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A *Drosophila* model for the discovery of inhibitors of protein-protein interactions

Ruben Artero, Estefanía Cerro, Carla Fuster, M. Beatriz Llamusi and Ariadna Bargiela-Schönbrunn

Department of Genetics, University of Valencia, Spain

INCLIVA Health Research Institute, Valencia, Spain

Protein-protein interactions (PPIs) play a crucial role in many biological processes. Abnormal PPIs constitute prime therapeutic targets for the development of medicines so that there is tremendous interest in developing methods to identify inhibitors of such interactions. Paradigmatic pathogenic PPIs are the increased formation of epidermal growth factor (EGF) receptor heterodimers ERBB2-ERBB3 and EGFR-ERBB2 as a result of ErbB2 over expression in breast cancer patients. ERBB2 (HER2) dimerization inhibitors (HDIs) constitute a new family of therapeutic agents whose founder member is pertuzumab. However, cumbersome administration regime, high production costs, acquired resistance and inability to cross the brain-blood barrier, which makes brain metastasis untractable, impel the identification of additional HDIs.

We are generating a humanized *Drosophila* model of target PPI coupled to a reporter gene, to search for small molecules with the ability to act as HDIs. This requires transformation of the *Drosophila* germ line with transgenes suitable for tissue directed expression. These transgenes will include constructs involving the extracellular domain of human EGFR and HER2 fused to N or C-terminal fragments of luciferase, to be expressed simultaneously in the same tissue. Should interaction occur, N and C-terminal fragments of luciferase reconstitute a functional reporter. In doing so, the physical interaction between the human proteins takes place in the context of the complex tissue and cell interactions that occur in a whole animal, improving the prospects for better efficacy and lower toxicity. This system will constitute a radically novel approach to drug discovery in *Drosophila*.

Biography

Ruben Artero is Associate Professor of Genetics at the University of Valencia-INCLIVA Biomedical Research Institute, where he leads the Translational Genomics group dedicated to discovering mechanisms of pathogenesis of human genetic diseases as well as to design novel *Drosophila* models for in vivo drug discovery, particularly in myotonic dystrophy, spinal muscular atrophy and breast cancer. Before his interest in biotechnology he performed basic research in the field of developmental genetics studying *Drosophila* myogenesis both in University of Valencia and in the Memorial Sloan-Kettering Cancer Center (NY, USA), where he spent some six years as postdoctoral fellow. He is co-founder of the Genera Biotech company, scientific advisor of Valentia BioPharma and inventor in four patents. He has participated in 30 international journal research publications and serves as academic editor for the PLoS ONE journal.

ruben.artero@uv.es