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Regenerative therapeutic approaches for kidney regeneration: Present and future

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hronic kidney diseases have worldwide an increasing prevalence (8-16%) and develop frequently in chronic renal failure requiring dialysis. Kidney transplantation has emerged as the "gold standard" therapy for end-stage renal failure as it improves both quality of life and survival. Despite the progress in short-term graft survival that is closely associated with the impressive reduction of acute rejections within the first year, long-term graft and patient survival remain almost unchanged and unsatisfactory. Incomplete control of chronic allograft injury but particularly the adverse effects of life-long required immunosuppression (graft toxicity, diabetes, cardio-vascular events, infections, tumors) continue to challenge the long-term success and cause high direct and indirect (management of adverse effects) costs (about 0.5-1.0 Million Euros/10 years). Consequently, there is a high medical need to develop new protocols that allow minimization or even weaning off chronic immunosuppression. The increased net-immunosuppression introduced during last decades can better control the undesired alloreactivity even in patients at risk but it also targets physiologic counter-regulatory processes that protect to inflammation/ immune reactivity. Therefore, minimizing chronic immunosuppression is only feasible if these endogenous counter-regulatory mechanisms are spared or even supported. Recently, we could demonstrate in a clinically relevant advanced rat kidney transplantation model that even under those challenging conditions the adoptive transfer of regulatory T cells (Treg) could reshape alloimmunity to "operational tolerance". In the process of translating these promising data into patients' treatment we faced several challenges. We developed a robust GMP-manufacturing process for isolation, activation and expansion of human Treg from just 40-50 ml blood as source. The Treg can be expanded about 1,000 fold without clonal bias, as shown by TCRrepertoire analyses using Next Generation Sequencing and without loss of regulatory function. We recently started a doseescalating phase I/IIa clinical first-in-man study with our Treg cell product and reached already the highest target dose without any safety issue. The modulation of endogenous immunological control mechanisms by Treg might be a novel approach to improve long-term allograft survival but also to control other undesired process to support endogenous regeneration. To address the shortage of donor organs, it would be useful to prolong the survival of injured kidneys. Reconstitution of injured kidneys by application of progenitor cells was not feasible so far because of lacking resources for those cells. The availability of human iPS technology opens new opportunities. However, the kidney is a very complex organ consisting of about 26 cell types embedded into matrix. Few groups, including ours are able to generate renal organoids from human iPS now. We could further improve the method and can efficiently generate renal precursor cells within 6 days and terminally differentiated kidney cells in 2-D culture within 14 days. The progress in this field makes the in vitro generation of human renal cells for disease modeling but also for putative therapeutic approaches a realistic option.

Biography

Since 2006, Andreas Kurtz is Head of the Laboratory for Stem Cell Research and Knowledge Management at the Berlin-Brandenburg Center for Regenerative Therapies, Berlin (Germany). He also holds a professorship at Seoul National University since 2008. Before he served as director of the German stem cell authority at the Robert-Koch-Institute. His research interest is the application of stem cells for therapy and the development of suitable *in vitro* models to assess their mode of action.. In addition, he coordinates the human pluripotent stem cell registry (hPScreg), an international data resource for iPSC and hESC.

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