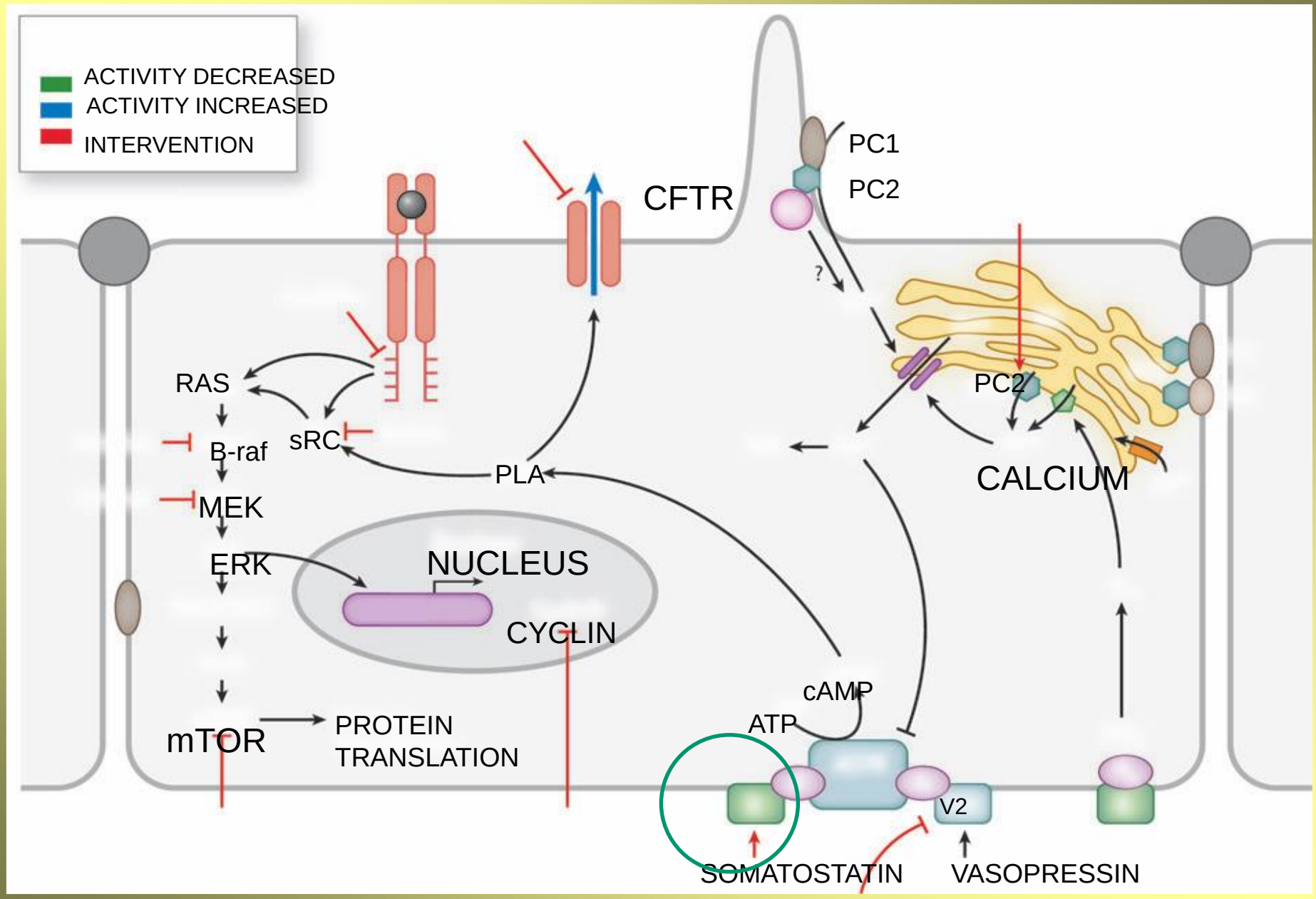
ACTIVITY DECREASED
ACTIVITY INCREASED
INTERVENTION
CFTR
PC1
PC2
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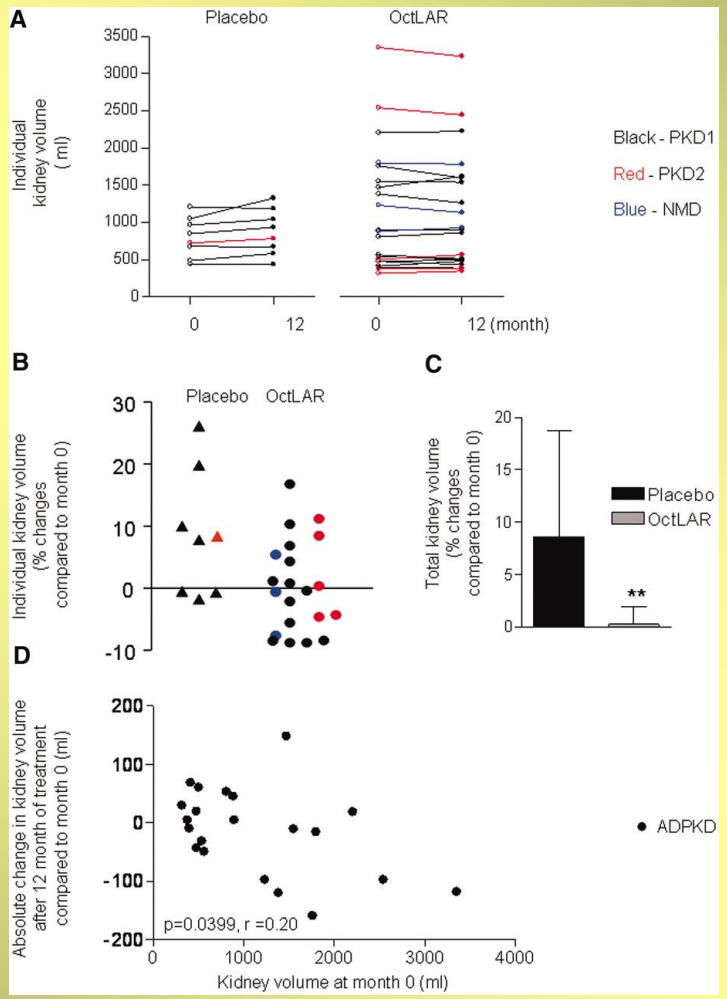
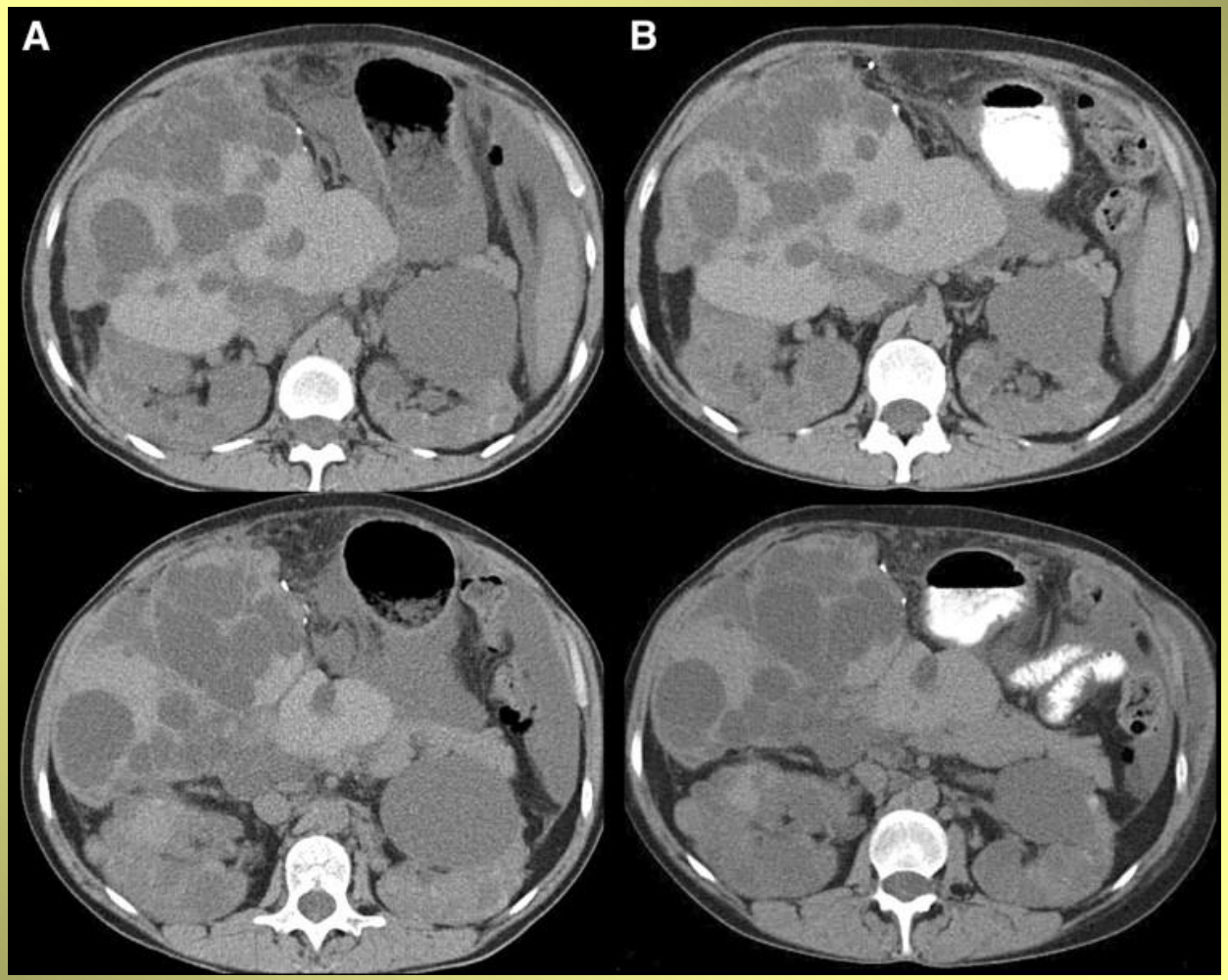
Figure 4. Octreotide therapy (OctLAR) stalled kidney growth in treated individuals



Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

Figure 1. Administration of octreotide LAR to a patient with severe PLD resulted in decreased liver and kidney volumes



Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

CONCLUSION

- UNDERSTANDING THE SIGNALS THAT PROMOTE CELL PROLIFERATION AND GOVERN SECRETION INTO THE CYSTS WILL EVENTUALLY LEAD TO INTERVENTIONS TO SLOW THE PROGRESSION OF APCKD