

# Contents

<b>CLINIGENE PARTNERS AND BOARDS</b> .....	IX
<b>ACKNOWLEDGMENTS</b> .....	XV
<b>LIST OF AUTHORS</b> .....	XVII

## INTRODUCTION

<b>In-1 Foreword</b>	
Lucio Luzzatto, Inder M. Verma .....	3
<b>In-2 Main achievements and prospects downstream of the CliniGene-NoE</b>	
Odile Cohen-Haguenaer .....	8

## PART I: TECHNOLOGIES AND PRE-CLINICAL STUDIES

### TECHNOLOGIES - Highlights on AAV mediated gene transfer

<b>A1-1 Highlights on AAV mediated gene transfer: introduction</b>	
Eduard Ayuso, Fatima Bosch .....	31
<b>A1-2 Preclinical studies of AAV gene therapy for inherited retinal dystrophies</b>	
Alexander J. Smith, Anastasios Georgiadis, Robin R. Ali .....	35
<b>A1-3 AAV-mediated gene therapy for MPS VI</b>	
Gabiella Cotugno, Patrizia Annunziata, Mark Haskins, Alberto Auricchio ..	41
<b>A1-4 Microdystrophin and myostatin gene therapy for Duchenne muscular dystrophy using adeno-associated virus vectors</b>	
Helen Foster, Taeyoung Koo, Alberto Malerba, Susan Jarmin, Takis Athanasopoulos, Keith Foster, George Dickson .....	46
<b>A1-5 AAV gene therapy for cardiovascular disorders</b>	
Serena Zacchigna, Mauro Giacca .....	55
<b>A1-6 AAV gene therapy for diabetes mellitus</b>	
Eduard Ayuso, Veronica Jimenez, David Callejas, Christopher Mann, Fatima Bosch .....	62
<b>A1-7 Approaches to large scale production of AAV-vectors</b>	
Otto-Wilhelm Merten, Philippe Moullier .....	71

<b>A1-8 Reference materials for the characterization of adeno-associated viral vectors</b>	
Eduard Ayuso, Véronique Blouin, Christophe Darmon, Fatima Bosch, Martin Lock, Richard O. Snyder, Philippe Moullier . . . . .	83

**TECHNOLOGIES - Retrovirus mediated gene transfer state-of-the-art**

<b>A2-1 Highlights on retrovirus mediated gene transfer</b>	
Pedro E. Cruz, Manuel J.T. Carrondo . . . . .	93
<b>A2-2 Retroviral vector development: reducing genotoxicity of integrated DNA and creating virus-like particles for transient cell modification</b>	
Melanie Galla, Tobias Maetzig, Julia D. Suerth, Ute Modlich, Axel Schambach, Christopher Baum . . . . .	100
<b>A2-3 Replication competent <math>\gamma</math>-retroviral vectors for tumor therapy</b>	
Thomas Schaser, Lydia Dürner, Klaus Cichutek, Christian J. Buchholz . . . . .	112
<b>A2-4 Modular retroviral producer cell lines</b>	
Ana Sofia Coroadinha, Dagmar Wirth, Ana F. Rodrigues, Leonor Gama-Norton, Caroline Duros, Alexandre Artus, Odile Cohen-Haguenaer, Paula Marques Alves, Pedro E. Cruz, Manuel J.T. Carrondo, Hansjörg Hauser . . . . .	118

**TECHNOLOGIES - Highlights on lentivirus mediated gene transfer**

<b>A3-1 Introduction</b>	
Matthias Schweizer, Klaus Cichutek . . . . .	127
<b>A3-2 MicroRNAs detargeting technology in the context of CNS applications</b>	
Angélique Colin, Mathilde Faideau, Noëlle Dufour, Gwennaëlle Auregan, Raymonde Hassig, Carole Escartin, Philippe Hantraye, Gilles Bonvento, Nicole Déglon . . . . .	129
<b>A3-3 Development of SIVsmmPBj vectors for gene transfer into myeloid cells</b>	
Matthias Schweizer, Klaus Cichutek . . . . .	134
<b>A3-4 Insulated retrovirus vectors using novel synthetic genetic insulator elements to circumvent enhancer-mediated genotoxicity</b>	
Caroline Duros, Alexandre Artus, Odile Cohen-Haguenaer . . . . .	138
<b>A3-5 Facing the challenges of downstream processing of lentiviral vectors</b>	
Vanessa Bandeira, Cristina Peixoto, Ana Sofia Coroadinha, Pedro E. Cruz, Manuel J.T. Carrondo, Otto-Wilhelm Merten, Paula Marques Alves . . . . .	150
<b>A3-6 Restrictions and requirements for stable lentiviral vector production in HEK293 cells</b>	
Leonor Gama-Norton, Hansjörg Hauser, Dagmar Wirth . . . . .	156

<b>A3-7 Novel lentiviral vector pseudotypes for stable gene transfer into resting hematopoietic cells</b>	
Els Verhoeyen, François-Loïc Cosset . . . . .	160

**TECHNOLOGIES - Highlights on gene-modified cell therapy**

<b>A4-1 Cell therapy: introduction</b>	
Gösta Gahrton . . . . .	185
<b>A4-2 <i>Ex-vivo</i> expansion of human mesenchymal stem cells</b>	
Pedro E. Cruz, Helder J.S. Cruz, Rita N. Bárcia, Jorge M. Santos, Susanne Pohl, Mari Gilljam, Kurt E.J. Dittmar, Werner Lindenmaier, Evren Alici . . . . .	187
<b>A4-3 Closed bag cultivation systems for the production of gene modified dendritic cells and MSC for clinical use</b>	
Werner Lindenmaier, Lars Macke, Wilhelm Meyring, Henk S.P. Garritsen, Kurt E.J. Dittmar, Kristina Lachmann, Michael Thomas . . . . .	194
<b>A4-4 Genetically modified NK cells for cancer treatment: facts and visions</b>	
Evren Alici, Gösta Gahrton . . . . .	201
<b>A4-5 Regulatory T lymphocyte depletion for cancer immunotherapies</b>	
Michelle Rosenzweig, François Lemoine, David Klatzmann . . . . .	208
<b>A4-6 Gene therapy of Fanconi's anaemia aplastic syndrome</b>	
Émilie Bayart, Caroline Duros, Alexandre Artus, Stéphanie Lemaire, Odile Cohen-Haguenaer . . . . .	216

**TECHNOLOGIES - Adenovirus mediated gene transfer: current developments**

<b>A5-1 Overview on adenovirus vectors</b>	
Stefan Kochanek . . . . .	229
<b>A5-2 Tumour barriers influencing adenovirus vector delivery and therapeutic efficacy</b>	
Tanja Lucas, Stefan Kochanek . . . . .	232
<b>A5-3 Tumor imaging with adenoviral vectors</b>	
Martina Anton, Bernd Gänsbacher . . . . .	238
<b>A5-4 Treatment of brain tumors with adenoviruses: preclinical development</b>	
Seppo Ylä-Herttuala . . . . .	242
<b>A5-5 Production and purification of Ad vectors: current status and future needs for adenovirus vector production</b>	
Ana Carina Silva, Daniel Simão, Marcos F.Q. Sousa, Cristina Peixoto, Pedro E. Cruz, Manuel J.T. Carrondo, Paula Marques Alves . . . . .	245

## **TECHNOLOGIES - Non-viral based gene transfer: a new era**

<b>A6-1 Non viral plasmid delivery and imaging of transgene expression</b>	
Pascal Bigey, Michel-Francis Bureau, Gonzalo Cordova, Virginie Escriou, Antoine Kichler, Nathalie Mignet, Daniel Scherman . . . . .	253
<b>A6-2 Overview of novel plasmid vectors and preclinical applications</b>	
Corinne Marie, Daniel Scherman . . . . .	266
<b>A6-3 Filling a gap: S/MAR-based replicating minicircles</b>	
Niels Heinz, Sandra Broll, Martin Schleef, Christopher Baum, Juergen Bode . . . . .	271
<b>A6-4 Manufacturing and QC of plasmid based vectors</b>	
Marco Schmeer, Martin Schleef . . . . .	277
<b>A6-5 <i>Sleeping Beauty</i> transposon based gene therapy</b>	
Zsuzsanna Izsvák, Zoltán Ivics . . . . .	284
<b>A6-6 Development of <i>minicircle</i> vectors</b>	
Marco Schmeer, Anja Rischmüller, Martin Schleef . . . . .	290
<b>A6-7 Exon skipping therapy for DMD using antisense oligomer technology</b>	
Linda Popplewell, Jagjeet Kang, Alberto Malerba, Keith Foster, George Dickson . . . . .	295

## **TECHNOLOGIES - Highlights on iPS induction, genetic stability and emerging technologies**

<b>A7-1 Induction of pluripotency from adult somatic cells: a review</b>	
Émilie Bayart, Odile Cohen-Haguenaer . . . . .	307
<b>A7-2 Genetic modification of adult stem cells and induced pluripotent stem cells with emerging transposon technologies</b>	
Thierry VandenDriessche, Marinee K.L. Chuah . . . . .	335
<b>A7-3 Targeted genome engineering approaches based on rare-cutting endonucleases: a tentative summary</b>	
Frédéric Pâques, Julianne Smith . . . . .	341
<b>A7-4 Targeted genome modifications with designer nucleases</b>	
Christien Bednarski, Eva-Maria Händel, Toni Cathomen . . . . .	354

## **PRE-CLINICAL STUDIES, BIOSAFETY AND ANIMAL MODELS - Preclinical assessment tools**

<b>B1-1 Preclinical assessment tools: imaging gene transfer to the brain</b>	
Yannic Waerzeggers, Thomas Viel, Sonja Schäfers, Parisa Monfared, Alexandra Winkeler, Andreas H. Jacobs . . . . .	371

<b>B1-2</b>	<b>Persistent luminescence nanoparticles for <i>in vivo</i> imaging: characteristics and targeting</b>	
	Thomas Maldiney, Daniel Scherman, Cyrille Richard . . . . .	386
<b>B1-3</b>	<b><i>Ex-vivo</i> evaluation of gene-transfer vectors: efficacy, tropism and safety</b>	
	Dror Kolodkin-Gal, Shay Tayeb, Abed Khalaileh, Gidi Zamir, Nikolai Kunicher, Amos Panet . . . . .	394
<b>PRE-CLINICAL STUDIES, BIOSAFETY AND ANIMAL MODELS - General biosafety: immune responses, immunotoxicity and genotoxicity</b>		
<b>B2-1</b>	<b>Assessing and taming unwanted immune responses induced by AAV gene transfer: current status, ongoing questions and future prospects</b>	
	Federico Mingozzi, Anne Galy, David Klatzmann . . . . .	405
<b>B2-2</b>	<b>Predicting immune responses to viral vectors and transgenes in gene therapy and vaccination: the coming of systems biology</b>	
	Bertrand Bellier, Adrien Six, Véronique Thomas-Vaslin, David Klatzmann . . . . .	420
<b>B2-3</b>	<b>Biosafety analysis in preclinical and clinical studies</b>	
	Manfred Schmidt, Stephanie Laufs, Alessandro Aiuti, Patrick Aubourg, Christopher Baum, Luca Biasco, Nathalie Cartier, Hansjörg Hauser, Eugenio Montini, Philippe Moullier, Richard O. Snyder, Dagmar Wirth, Christof von Kalle . . . . .	432

## **PART II: CLINICAL TRIALS AND REGULATORY ISSUES**

### **CLINICAL TRIALS**

<b>C1-1</b>	<b>A clinical trial of AAV-mediated gene therapy for Leber congenital amaurosis 2</b>	
	Alexander J. Smith, Robin R. Ali . . . . .	447
<b>C1-2</b>	<b>Gene therapy for X-linked adrenoleukodystrophy based on lentiviral correction of hematopoietic stem cells</b>	
	Nathalie Cartier, Salima Hacein-Bey-Abina, Cynthia C. Bartholomae, Manfred Schmidt, Christof von Kalle, Pierre Bougnères, Alain Fischer, Marina Cavazzana-Calvo, Patrick Aubourg . . . . .	452
<b>C1-3</b>	<b>Immune reconstitution after gene therapy for adenosine deaminase severe combined immunodeficiency (ADA-SCID)</b>	
	Immacolata Brigida, Alessandro Aiuti . . . . .	459
<b>C1-4</b>	<b>Gene therapy in Alzheimer disease patients</b>	
	Maria Eriksson-Jönhagen, Bengt Linderöth, Per Almqvist, Göran Lind, Helga Eyjolfsson, Erik Sundström, Åke Seiger, Lars Wahlberg . . . . .	465

<b>C1-5 Cardiovascular gene therapy trials</b>	
Seppo Ylä-Herttuala . . . . .	475
<b>C1-6 AAV-mediated gene therapy for haemophilia B</b>	
Deepak Raj, Edward G.D. Tuddenham, Arthur W. Nienhuis, Ulrike Reiss, Andrew M. Davidoff, Amit C. Nathwani . . . . .	479
<b>C1-7 ProSavin®: a lentiviral vector approach for the treatment of Parkinson’s disease</b>	
Stéphane Palfi , R. Scott Ralph, Kyriacos Mitrophanous . . . . .	486

**ETHICAL AND REGULATORY ISSUES**

<b>C2-1 Ethics in translation from research to therapy</b>	
Nancy M.P. King, Odile Cohen-Haguenaer, Alastair Kent . . . . .	495
<b>C2-2 Centralised regulation of gene therapy in Europe</b>	
Odile Cohen-Haguenaer . . . . .	504
<b>C2-3 The necessity for data sharing towards advancement of clinical translation: building up sample IMPD and substantiating master files</b>	
Odile Cohen-Haguenaer . . . . .	517

**INTEGRATION AND DISSEMINATION**

<b>C3-1 European Union support to gene transfer and gene therapy</b>	
Ruxandra Draghia-Akli . . . . .	531
<b>C3-2 Database of clinical trials</b>	
Bernd Gänsbacher . . . . .	533
<b>C3-3 CliniGene and ESGCT shared vision for gene therapy in Europe: past, present and future prospects</b>	
Thierry VandenDriessche, Bernd Gänsbacher, George Dickson, David Klatzmann, Seppo Ylä-Herttuala, Luigi Naldini, Alastair Kent, Odile Cohen-Haguenaer . . . . .	536

<b>AUTHOR INDEX . . . . .</b>	<b>541</b>
-------------------------------	------------