Adaptation of a Published Kidney Disease QSP Model to Represent Autosomal-Dominant Polycystic Kidney Disease and Evaluate Treatment Options

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Objectives

Explore treatment options for ADPKD

- Autosomal-dominant polycystic kidney disease (ADPKD) is a genetic disease in which cysts proliferate in the kidney
- Cyst growth affects function and leads to pain, hypertension, and kidney failure
- Tolvaptan, a vasopressin receptor antagonist, reduces cyst growth
- A quantitative systems pharmacology (QSP) model would facilitate better understanding of disease mechanisms and predictions for novel therapies

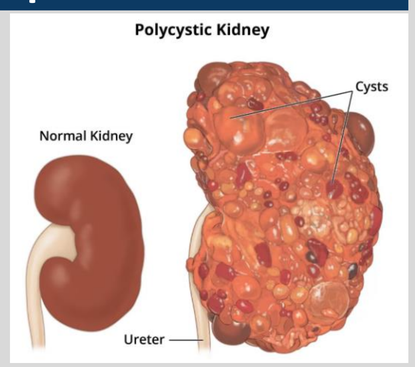

Figure 1. ADPKD effects on kidney morphology[1].

Methods

Adapt published QSP models

- Several QSP models of renal function have previously been published[2,3]
- The models were combined and adapted by:
  1. Reducing scope and complexity where possible
  2. Adding cyst growth dynamics and cyst effects on kidney function
  3. Adding tolvaptan dosing, pharmacokinetics (PK) and mechanism of action
- An ADPKD Virtual Population (VPop) was developed that matched untreated and tolvaptan-treated outcomes

Conclusions

QSP model and VPop enable predictions

- We successfully adapted established models of renal dynamics to include cyst growth and effects on kidney function as observed in ADPKD patients
- Tolvaptan effects were reproduced mechanistically at the population level
- The ADPKD VPop can now be used to:
  - ❖ Predict response to novel therapies for ADPKD
  - ❖ Evaluate short-term biomarkers of longer-term efficacy
  - ❖ Identify patient sub-types
  - ❖ Optimize dosing for the full VPop or specific patient sub-types

QSP Model

Focused ADPKD PhysioPD Platform with tolvaptan

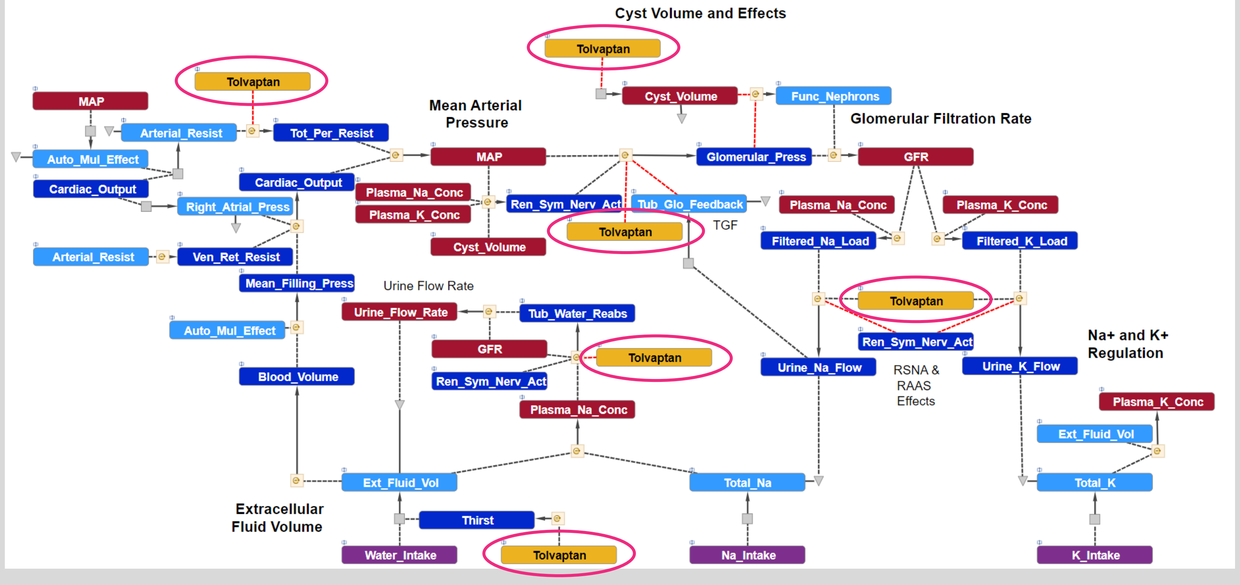

Figure 2. The ADPKD PhysioMap®, a graphical representation of the model, implemented in MATLAB® SimBiology®.

- Published models[2,3] were both simplified and enhanced to focus on biological processes key to ADPKD, including:
  - ○ Cyst growth and effects of functional nephrons on glomerular filtration rate (GFR)
  - ○ Glomerular filtration and tubuloglomerular feedback (TGF) triggered by changes in Na+ filtering, including by tolvaptan
  - ○ Regulation of plasma Na+ and K+ by renin-angiotensin-aldosterone system (RAAS)
  - ○ Regulation of tubular water reabsorption and urine flow
  - ○ Regulation of blood volume and mean arterial pressure
- Tolvaptan effects were included where vasopressin signaling has been shown to play a role (pink ovals on Figure 2)
  - ○ Tolvaptan is an aquaretic drug used to treat hyponatremia
  - ○ Vasopressin and its second messenger adenosine-3′,5′-cyclic monophosphate (cAMP) are promoters of kidney-cyst cell growth
  - ○ Tolvaptan inhibits vasopressin V2R signaling and has been shown to slow cyst growth in ADPKD patients[4]

Results

Clinical trial results and variability are captured

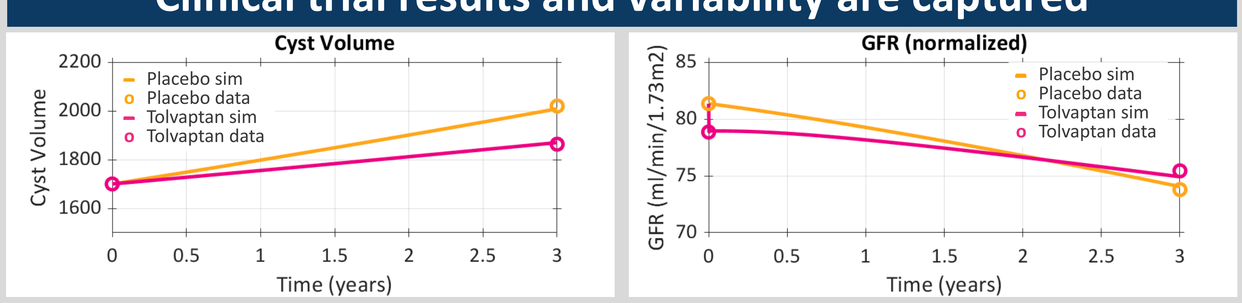

Figure 3. Reference VP time-course plots for cyst volume and GFR.

- Cyst volume was calculated based on total kidney volume, and kidney growth was assumed to derive from cyst growth
- A reference Virtual Patient (VP) was calibrated to the mean response observed in the TEMPO 3/4 clinical trial[4]
- GFR effects of tolvaptan treatment captured both the acute initial drop (due to TGF) and the long-term benefits due to reduction in cyst growth (Figure 3)

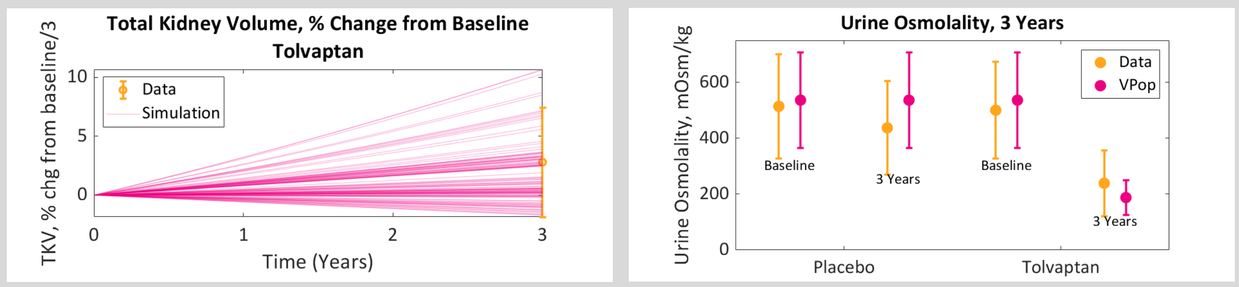

Figure 4. VPs in the VPop had appropriate TKV progression over time (left, data represents mean ± SD for annual slope after 3 years from Torres[4]) and urine osmolality (right, data represents mean ± SD from Devuyst[5]).

- A VPop was generated to match data and have variability in baseline status, sensitive pathways, and tolvaptan PK and PD parameters (Figure 4)
- VPop results were consistent with a range of outcomes and biomarkers
- The VPop can be used to explore alternate dosing options for all patients, or to analyze sub-groups to customize treatment

REFERENCES
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