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Commentary

Informatics-guided drug repurposing for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common monogenic human disorders, affecting an estimated 0.04–0.1% of individuals. ADPKD is caused by mutations disabling the *PKD1* or *PKD2* genes, which encode polycystin-1 and polycystin-2, respectively. In normal tissues, PKD1 and PKD2 heterodimerize on cell surfaces and serve as transponders for extracellular signals which regulate cell growth. The most prominent feature of ADPKD is the uncontrolled proliferation of renal epithelial cells, which gives rise to a large number of renal cysts in pathologically enlarged kidneys that undergo progressive failure over decades. Several studies aimed at understanding the disruption of signaling cascades in ADPKD due to *PKD1* or *PKD2* mutations have ascertained various canonical defects. These include reduced somatostatin receptor (SSTR) activity and intracellular Ca^{2+} levels, coupled with an increase in vasopressin receptor V2R activity that leads to elevated cAMP levels. This increase in levels of cAMP stimulates PKA kinase activity, in turn stimulating the CFTR Cl^- channel and causing fluid secretion into enlarging cysts. Additionally, patients with ADPKD suffer from hematuria, kidney and back pain, high blood pressure, cardiovascular abnormalities, headaches, urinary tract infections, and formation of kidney stones [1].

To date, there is no cure for ADPKD, although some therapeutic approaches have long been used to ameliorate symptoms and prolong eventual progression to kidney failure. These approaches include medications that control blood pressure and relieve pain and dialysis to maintain kidney function at late stages of the disease. In 2018, a selective V2R antagonist, tolvaptan, was approved by the US FDA as the first targeted drug for ADPKD treatment, based on evidence that it effectively decelerates the growth in total kidney volume and delayed decline in estimated glomerular filtration rate. However, tolvaptan administration causes a variety of side effects, including extensive diuresis, and can compromise liver function. Hence, the search for more effective ADPKD drugs continues to be of high interest, but poses some specific challenges; in particular, as ADPKD progresses over decades and is associated with compromised kidney function, drugs must have exceptionally strong profiles of safety and tolerability [1].

Given the high cost and long timeline of drug discovery and development, repurposing of drugs originally developed for other indications has been an attractive strategy to explore for ADPKD and other chronic kidney diseases [2]. As there are marked similarities between the signaling defects in ADPKD and other diseases such as cancer [3], for which a large number of FDA-approved clinically validated drugs exist, there have been a growing number of preclinical studies to evaluate the potential of repurposing individual agents selected on the basis of functionally defined signaling targets for ADPKD [4–6] and many others.

In a recent study published in *EBioMedicine*, Malas et al. used a comprehensive multi-step approach combining gene expression, bioinformatic analysis of response profiles, and cheminformatics data to identify a number of novel drug repurposing candidates for ADPKD treatment. In detailed profiling of mouse model for ADPKD, the authors of the study analyzed the gene expression profile of *Pkd1*$^{-/-}$ murine kidneys collected at different stages of disease progression [7]. This work defined the changes in gene expression profiles occurring over the course of disease progression and identified gene expression clusters specific to the early, moderate or advanced stages of ADPKD. They also compared mRNA profiles obtained from kidneys of untreated animals with those from mice treated with various compounds that have been explored as candidates to reduce ADPKD symptoms. From 1162 genes showing differential expression as a consequence of disease progression from *Pkd1*$^{-/-}$ mouse kidneys, the authors focused on genes with expression altered by the response to treatment [7].

They then analyzed the ChEMBL database of bioactive molecules to identify protein-targeted drugs corresponding to this refined gene set. Integrating and prioritizing the gene-protein-drug matches led to 116 drugs targeting 29 proteins, some of which had previously been identified as candidates for ADPKD. Of these, 6 (Zileuton, indometacin, meclofenamic acid, gamolenic acid, icosapent, and birinapant) were further assessed; birinapant, a SMAC-mimetic and inhibitor of

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apoptosis protein antagonist showed the most potential to reduce cyst growth in an *in vitro* cystogenesis assay. These compounds await further validation for control of cystic growth *in vivo*.

Importantly, this drug identification pipeline provides a generalizable approach to identifying effective therapeutic options. As transcriptomic and proteomic data are increasingly being considered for routine diagnosis of ADPKD [8,9] and other diseases (e.g. [10]), drug repurposing strategies are proving usefulness in findings effective treatments for complex and challenging disorders. There is a hope that collective efforts aimed at improving the understanding of mechanisms that drive disease development will facilitate the identification of effective treatments for ADPKD and other chronic disorders that currently lack a cure.

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