

## **“From ornamental fish to disease model - Oncogenic allelic interaction in *Xiphophorus* highlights hybrid incompatibility”**

**Abstract:** Mixing genomes of different species by hybridization can disrupt species-specific genetic interactions that were adapted and fixed within each species population. Such disruption can predispose the hybrids to abnormalities and disease that decrease the overall fitness of the hybrids and is therefore named as hybrid incompatibility. Interspecies hybridization between southern platyfish and green swordtails leads to lethal melanocyte tumorigenesis. This occurs in hybrids with tumor incidence following progeny ratio that is consistent with two-locus interaction, suggesting melanoma development is a result of negative epistasis. Such observations make *Xiphophorus* one of the only two vertebrate hybrid incompatibility examples in which interacting genes have been identified. One of the two interacting loci has been characterized as a mutant epidermal growth factor receptor. However, the other locus has not been identified despite over five decades of active research. Here we report the localization of the melanoma regulatory locus to a single gene, *rab3d*, which shows all expected features of the long-sought oncogene interacting locus. Our findings provide insights into the role of *egfr* regulation in regard to cancer etiology. Finally, they provide a molecular explainable example of hybrid incompatibility.

### **References:**

Lu, Y., Sandoval, A., Voss, S., Lai, Z., Kneitz, S., Boswell, W., Boswell, M., Savage, M., Walter, C., Warren, W., Scharl, M., & Walter, R. (2020). Oncogenic allelic interaction in *Xiphophorus* highlights hybrid incompatibility. *Proc Natl Acad Sci U S A*, 117(47), 29786-29794. doi:10.1073/pnas.2010133117