Life Sciences

# Engineered iTreg-Mediated Immune Tolerance in Zebrafish Overcomes Allograft Rejection for Rapid Gamete Production

The generation of genetically modified lines in model and economically important species typically requires months or even years. Developing strategies to accelerate this process thus represents a critical need in the field. Transplantation of allogeneic gonadal primordia into near-mature recipients offers a promising route to rapid gamete production. However, a major obstacle lies in overcoming the immune rejection of donor tissues.

A key unresolved question is whether immune tolerance can be induced in host organisms by exploiting the central role of Foxp3-mediated regulatory T cells (Tregs) in maintaining immune homeostasis.

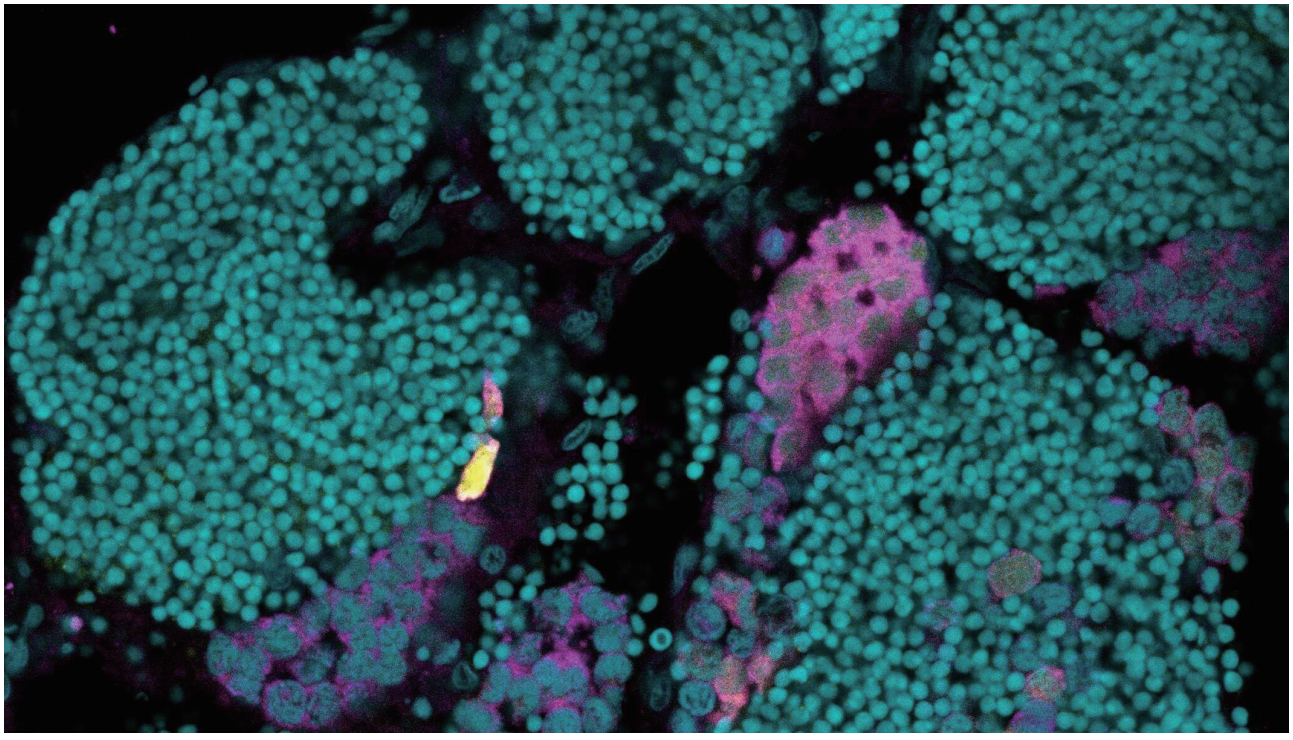
Recently, a research team led by Prof. SUN Yonghua from the Institute of Hydrobiology (IHB) of the Chinese Academy of Sciences established an inducible Treg (iTreg)-mediated immune-tolerant host system that overcomes the immune rejection barrier in subcutaneous transplantation of allogeneic gonadal primordia.

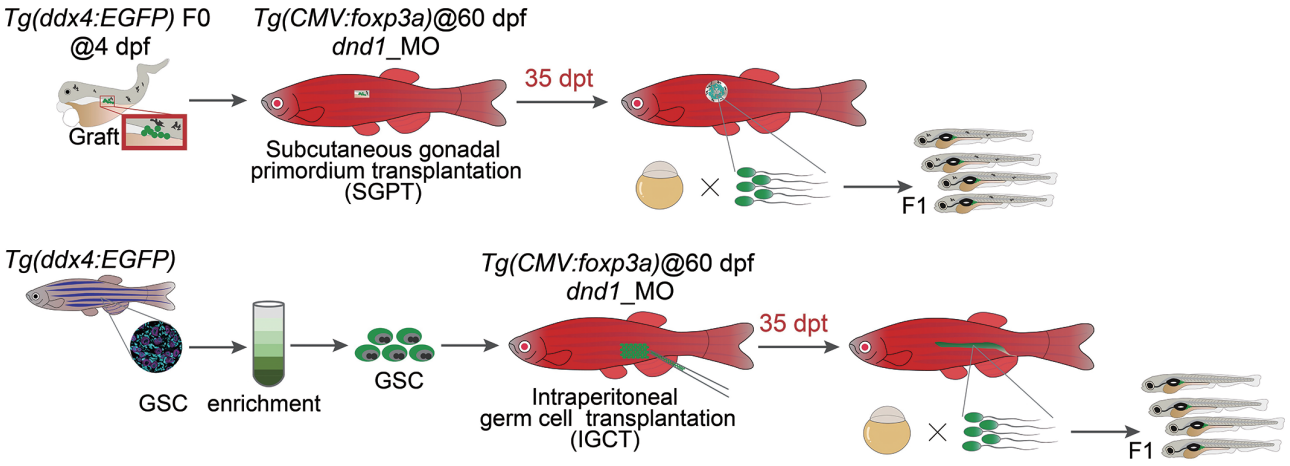
The findings were recently published in *Journal of Genetics and Genomics* (doi: 10.1016/j.jgg.2026.02.024).

In this work, the team first generated an immune-tolerant zebrafish line, *Tg(CMV:foxp3a)*, via overexpression of the core Treg transcription factor *foxp3a*. Unlike immunodeficient models, this line displays normal growth and fertility under standard conditions.

Multi-omics analyses revealed that *foxp3a* overexpression reshapes the host immune landscape: It reduces effector T

**Engineering iTreg-mediated immune tolerance in zebrafish overcomes allograft rejection. (Image by IHB)**






**iTreg-mediated immune-tolerant zebrafish enable ultra-rapid strain generation via subcutaneous gonadal primordium transplantation (SPGT) and intraperitoneal germline stem cell transplantation (IGCT). (Image by IHB)**

and B cells involved in rejection while elevating resting T cells capable of rapidly differentiating into functional iTregs, thereby enhancing systemic immune tolerance.

To accelerate donor gonad development, the researchers isolated allogeneic gonadal primordia and transplanted them into the dorsal subcutaneous region of two-month-old wild-type hosts whose endogenous germ cells had been depleted. In wild-type fish, all grafts were completely rejected within 14 days, and no ectopic gonadal development was observed. By contrast, when *Tg(CMV:foxp3a)* fish served as hosts, roughly one-quarter of them supported the successful engraftment and expansion of donor tissue, forming enlarged ectopic gonadal masses — evidence of effective iTreg-mediated immune tolerance.

Further analyses demonstrated that donor-derived germ cells within these grafts underwent ultra-rapid spermatogenesis in two-month-old recipients, generating donor-derived transgenic or gene-edited F1 offspring in approximately one month.

In summary, *foxp3a* overexpression reprograms the host immune microenvironment, surmounts allograft rejection, and enables the ultra-fast maturation of donor-derived gametes. This study lays an immunoregulatory foundation for the large-scale application of allogeneic surrogate reproduction and provides a novel strategy for the rapid generation of genetically modified lines in both model and economically valuable species.

(Source: IHB)