PHARMACOLOGY

Transplanted human organoids for preclinical drug testing

Westerling-Bui, A.D. et al. *Sci. Adv.* **8**, eabj5633 (2022)

Determining safety and efficacy parameters are critical for drug development and for subsequent regulatory approval for human use. Animal models have a pivotal role in the drug development process, serving as 'proof-of-concept' for the safety and efficacy of new drug molecules. However, several drugs that show efficacy in preclinical studies are not beneficial clinically, calling into question the predictive validity of traditional animal models.

A study in *Science Advances* reports the development a new approach for pharmacodynamic (PD) studies using human kidney organoids transplanted in animals. "The PD studies in rats carrying transplanted organoids provide unprecedented preclinical confidence in the human relevance of specific targets and compounds, marking a substantial advance that overcomes previous limitations of animal models," explain Westerling-Bui and colleagues in their report. The investigators used the new approach to evaluate the preclinical efficacy of GFB-887, a new podocyte-targeting, transient receptor potential canonical 5 (TRPC5) inhibitor that was designed to treat individuals with kidney diseases, and is now in phase 2 trial.

First, the team optimized previously published in vitro differentiation protocols to generate high-quality kidney organoids from human induced pluripotent stem cells. Second, they established the optimal conditions to produce suitable organoids for in vivo drug testing by transplanting day-14 organoids under the kidney capsule of athymic rats, and keeping them in vivo for several weeks to allow cell differentiation and organoid vascularization/perfusion.

Next, the researchers evaluated the in vitro and in vivo efficacy of GFB-887 in organoids using the protamine sulfate (PS) model of podocyte injury, which is known to activate TRPC5. After showing that the drug protected podocytes in vitro from PS-induced TRPC5-mediated synaptopodin degradation and actin aggregation, the team conducted PD studies with transplanted organoids. Using a novel high-throughput approach for the quantification of synaptopodin protein abundance that combines fluorescence and super-resolution in vivo microscopy, they showed that GFB-887 administration (either coperfusion with PS or orally before PS perfusion) prevented the loss of synaptopodin induced by PS in rat kidney and human organoids.

By showing that GFB-887 can protect human podocytes in transplanted organoids, these findings confirm the preclinical efficacy of the drug and establish its human relevance. The study also shows that that PD studies using transplanted organoids are valuable for the assessment of novel therapeutic candidates before going into clinical trials.

Alexandra Le Bras

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