Drug repurposing in kidney disease

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Drug repurposing, is the re-tasking of known medications for new clinical indications. Advantages, compared to *de novo* drug development, include reduced cost and time to market plus the added benefit of a known pharmacokinetic and safety profiles. Suitable drug candidates are identified through serendipitous observations, data mining, or increased understanding of disease mechanisms. This review highlights drugs suited for repurposing in kidney disease. The main cause of mortality in patients with chronic kidney disease is cardiovascular disease. Hence, we have included CV endpoints for the drugs. This review begins with candidates in acute kidney injury: vasodilators levosimendan and vitamin D, followed by candidates in CKD, with particular focus on diabetic kidney disease, autosomal dominant polycystic kidney disease, and focal segmental glomerulosclerosis. Examples include glucose-lowering drugs (sodium glucose co-transporter 2 inhibitors, glucagon-like peptide 1 agonists, and metformin), which have mechanistic potential for cardiac and/or renal protection beyond glucose lowering, with broader applicability to the nondiabetic population; xanthine oxidase inhibitors (allopurinol, febuxostat), selective endothelin receptor A antagonist (atrasentan), Janus kinase inhibitor (baricitinib), selective costimulation modulator (abatacept), pentoxyfylline, and the DNA demethylating agent/vasodilator (hydralazine).

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Drug repurposing is a cost-effective pragmatic strategy to treat patients with kidney disease. Often the pharmacokinetic, pharmacodynamics, and safety profile is already known. This review focuses on potential suitable candidates for drug repurposing in acute kidney injury (AKI) and chronic kidney disease (CKD).

The International Diabetes Federation estimated in 2007 that the number of people with diabetes will reach 380 million in 2025. The startling fact is that in 2015 this figure was already 415 million worldwide. In high-income countries, diabetes is the leading cause of cardiovascular (CV) disease and kidney failure, consuming 12% of global health expenditure.[1] There are clear barriers which have limited drug development in this area, despite a wealth of relevant research, leaving translatable therapeutics an area of significant unmet needs. These include cost, time to hard endpoints, and targets that are not easily reached by drugs. Ideally *de novo* drug development should occur in parallel with drug repurposing.

Screening for novel targets often involves large data mining where genes or proteins are screened for differences between diseased and nondiseased states.[2] Identified targets require validation to determine if the differences are associative or causative. Once proof of concept is established preclinically, it is followed by a lengthy process of preclinical toxicity testing and establishing pharmacokinetic and dynamic profiles in humans before it can enter into phase 2 trials, which provide interim endpoints to support a costly phase 3 trial. If endpoints are positive, this allows entry into the commercially competitive market. The Tufts Centre for the Study of Drug Development recently published a study that estimated the cost to develop and gain marketing approval for a new drug to be approximately $2.6 billion.[3] Clearly, costs to the pharmaceutical industry are compounded by the large number of targets that "fall over" or do not make it at multiple points in the development process.

In drug repurposing, a similar approach to data mining coupled with bioinformatics and preclinical studies can identify whether an existing drug can be used for other indications. The impetus to repurpose can be based on serendipitous observations during preclinical studies or clinical use. As for novel drugs, new indications must be rigorously tested in clinical trials. The main advantages of repurposing are the known side effects and/or toxicities, which inevitably mean less cost, less time, and a better safety profile (Figure 1).

One of the best examples of drug repurposing is thalidomide. Used as an over-the-counter antiemetic in the 1950s, it was subsequently withdrawn after it was recognized as the cause of horrific birth defects. Thalidomide was reintroduced

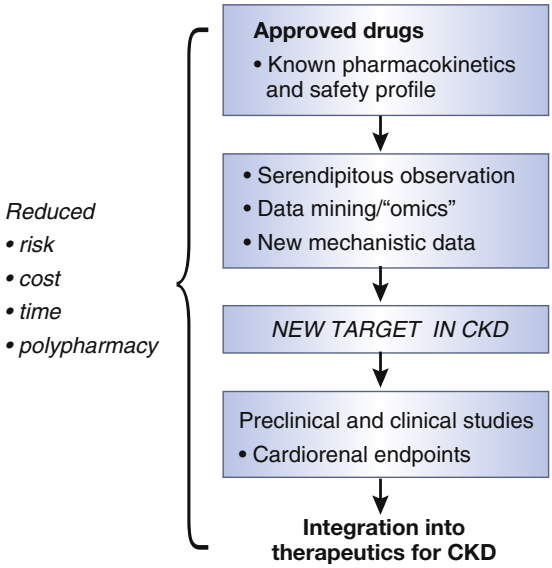

Figure 1 | Summary of drug repurposing pathway. This diagram summarizes the pathway of drug repurposing in chronic kidney disease. It highlights the advantages over *de novo* drug development.

Figure 2 | Features of an ideal drug for a patient with kidney disease are highlighted.

under strict guidelines for new indications and approved by the US Food and Drug Administration in 1998 for use in treating leprosy and again in 2006 for treating multiple myeloma.

In this review, we highlight examples of drugs that, when repurposed, may be useful to treat both AKI and CKD. As the main cause of mortality in CKD is CV in its origin, it is important that both CV and renal endpoints are addressed. Most recent trials are designed for safety and use as the primary outcome "major adverse cardiac events." For this reason, the examples provided in this review are heavily focused on meeting those endpoints. In addition, drug dosages are an important consideration, given that the kidney is one of the main organs in drug elimination. Additionally, the repurposed drug is attractive if it is inexpensive and globally accessible (Figure 2).

Acute kidney injury

In contrast to previously held beliefs, it is now well recognized that AKI is independently associated with risk of death, CV events, and incident/progressive CKD,[4,5] and is viewed as part of a continuum to CKD. As such, it is a global health priority to reduce or prevent AKI.[6]

Vasodilator: levosimendan. Levosimendan is a calcium sensitizer and adenosine triphosphate-dependent potassium (K_{ATP}) channel agonist with vasodilatory and inotropic effects originally developed for treating acute cardiac failure. Given its mechanism of action, it is not surprising that levosimendan has pleiotropic effects beyond improved cardiac function. An expert panel position paper published in 2016 highlighted potential novel applications which included kidney injury.[7]

Preclinical studies have shown that levosimendan offers renoprotection in ischemia reperfusion injury as a result of activation of the mitochondrial ATP-sensitive potassium channel and nitric oxide (NO) synthase[8] and in experimental endotoxemic acute renal failure in mice, most likely as a result of vasodilator properties.[9]

Meta-analyses suggest that perioperative levosimendan may reduce renal injury in adult patients undergoing cardiac surgery,[10,11] presumably due to vasodilation increasing blood flow, glomerular filtration rate (GFR), and renal oxygenation. Previous negative trials with vasodilators in this setting temper the enthusiasm with levosimendan. We cautiously await the outcome of clinical trials evaluating the efficacy of levosimendan in AKI in adult intensive care patients (Clinical Trials.gov identifier: NCT01720030) and in patients undergoing cardiac surgery (Effects of Levosimendan in Acute Kidney Injury After Cardiac Surgery [LEVOAKI] study; NCT02531724).

Vitamin D. Vitamin D is involved in calcium homeostasis and bone metabolism. Vitamin D status also influences other systems including the immune system and CV and endothelial systems, all of which can impact kidney function.[12]

Vitamin D may reduce inflammatory and profibrotic pathways relevant to kidney disease through multiple mechanisms. Preclinical studies in rats have shown that vitamin D deficiency contributes to vascular damage, aggravating ischemic AKI.[13,14] Vitamin D suppresses transforming growth factor-beta-mediated tubular epithelial-to-mesenchymal transition and renal fibrosis in a vitamin D receptor-dependent manner.[15] Activated vitamin D receptor is also involved in translocation and activation of nuclear factor-κβ (NF-κβ) in kidney cells.[16] Vitamin D pretreatment regulates renal inflammatory responses in lipopolysaccharide-induced AKI by repressing NF-κβ in the renal tubules. Lipopolysaccharide, which activates renal NF-κβ, reciprocally suppresses renal vitamin D receptor and its target gene.[17] Patients with AKI manifested a marked decrease in vitamin D level at the time of AKI diagnosis, which increased with the severity of AKI. No association between serum vitamin D level at the