



## Animal Models by Genetic Manipulation

In our laboratory, we are interested in understanding how mammalian expression domains work and how they are organised within genomes.

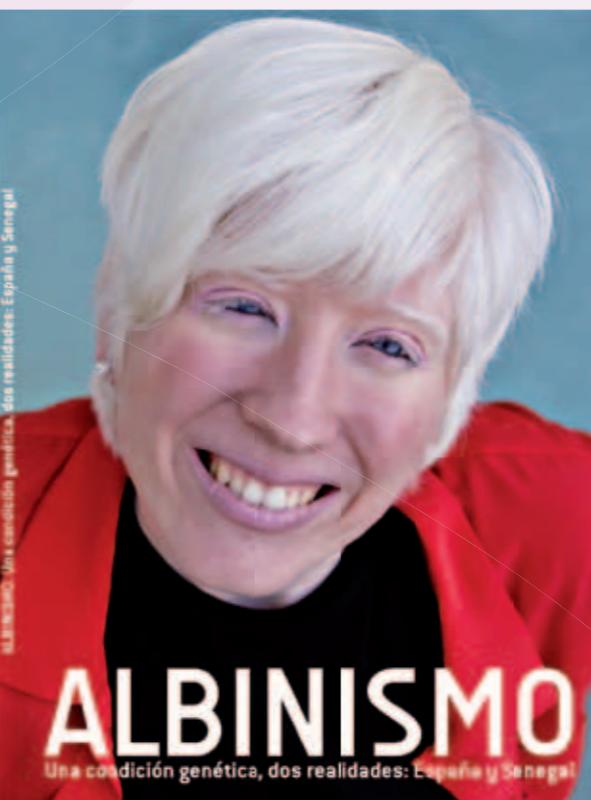
In particular, we focus on the identification and characterisation of genomic boundaries or insulators. By studying insulator elements, we aim to contribute to understanding of the functional and structural organization of vertebrate genomes. Insulators can be used effectively in biotechnological applications, as spacers, as boundaries, in any gene expression construct to be used in gene transfer experiments. They prevent inappropriate expression transgenes or gene therapy constructs and insulate them from neighbouring sequences at the insertion site in the host genomes. We are searching for new insulator sequences in vertebrate genomes, through initial bioinformatic analyses. Insulator candidates are functionally validated *in vitro* using cells and the enhancer blocking assay, and possibly *in vivo*, using transgenic animals bearing appropriate constructs (zebrafish in collaboration with JL Gómez-Skarmeta at the CABD, and mice at the CNB).

In addition, our laboratory generates and analyses new animal models to study neural alterations in vision, as well as in hearing, associated with albinism, a rare disease whose research effort is the focus of work within the CIBERER ([www.ciberer.es](http://www.ciberer.es)). Using transgenic pigmented and albino mice in collaboration with the laboratory of I Varela-Nieto (IIB-CSIC/UAM), we showed that albino mice display premature severe hearing loss and do not recover after a noise-induced hearing loss, compared to their pigmented counterparts.

We collaborate with ALBA ([www.albinismo.es](http://www.albinismo.es)), the Spanish association in support of people with albinism, and have published a book to inform society about the different types of albinism and their phenotypic consequences.

The expertise of our laboratory and its leadership in the Mouse Embryo Cryopreservation and Histology Facilities at the CNB have also been fundamental for our participation in the FP7 European Projects within the field of mouse functional genomics (INFRAFRONTIER) and in EMMA,

the European Mouse Mutant Archive, whose Spanish node at the CNB began operation in 2009 under our coordination. This work has produced additional publications within the field of animal transgenesis.



Cover of the book on albinism published by ALBA (2009) with the collaboration of L Montoliu (photo by A Yturralde).

Finally, through collaborations, we have generated and are analysing a number of additional animal models (transgenic mice) to study human diseases, including Alzheimer, exploiting our technology of yeast artificial chromosome (YAC)-type of transgenes, which have been instrumental in the execution of scientific contracts with biotechnology and pharmaceutical companies.

## PUBLICATIONS

Moltó E, Fernández A, Montoliu L (2009) Boundaries in vertebrate genomes: different solutions to adequately insulate gene expression domains. *Brief Funct Genomic Proteomic* 8:283-96.

Bessa J, Tena JJ, de la Calle-Mustienes E, Fernández-Miñán A, Naranjo S, Fernández A, Montoliu L, Akalin A, Lenhard B, Casares F, Gómez-Skarmeta JL (2009) Zebrafish enhancer detection (ZED) vector: a new tool to facilitate transgenesis and the functional analysis of cis-regulatory regions in zebrafish. *Dev Dyn* 238:2409-17.

Zurita E, Chagoyen M, Cantero M, Alonso R, González-Neira A, López-Jiménez A, López-Moreno JA, Landel CP, Benítez J, Pazos F, Montoliu L (2010) Genetic polymorphisms among C57BL/6 mouse inbred strains. *Transgenic Res* May 27 [epub] PMID: 20506040.

Murillo-Cuesta S, Contreras J, Zurita E, Cediel R, Cantero M, Varela-Nieto I, Montoliu L (2010) Melanin precursors prevent premature age-related and noise-induced hearing loss in albino mice. *Pigment Cell Melanoma Res* 23:72-83.

Fielder TJ, Barrios L, Montoliu L (2010) A survey to establish performance standards for the production of transgenic mice. *Transgenic Res* 19:675-81.

A black and white photograph of a transgenic zebrafish embryo expressing GFP is shown at the bottom right.

Transgenic zebrafish expressing GFP, used to validate insulator function of selected vertebrate genome elements. See Bessa et al. (2009) for additional information (photo by JL Gómez Skarmeta (CABD)).