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Lentiviral Vectors

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With 32 Figures and 8 Tables

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Preface

"Felix qui potuit rerum cognoscere causas (Virgil)
(Happy the one who could penetrate the secret causes of things)"

In the 20 years of war against HIV, the cause of one of the most dreadful health disasters of all times, a few battles have been won: the virus's major modes of transmission were quickly identified, a blood test was created, and highly active antiviral therapies were developed which have changed the face of the disease in wealthy parts of the world. The fight against HIV will not abate short of a vaccine and of affordable, easy to take and nontoxic therapies. Yet AIDS research has, in addition, provided insights into many basic biological and medical questions. One of its unexpected spin-offs has been the development, a few years ago, of a new system of gene transfer that holds great promises for gene therapy: the lentiviral vectors.

Retroviral vectors had long been considered as formidable gene delivery tools, owing to their large cloning capacity (close to 10kb), their ability to integrate into the chromosomes of target cells (a likely requisite for long term expression), and their failure to transfer virus-derived coding sequence (an immunological blessing). In spite of these assets, however, the clinical perspectives of retroviral vectors seemed rather narrow because, as derivatives of oncoretroviruses such as MLV, they could not transfer genes into nondividing cells. A sobering limitation since most of the potential targets of gene therapy are cells that rarely if ever proliferate, be they neurons, hepatocytes, myocytes or hematopoietic stem cells.

The recognition that HIV can infect nonmitotic cells by hijacking the cell nuclear import machinery and a quite refined mapping of the molecular determinants of this property led to the development of lentiviral vectors. Following the demonstration that lentivectors can govern the efficient in vivo delivery, integration and long-term expression of transgenes into nonmitotic cells, the last 4 years have witnessed a spectacular eruption of this system on the scientific scene.

Tissues that long appeared irremediably refractory to stable genetic manipulation can now be reached, and the concrete proposal for the clinical use of a lentiviral vector seems imminent. This volume describes these exciting developments. The first chapter sums up our current understanding of the biology of lentivirus-mediated gene transfer, an essential starter. We then move on to describe how this information is utilized to derive vectors from a variety of primate and nonprimate lentiviruses. State-of-the-art techniques of lentivector production are discussed in detail, and the all important question of biosafety is addressed. Emerging data on vector targeting, whether at the entry or at the integration level, are also presented. Finally, special emphasis is given to what are currently the most promising clinical applications of lentiviral vectors, in particular in the fields of neurological and lympho-hematopoietic disorders, including AIDS itself.

I hope that this book will encourage nonspecialists to take advantage of lentiviral vectors. The ability of this delivery system to transduce cells otherwise refractory to genetic manipulation could be used broadly, for instance in developmental and stem cell biology or in the neurosciences. I also hope that the contents of this volume will stimulate many investigators to embark in research aimed at pursuing the development of lentivectors, at dissecting and surmounting the current shortcomings of this tool, and at exploiting its potential for therapy. Importantly, I hope that these efforts will contribute to further our comprehension of HIV virology. This would be a most appropriate payback.

Finally, I wish to thank all the authors who took time from their many commitments and generously agreed to contribute a chapter to this collection.

November 2001, Geneva D. TRONO

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(Their addresses can be found at the beginning of their respective chapters.)