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Growing organs in vivo: iPS cell-derived, xeno-created organs for transplantation

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Organ transplantation remains the only cure for a growing number of patients suffering from a broad range of debilitating and fatal diseases. However, an absolute lack of donor organs is a major roadblock to this therapy. Attempts have made to use animal organs such as baboons or pig for transplantation. However, these xenogeneic organs caused strong immune reactions and immediately rejected. With the advancement of genome editing technology, genetically modified, hypoimmunogenic pigs have been generated. Recently, a heart from the hypoimmunogenic pig was transplanted into a patient with end-stage heart failure, and the patient survived for two months without any clear evidence of immunological rejection. This is an important step toward the use of xenogeneic organs for clinical transplantation. In contrast to above approach, we propose to use developing pig embryo's environment to form human iPS cell-derived organs (Figure 1). We first postulated that "organ niche" exists in a developing animal and that this niche is empty when development of an organ is genetically disabled. This organ niche, we reasoned, should be compensated developmentally by blastocyst complementation using wild-type pluripotent stem cells. We generated functionally normal mouse-sized rat pancreases in mice (Kobayashi et al., ***Cell***. 2010) and in the reverse experiment, we generated functional rat-sized mouse pancreases in rats. Islets prepared from these mouse pancreata generated in rats were transplanted into mice with streptozotocin-induced diabetes. The transplanted islets successfully maintained normal host blood glucose levels for over 370 days without immunosuppression (Yamaguchi and Sato et al. ***Nature***. 2017). These data provide proof-of-principle evidence for the therapeutic potential of PSC-derived organs generated by interspecies organogenesis. However, interspecies chimeras with high donor chimerism also display embryonic lethality and malformation during early embryogenesis, hindering high chimeric fetus formation. To circumvent this problem, we used Insulin-like growth factor 1 receptor (Igf1r) deficient embryos as a host. Since the Igf1r deletion increases donor chimerism from the mid to late developmental stages, highly chimeric fetuses can evade the early developmental arrest observed in interspecies chimera formation. Indeed, Igf1r KO hosts create what we have termed, "cell competitive niche", which significantly increases donor chimerism in both intra- and inter-species chimeras. The enhanced donor chimerism

continuously increased and even took over the whole organs in intra-species chimeras as well as inter-species chimeras (Nishimura et al. ***Cell Stem Cell*** 2021). This approach, now being tested in large animals, should facilitate donor cell contribution to host tissues, which may result in in whole-organ generation across wide evolutionary distances.