Cord Brakebusch
Taina Pihlajaniemi
Editors

Mouse as a Model Organism

From Animals to Cells

Springer

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Preface

The importance of mice as model organism has continuously increased throughout the last decades due to the widespread use of genetically modified mice. These mice significantly increased our understanding of the function of specific genes in a living mammalian organism during development and in disease. Ongoing efforts to create knockouts and conditional knockouts of all mouse genes by high-throughput gene targeting and phenotyping are expected to further boost the use of mice in biomedical research. In June 2009, a symposium on "Mouse as a Model Organism – From Animals to Cells" was held in Rovaniemi, Finland, trying to give an overview about recent developments and future directions in the filed. This conference, organized by the "Nordish Infrastructure for Mouse Models" (www.norimm.org) and supported by NordForsk, brought together distinguished scientists from all over the world to discuss these topics together with students from many places in Europe in the immediate vicinity of the polar circle.

Great research, the special atmosphere of Finnish Lapland in late spring with endless days and midnight sun, and not the least a meeting with Santa Claus himself in the nearby Santa Claus Village made the symposium a very unique experience. Out of that spirit and at the last day of the conference, the idea was born to combine review articles on different topics presented at that conference in a book. The response was very positive and the result can be seen on the following pages.

The first four chapters cover general aspects of generation and phenotyping of genetically modified mice, including the use of genomic insulators in transgenic constructs, the running of a "Mouse Clinic" for high-throughput phenotyping, the effects of genetic background and environment on the phenotype of mutant mice, and the requirements for a phenotyping database. The next chapters will then illustrate the use of mice as disease models and as a source for primary cells with cancer research as an example. This includes an overview about cancer models in mice and ex vitro and in vivo models for angiogenesis followed by a review on cancer associated fibroblasts and in vitro invasion assays. Finally, mouse models for investigating systemic cancer effects on indolent tumors will be described.

We hope that this book gives a good introduction into current possibilities in using mouse models to understand the molecular pathways underlying human diseases, and that it gives an outlook to the results to be expected from the high-throughput phenotyping of mouse mutants within the next years.

Copenhagen, Denmark — Cord Brakebusch
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Chapter 1
Genomic Insulators in Transgenic Animals

Eduardo Moltó, Cristina Vicente-García, Almudena Fernández, and Lluís Montoliu

Abstract Vertebrate genomes are functionally and structurally organised as gene expression domains. These domains contain all regulatory elements required for the gene (or genes) to be expressed correctly, and include those required to shield each domain, thereby blocking any non-desirable interaction from their neighbours. These elements are known as "boundaries" or "insulators" and their function is to insulate gene expression domains in genomes allowing the protected locus to be expressed according to internal regulatory elements, without suffering from the adverse effects of flanking loci and without transmitting the effect of the internal regulatory elements beyond the protected domain. Insulators can act as "enhancer blockers", preventing a distal enhancer from interacting with a proximal promoter, when placed in between, and/or as "barriers", preventing chromosomal position effects associated with the genomic location. In addition, insulators are known to contribute to the chromatin and nuclear structural organization. A variety of molecular mechanisms have been associated with boundary function, probably reflecting the diversity of functional elements that can efficiently insulate genomic sequences. Insulator elements can be used in biotechnological applications, as spacers, as boundaries, and be applied to any gene expression construct to be used in gene transfer experiments (i.e. transgenesis, gene therapy), thereby preventing the inappropriate expression patterns of constructs and shielding them from neighbouring sequences surrounding the place of insertion in the host genomes.

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