Animal models by genetic manipulation

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We are interested in understanding the function of regulatory elements necessary to identify gene expression domains in mammalian genomes and that help to specify gene expression patterns in space and time. Our basic aim is to improve adequate interpretation of the genome, especially the function of intergenic sequences, where most regulatory elements are located, and to improve the design of gene transfer strategies applied in animal transgenesis and gene therapy.

One of the experimental models in the lab is the tyrosinase gene, which encodes an enzyme that activates synthesis of the pigment melanin, which is regulated throughout development and is tissue-specific (expressed only in melanocytes and retinal pigment epithelium cells). This locus served to identify genome boundaries or insulators, which protect the tyrosinase gene from surrounding genes. In transgenic zebrafish and mice, we use different types of gene constructs based on plasmids and artificial chromosomes, which we modify by homologous recombination to study the relevance of specific sequences. Functional analysis of regulatory elements within the intergenic sequences can be now addressed more efficiently, thanks to the new CRISPR-Cas9 gene modification system that we have implemented successfully in our laboratory.

In addition, we generated and analysed new animal models to study visual abnormalities, including anomalies that affect retina development associated with albinism, as well as other retinopathies such as achromatopsia. In transgenic mice, we identified deficiency in L-DOPA (one of the intermediate metabolites in the melanin synthesis pathway) as the principal cause of the visual alterations in albinism. Within our participation in the CIBERER-ISCIII, we developed various additional animal models (transgenic and knockout) for the study of rare human diseases. In collaboration with Ángel Carracedo (Universidad de Santiago de Compostela) and Carmen Ayuso (Fundación Jiménez Díaz), we have established an experimental approach for the universal genetic diagnosis of all known mutations in the various albinism genes; in cooperation with ALBA, the Spanish association in support of people with albinism, we are already applying this approach to people with albinism and their relatives.

SELECTED PUBLICATIONS

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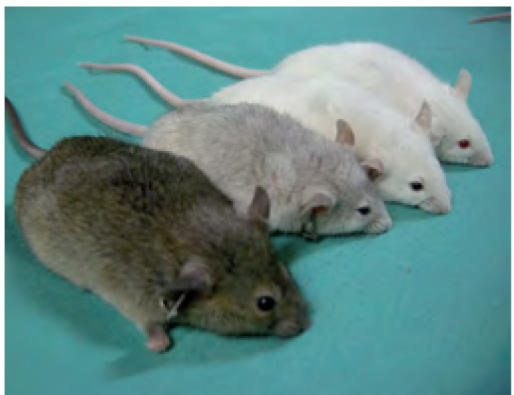

1 *Child with oculocutaneous albinism type I (OCA1) (Photo: Ana Yturralde)*

2 *Mouse models to study tyrosinase gene expression and albinism (Photo: Davide Seruggia)*