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Editorial

An introduction to the pharmacology of kidney regeneration

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Kidney diseases are becoming increasingly common and are difficult to combat (Jha et al., 2013). The origin of kidney diseases is diverse and can include acquired injuries due to exposures to toxic agents, diabetes, inflammation, sepsis or ischemic episodes, as well as inborn and developmental errors. In acute kidney injury, the organ still has the capacity to regenerate damaged cells, provided that the kidneys architecture is unharmed and the injury itself limited. However, insufficient repair and/or extended insults lead to progression of the disease into chronic kidney failure and, eventually, end stage kidney disease. For these patients, the most adequate treatment option is kidney transplantation, but this therapy is hampered by a major shortage of donor organs as well as complications related to immunosuppression. Building human kidneys from stem cells is a solution and recently great progress has been made by the production of kidney-like organoids (Morizane et al., 2015; Takasato et al., 2015), but there is still a long way to go until clinically transplantable human kidneys will become available. Therefore, understanding the pathways that can be pharmacologically triggered in order to enhance repair and regeneration processes after injury is of major importance.

Regenerative nephrology is a multidisciplinary and translational research area that rapidly evolves. Its major aim is to develop technologies for the repair and replacement of damaged nephron segments and kidneys (Christ et al., 2013). The first section of this issue of European Journal of Pharmacology presents technologies that can be used to study kidney development or replacement. Stem cell-derived kidney organoids have been developed to understand kidney regeneration from a developmental point of view, but also to present a platform that can be used for drug efficacy and safety screenings. Novel platforms in regenerative nephro-pharmacology include the application of decellularized kidneys from animals and human as 3D biological scaffolds. These scaffolds can be used as templates for functional kidney reconstruction after recellularization with autologous stem cells or differentiated cells, and, ultimately, be used as a transplantable organ. Regenerative pharmacology not only applies to the use of molecular therapies or stem cells for organ repair, but also to the development of functionalized “living” materials that can replace (in part) the organ's function. An example of such development is an upscaled living membrane for bioartificial kidney development suitable for extracorporal clearance of waste products from normal metabolism.

In the second section, *in vitro* models to study kidney disease development and repair processes are compiled. *In vitro* models can be very valuable in experimental pharmacology, but clearly also have their limitations. Current developments in cell culturing demonstrate preferential use of 3-dimensional conditions over conventional 2-dimensional cultures, thereby improving physiological performance of the tissue. This can be enhanced further when flow is implemented in the culture conditions. Downscaling the size with microfluidics towards a so-called ‘kidney-on-a-chip’ using human or patient-derived cells has great potential for drug screenings, but is also hampered by technological hurdles that will most likely be taken in the near future. Obviously, the choice of cell types in these models is crucial in fully understanding the pharmacological manipulation that may lead to the successful development of a new therapeutic strategy in the end. As discussed further, native tissue slices have the advantage of making use of native cross-talk between multiple cell types, study species differences and model chronic kidney disease conditions, including fibrosis. But the tissue slices have a relatively short life span.

The third section addresses the *in vivo* potential and translational aspects of regenerative strategies. The origin and fate of resident renal progenitor cells is discussed for which transgenic mouse models that allow lineage tracing of regenerating cells have been highly instrumental. Further, cell-based regenerative medicine therapies have shown great promise in kidney repair in rodents. In addition, the potential of extracellular vesicles to amplify renal repair through paracrine signaling is presented. An overview is given on methods for the functional assessment of kidney repair *in vivo* using innovative markers for filtration, but also with innovative imaging technologies that allow labeled (stem) cells or cellular particles to be traced when therapeutically administered. Finally, gene-based therapies to target complex molecular

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pathways in kidney disorders are discussed, including new technologies such as repair through CRISPR/Cas9, which are powerful tools in the treatment or cure of kidney diseases that otherwise may not be targeted.

The complexity of, endogenously triggered, kidney regeneration, the shortage of donor organs and the increasing life span of humans have created a demand for regenerative nephro-pharmacology (Peloso et al., 2015). Obviously, uniting multidisciplinary and translational research strengths should lead to the development of novel therapies for severe kidney disease patients. As presented in this issue of European Journal of Pharmacology, the combined efforts within tissue engineering and regenerative medicine have resulted in innovative (experimental) platforms to study disease modeling and functional kidney repair.

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