

New treatments for Autosomal Dominant Polycystic Kidney Disease

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Faculty/Presenter Disclosure

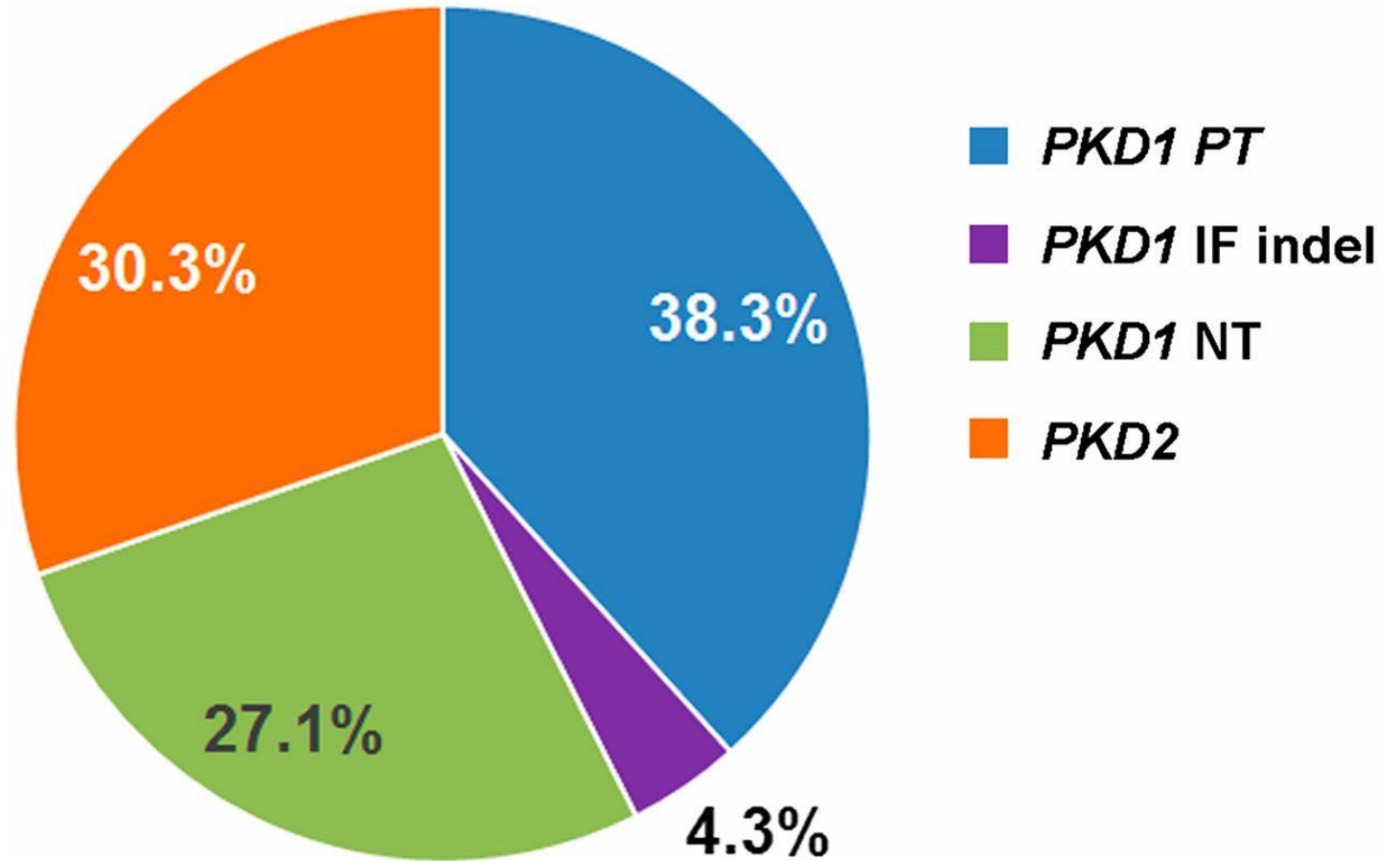
- **Faculty:** Matthew Lanktree MD, PhD, FRCPC
- **Relationships with financial sponsors:**
 - **Grants/Research Support:** American Society of Nephrology, Canadian Society of Nephrology, Canadian Institutes of Health Research, and Canadian Kidney Foundation
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 - **Consulting Fees:** Otsuka
 - **Patents:** None
 - **Other:** None

Objectives

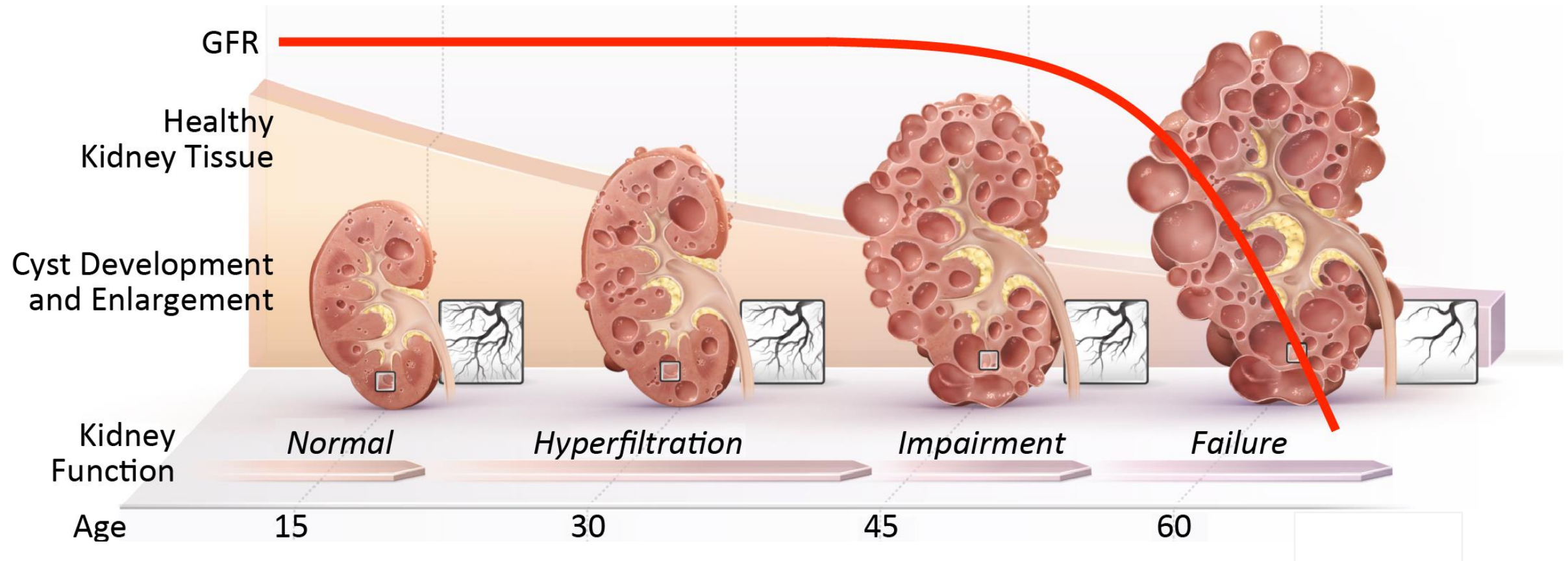
- Summary of ADPKD
- Precision medicine approach to ADPKD
- Conservative treatments for ADPKD
- Strategies currently under study:
 - Vaptans (tolvaptan, lixivaptan)
 - mTOR inhibitors (everolimus, sirolimus)
 - Somatostatin (lantreotide, pasireotide, octreotide)
 - Tyrosine kinase inhibitors (bosutinib, tesevatinib)
 - Glucose metabolism (metformin, salsalate)
 - Glucosylceramide inhibitor (venglustat)
 - Bardoxolone
 - Cyst sclerotherapy

ADPKD is bad luck

- ~1 in 1000
- 70% have kidney failure by age 70



Natural History of ADPKD



GFR: glomerular filtration rate.

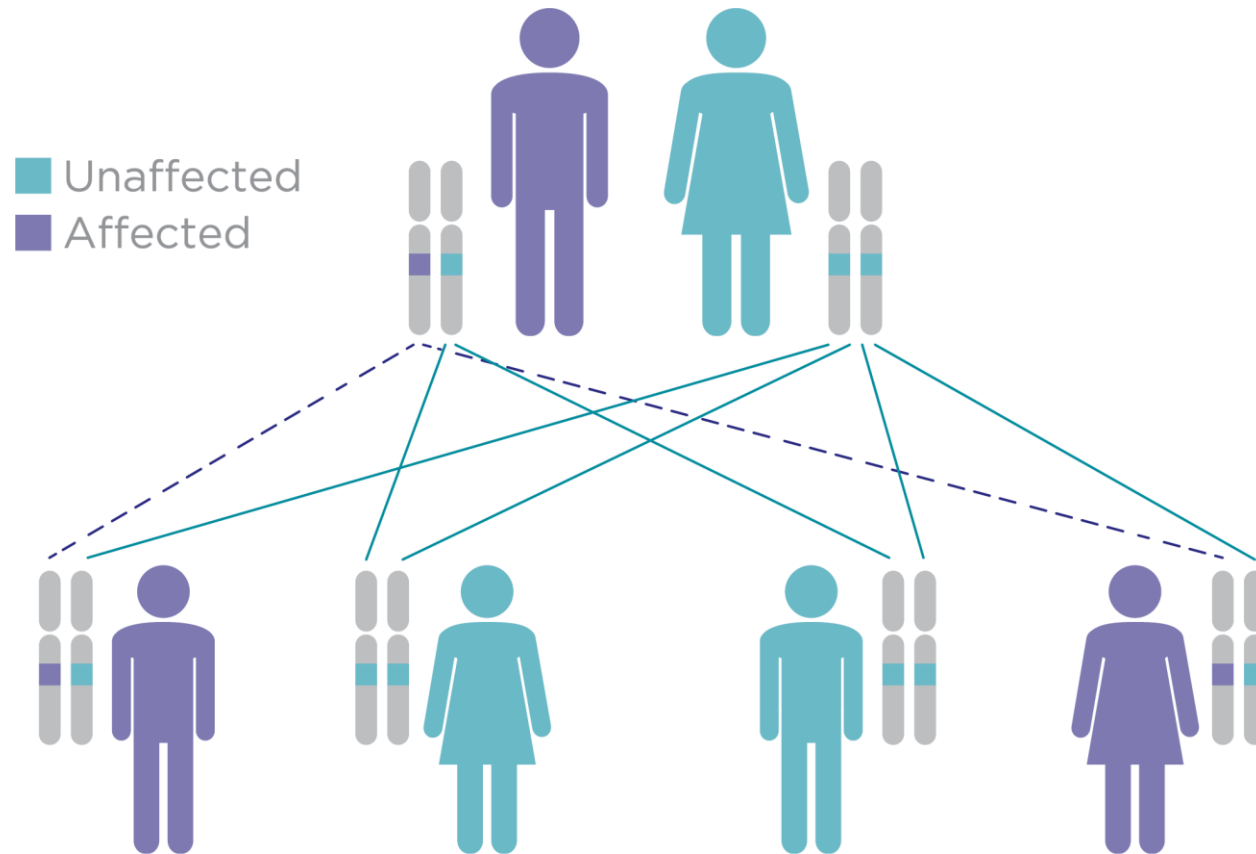
Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. *N Engl J Med* 2006; 354(20):2122-30.

Renal and Extrarenal Manifestations of ADPKD

Manifestation	Incidence in adults with ADPKD
Hematuria	42%
Urine concentration defects	100%
Proteinuria	18%
Microalbuminuria	19-40%
Hepatic cysts	85-94%
Intracranial aneurysms	5-10%
Mitral valve prolapse	26%
Hypertension	~100%
Renal function decline	~100%*
Hypertension before renal function decline	60-75%

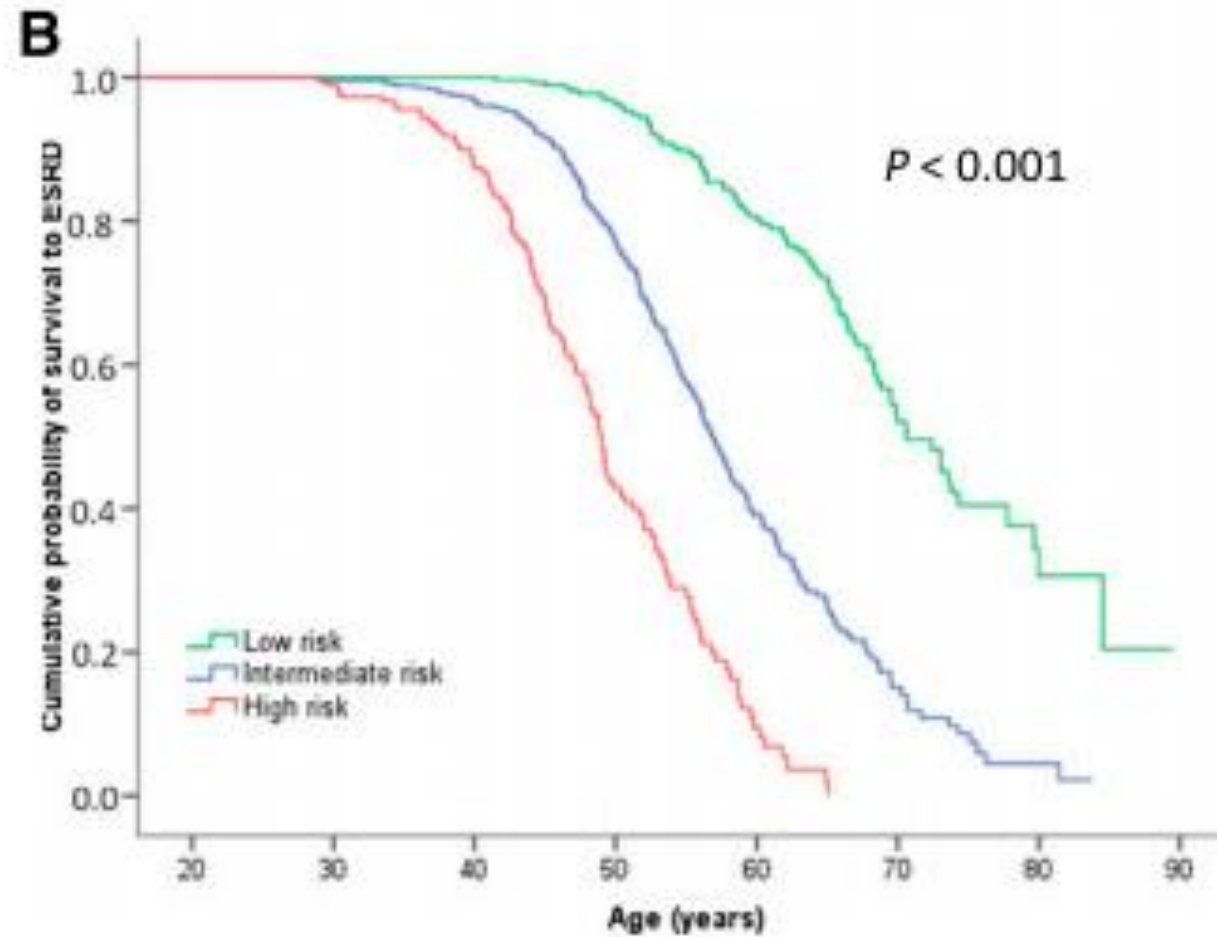
*~70% of patients with ADPKD progress to ESRD at a median age of 58 years

Heritability of ADPKD



~10% of patients with ADPKD have *de novo* disease due to a spontaneous mutation

Variability in ADPKD severity



Precision medicine?

- Classical definition of disease, family history
- Advanced genetic, imaging and biomarker data
- Patient values and preferences
- Stratify risk, maximize therapeutic potential while mitigating therapeutic burden



Conservative strategies

Have plenty of
vegetables and fruits

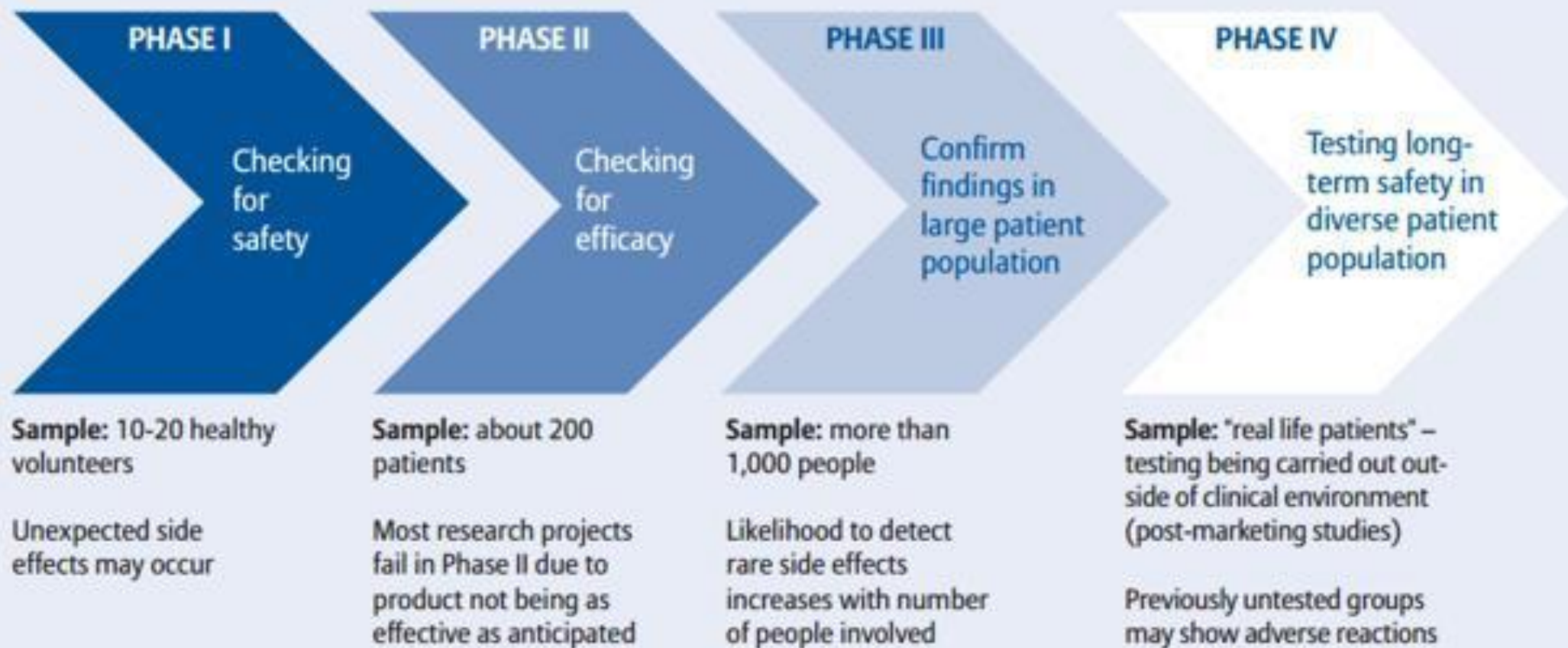
Eat protein foods

Make water
your drink
of choice

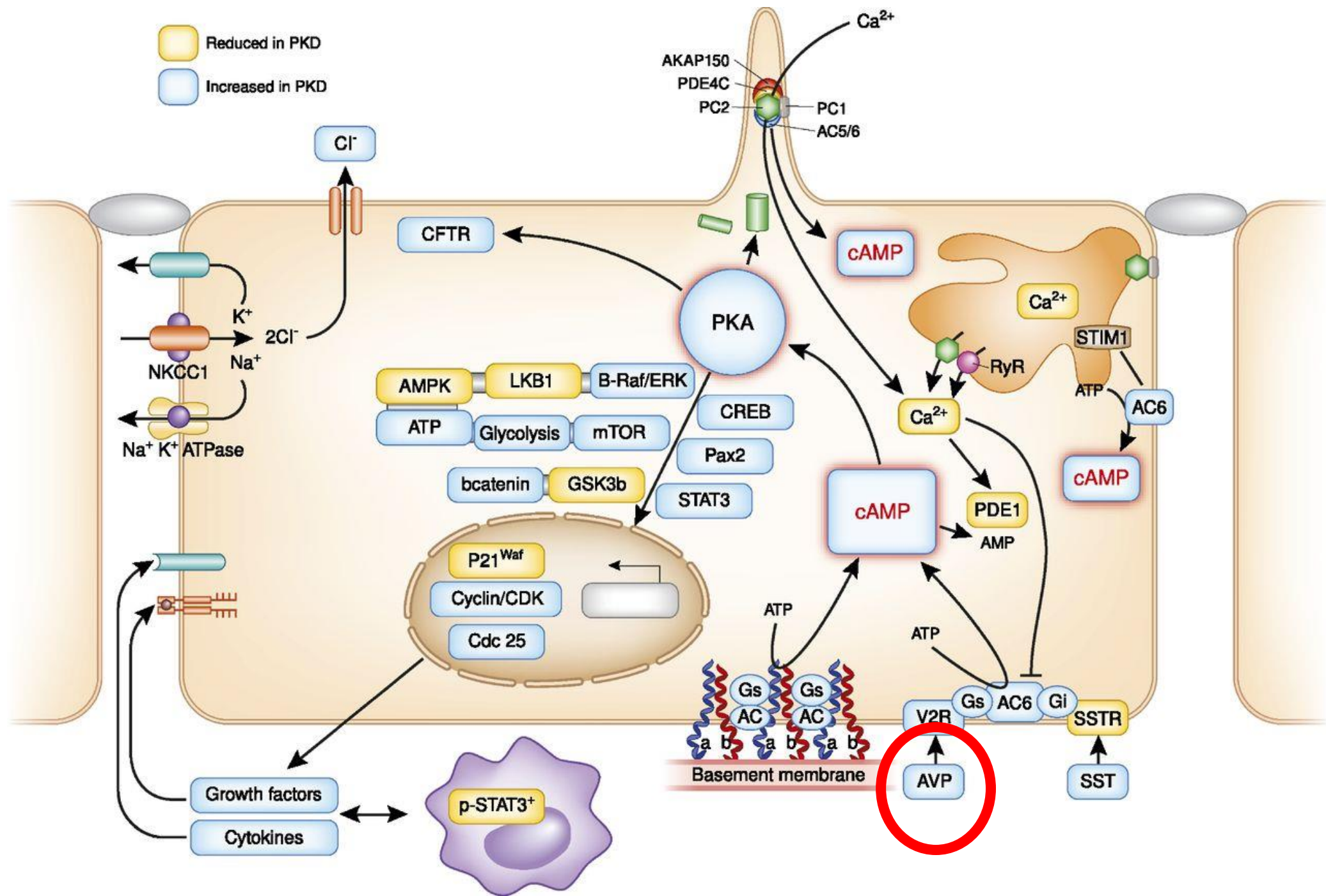
Choose
whole grain
foods



WATCHING YOUR STEP – THE DIFFERENT STAGES OF CLINICAL DEVELOPMENT AND WHAT THEY EXAMINE



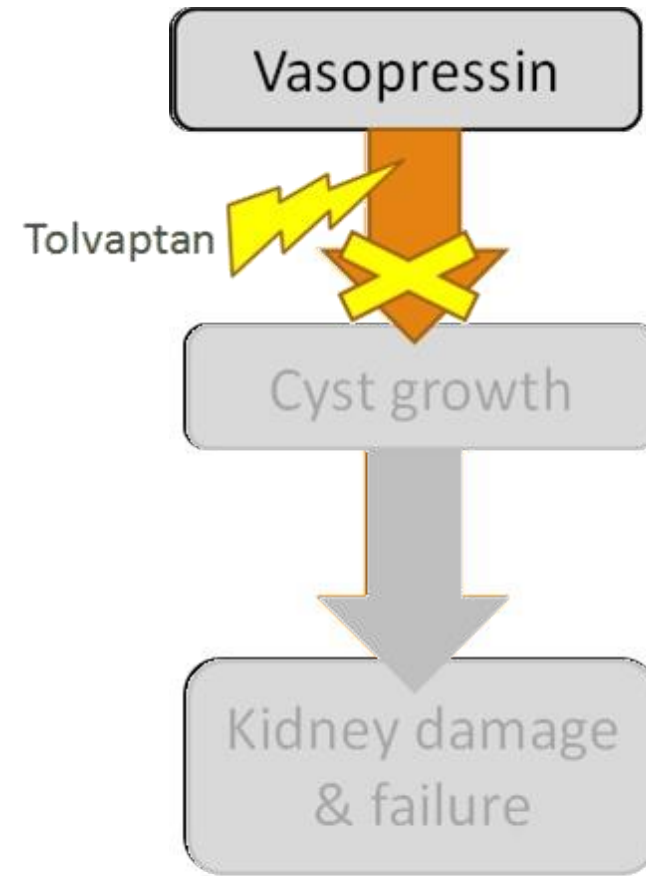
Source: AGCS



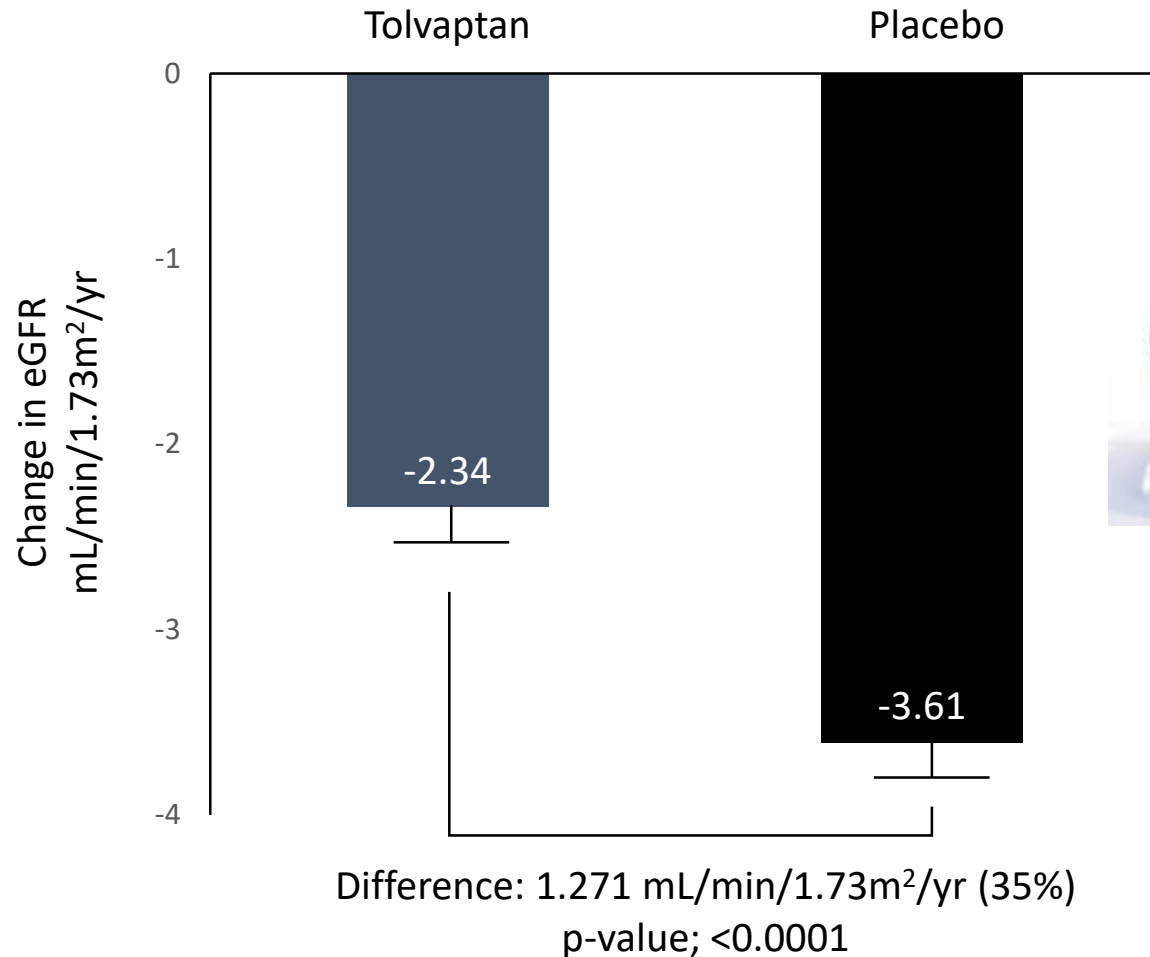


Tolvaptan Mechanism of Action

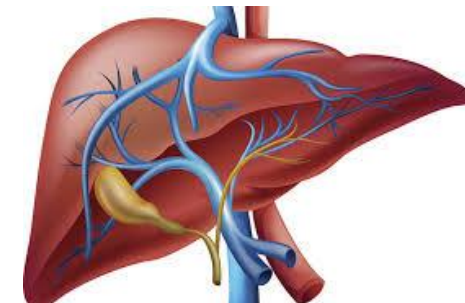
- Vasopressin promotes cyst growth in the kidneys in patients with ADPKD
- Tolvaptan blocks these effects through inhibition of the vasopressin V2 receptor



Tolvaptan: 1-year change in kidney function

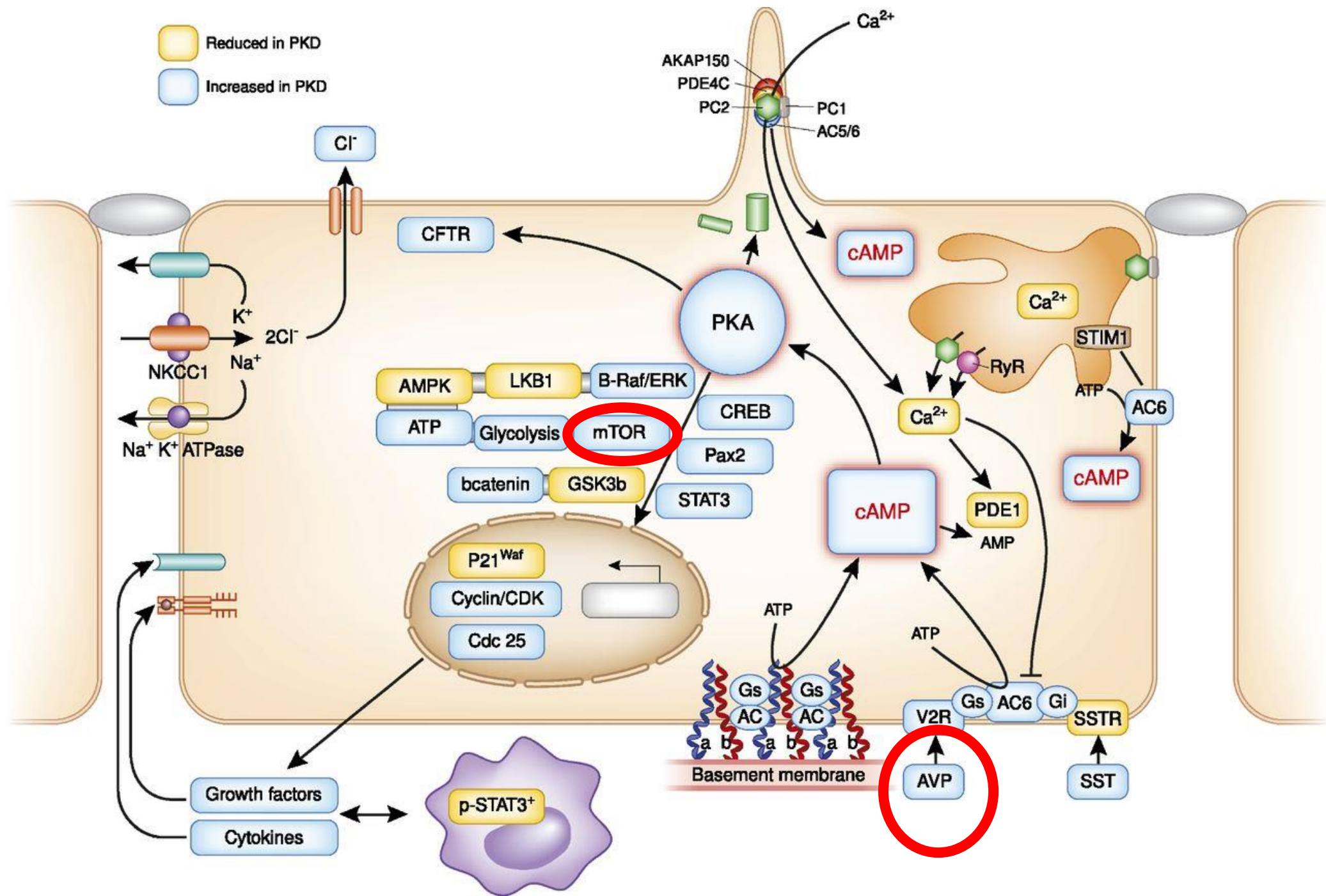


Tolvaptan slowed the rate of kidney function decline by 35% over 1 year compared to placebo.



ELISA trial: Lixivaptan

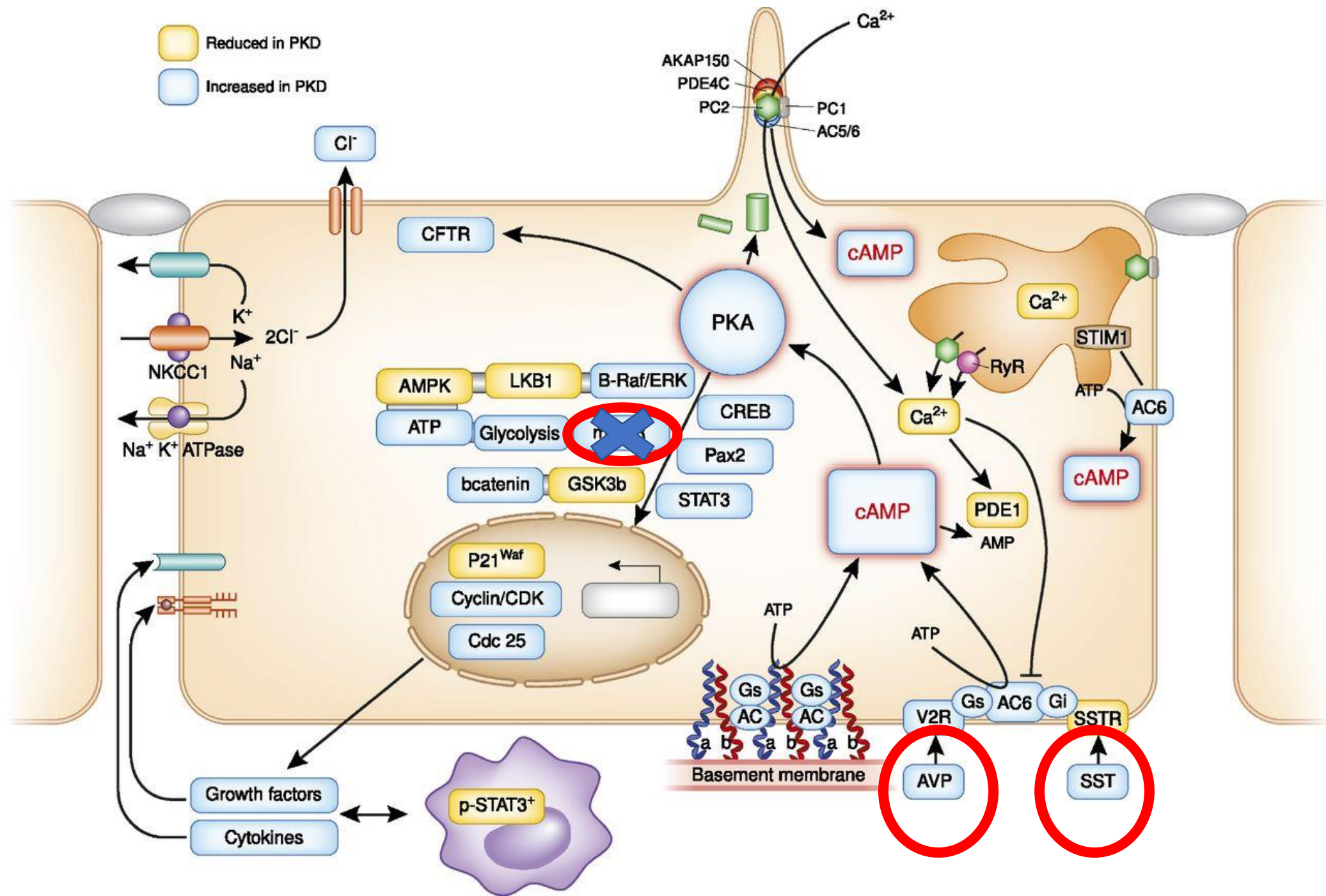
- Same mechanism of action as tolvaptan
- Avoid liver toxicity, less blood work?
- Currently in phase II, end Sept 2019



mTOR inhibitors

- Everolimus (Affinitor), sirolimus (Rapamune)
- Immunosuppressant post kidney transplant
- Cancer treatment
- Tuberous sclerosis complex
- Cardiac stents
- Worked well in pre-clinical studies
- 3 negative trials in ADPKD
- Dose limited by side effects?



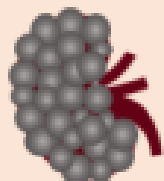



Somatostatin


- Inhibitory hormone secreted by gut
 - Decrease growth hormone, prolactin, insulin and glucagon
 - Decrease thyroid stimulating hormone
 - Decrease cAMP
 - Slows movement of food through intestines
- Analogs: octreotide, lanreotide, pasireotide
- Promising in pre-clinical animal studies and small Phase II clinical trials

Can Lanreotide slow the progression of autosomal dominant polycystic kidney disease? The DIPAK1 trial

 Open label RCT
4 Outpatient clinics

 **n = 309**
eGFR 30-60 ml/min
ADPKD

 Age 48.4 yrs

 Women 53.4%

Randomization

2.5 yr

 **140/90**
Standard care
n = 154

 Lanreotide +
Standard care
n = 155

Primary Outcome

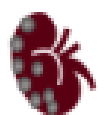
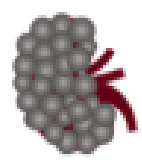

eGFR Decline

-3.46
ml/min/yr
(-3.9, -3.0)

NS

-3.53
ml/min/yr
(-4.0, -3.1)

Secondary Outcome

 
Kidney Volume Growth

5.5%
Per yr

p = 0.02

4.1%
Per yr

 
Quality of life

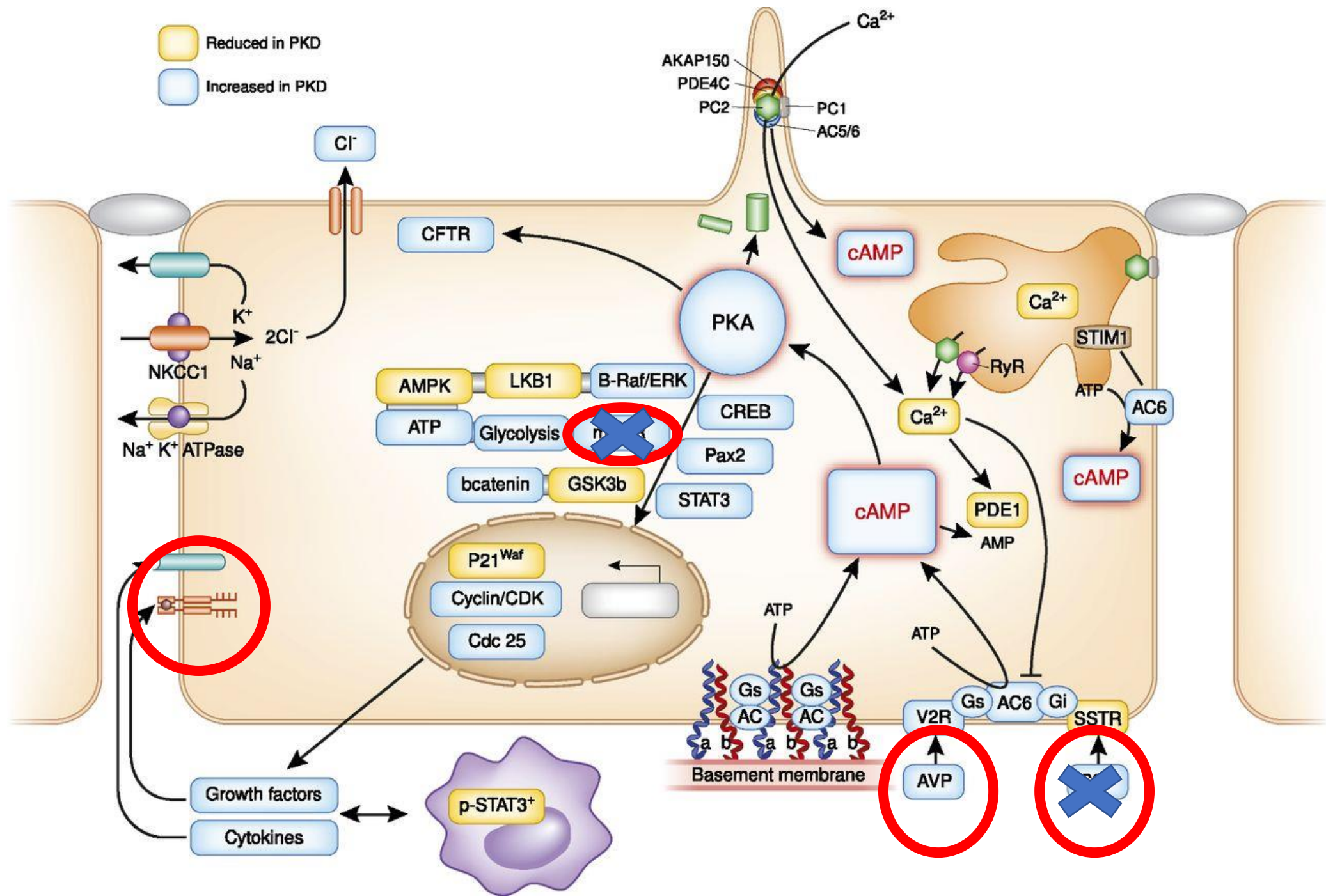
0.07
Composite Score

NS

0.05
Composite Score

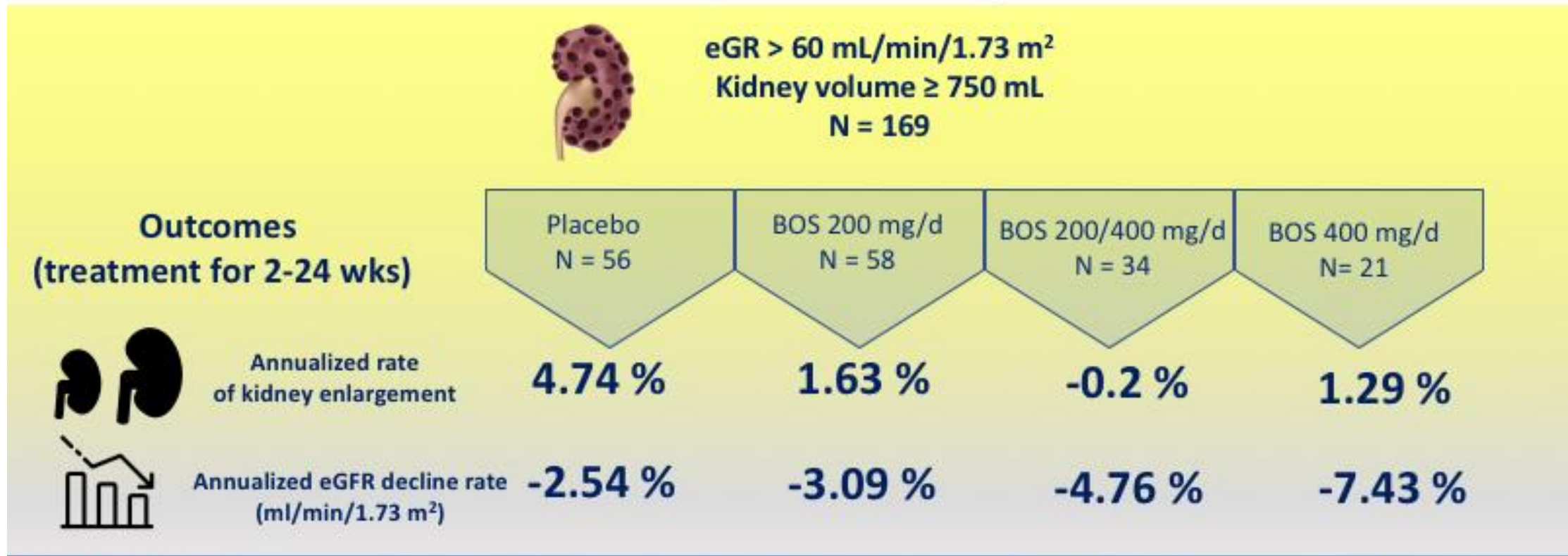
 28% had serious adverse events in Lanreotide group

Conclusion: Lanreotide was not effective in slowing the decline in kidney function in patients with later-stage ADPKD over 2.5 years of follow-up

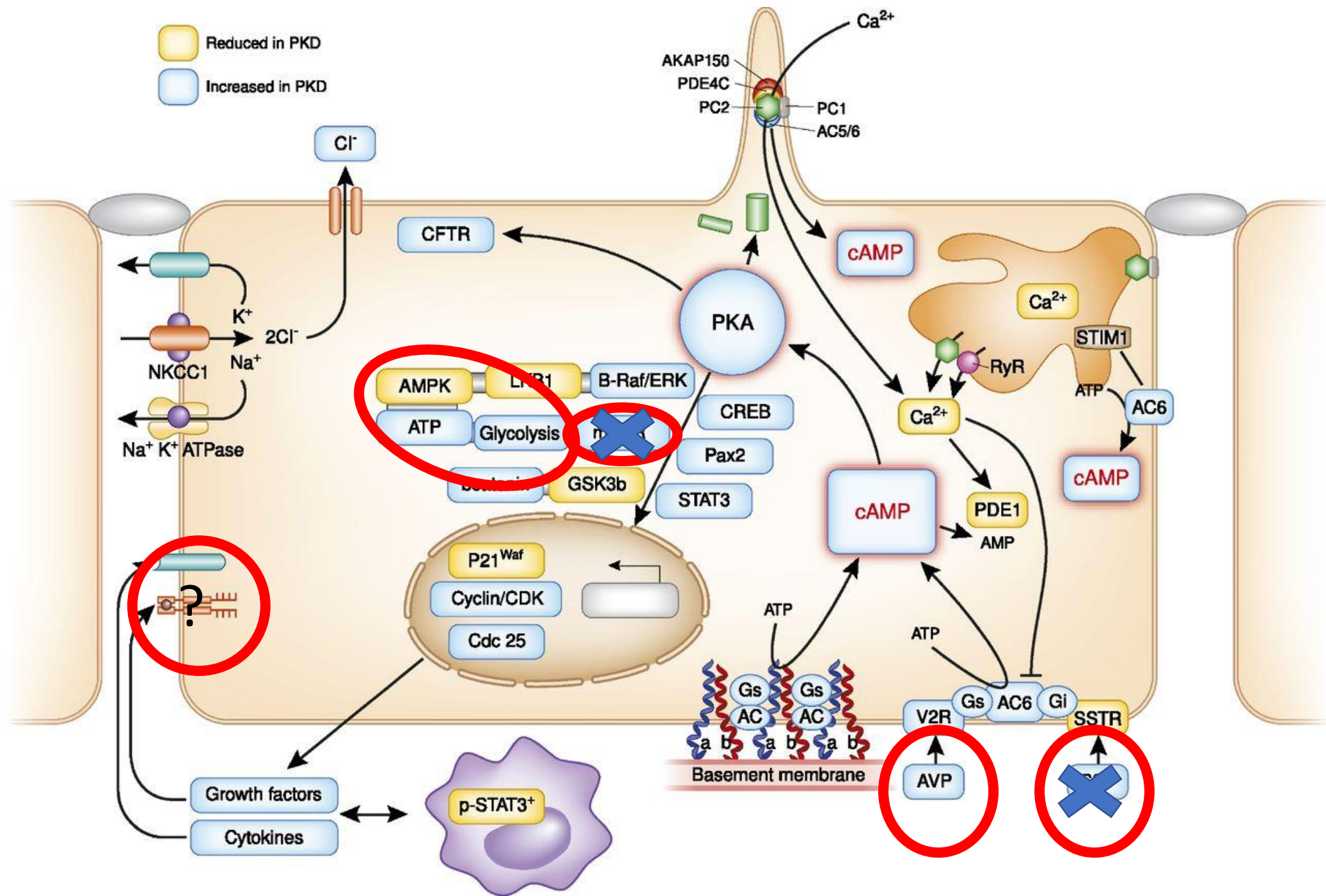


Tyrosine kinase inhibitor in Phase II

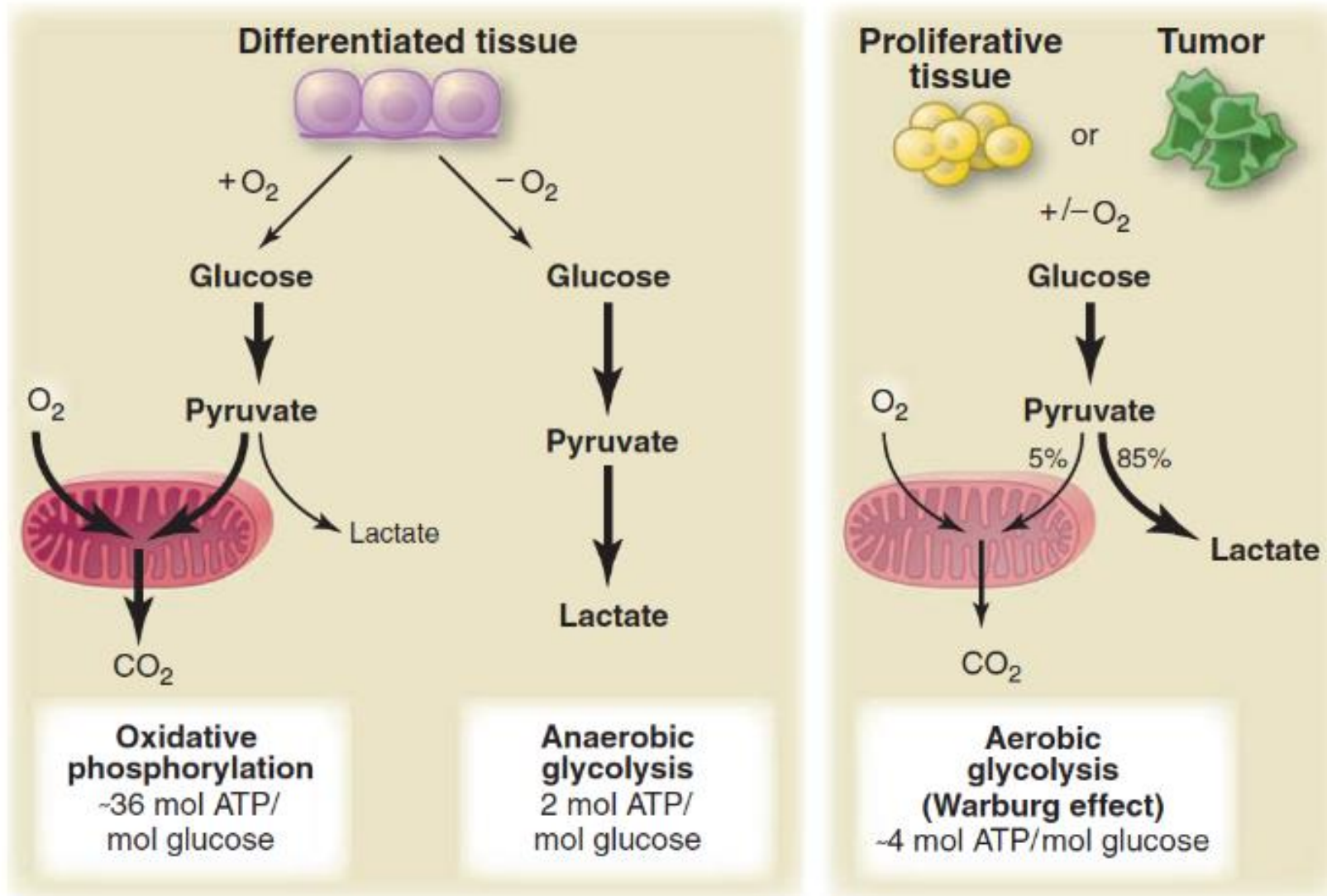
Bosutinib (BOS) vs. Placebo for ADPKD Phase 2, Multisite Study



CONCLUSION: Compared with placebo, bosutinib at 200 mg/d reduced kidney growth in patients with ADPKD (p = 0.01), though the eGFR decline rate was similar (p = 0.71).

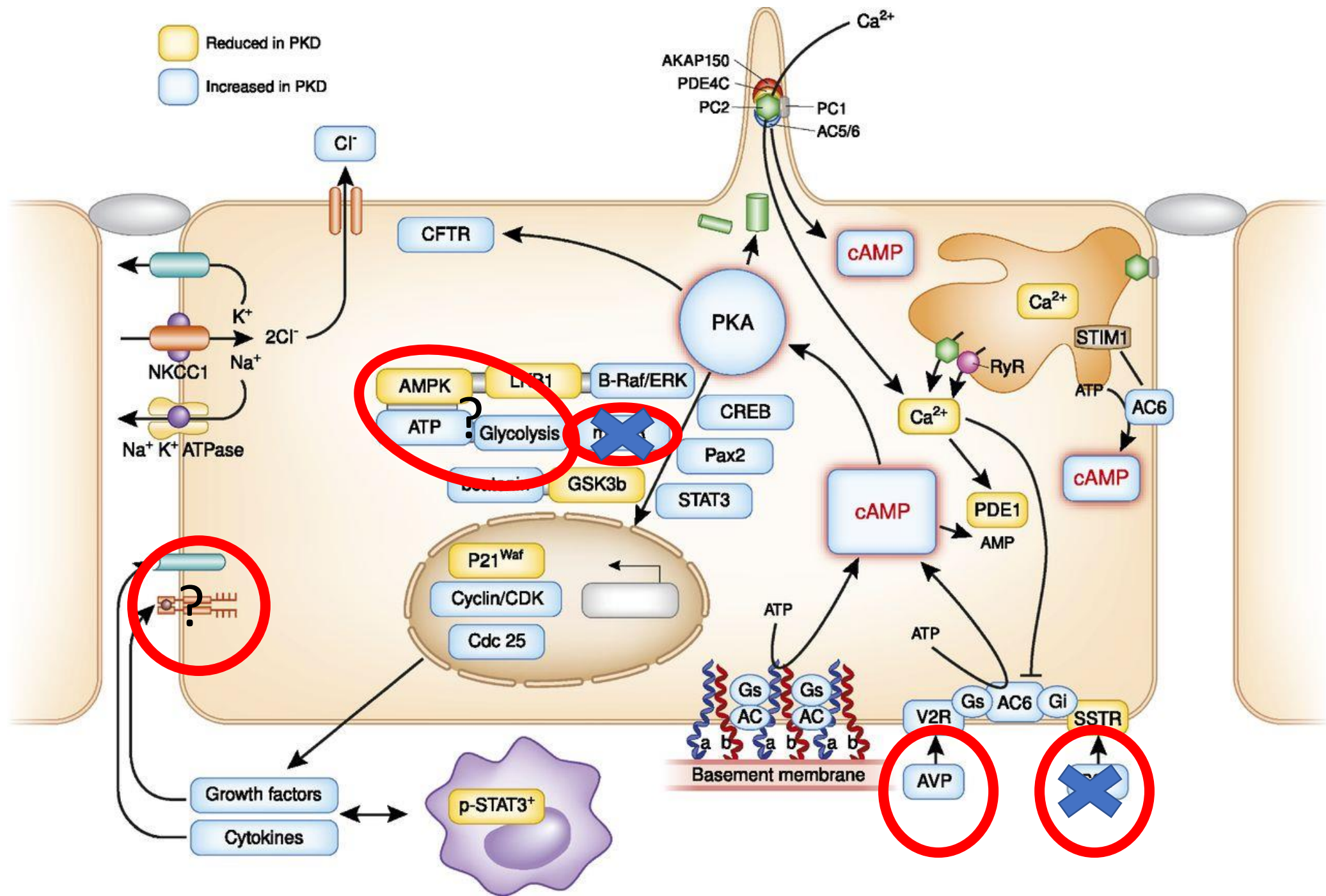


The Warburg Effect



Inhibition of aerobic glycolysis

- Metformin
 - Baltimore: ongoing; placebo; 100 patients; end December 2020
 - Colorado: ongoing; placebo; 50 patients; end March 2020
 - Italy: enrolling; vs. tolvaptan; 150 patients; end Jan 2022
- Pioglitazone
 - Indiana: ongoing; 18 patients; end Oct 2020
- Salsalate (NOT salicylate, ASA, aspirin)
- Intermittent fasting
 - Colorado: recruiting: 40 obese patients; end Sept 2020



Glucosylceramide inhibitor (Venglustat)

- Used to treat Fabry & Goucher disease



- Multi-national Phase II trial 560 patients now enrolling

Bardoxolone

- Activator of Nrf2 pathway (increases production of anti-oxidants)
- Nrf2 is suppressed in chronic inflammation
- Studied in diabetic nephropathy, Alport syndrome, nephrotic syndrome, IgA nephropathy
- Largest trial stopped early due to concern about cardiac toxicity
- One trial in ADPKD ongoing, expected end August 2019

Cyst sclerotherapy

- Interventional radiology procedure
- >5 cm cysts
- Sodium tetradecyl sulphate (STS)



Statins

- Lower LDL cholesterol, reduce inflammation
- One trial suggested benefit in pediatric population
- Already at elevated cardiovascular risk
- One trial recruiting in Colorado, 250 patients, expected end date December 2021

Water prescription

- Inhibit vasopressin secretion
 - as opposed to blocking vasopressin action like tolvaptan
- When water can be bad?
- PREVENT-ADPKD: multi-national Australian led
 - 3 years, recruiting now, 180 patients; usual vs. prescribed water intake
- DRINK trial: UK
 - 8 weeks, done, 42 patients, feasibility study

Conclusions

- Precision medicine
- Conservative measures
- Tolvaptan?
- More to come...

Vaptans (tolvaptan, lixivaptan)

mTOR inhibitors (everolimus, sirolimus)

Somatostatin (lantreotide, pasireotide, octreotide)

Tyrosine kinase inhibitors (bosutinib, tesevatinib)

Glucose metabolism (metformin, salsalate)

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