Preface

A Brief Outline of the Aims and Target Audience of Liver Stem Cells

The role of a putative stem cells and liver-specific stem cell in regeneration and carcinogenesis is reviewed in this book.

There is increasing evidence that there is a liver stem cell that has the capacity to differentiate into parenchymal hepatocytes or into bile ductular cells. These stem cells may be activated to proliferate after severe liver injury or exposure to hepatocarcinogens. Stem cell replacement strategies are therefore being investigated as an attractive alternative approach to liver repair and regeneration. In this book, we focus on recent preclinical and clinical investigations that explore the therapeutic potential of stem cells in repair of liver injuries. Several types of stem cells, such as embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, haematopoietic stem cells, and mesenchymal stem cells, can be induced to differentiate into hepatocyte-like cells in vitro and in vivo. Stem cell transplantation has been shown to significantly improve liver function and increase survival in experimentally induced liver-injury models in animals. Furthermore, several pilot clinical studies have reported encouraging therapeutic potential of stem cell-based therapies. This book consists of five main categories: (1) Several hepatic progenitor cells; (2) Hepatic differentiation from stem cells; (3) Bile ductal cell formation from stem cells; (4) Liver stem cells and hepatocarcinogenesis; and (5) Application of liver stem cells for cell therapy. All these current topics shed light on stem cell technology which may lead to the development of effective clinical modalities for human liver diseases.

I believe this book will become the gold standard on this topic and will be widely distributed and read by people in many scientific fields, such as cellular biology, molecular biology, tissue engineering, liver biology, cancer biology, and stem cell therapy.

Tokyo, Japan

Takahiro Ochiya
## Contents

*Preface* ................................................................. v  
*Contributors* .......................................................... ix  

### PART I  SEVERAL HEPATIC PROGENITOR CELLS

1 Purification and Culture of Fetal Mouse Hepatoblasts that Are Precursors of Mature Hepatocytes and Biliary Epithelial Cells ............................ 3  
*Nobuyoshi Shiojiri and Miho Nitou*  

2 Clinical Uses of Liver Stem Cells ......................................... 11  
*Yock Young Dan*  

3 Identification and Isolation of Adult Liver Stem/Progenitor Cells .............. 25  
*Minoru Tanaka and Atsushi Miyajima*  

4 Isolation and Purification Method of Mouse Fetal Hepatoblasts ............. 33  
*Luc Gailhouste*  

5 Isolation of Hepatic Progenitor Cells from the Galactosamine-Treated Rat Liver ................................................................. 49  
*Norihisa Ichinohe, Junko Kon, and Toshihiro Mitaka*  

### PART II  HEPATIC DIFFERENTIATION FROM STEM CELLS

6 Purification of Adipose Tissue Mesenchymal Stem Cells and Differentiation Toward Hepatic-Like Cells ......................................................... 61  
*Agnieszka Banas*  

7 Development of Immortalized Hepatocyte-Like Cells from hMSCs. .......... 73  
*Adisak Wongkajornsilp, Khanit Sa-ngiamsuntorn, and Suradej Hongeng*  

8 Isolation of Adult Human Pluripotent Stem Cells from Mesenchymal Cell Populations and Their Application to Liver Damages ..................... 89  
*Shohei Wakao, Masaaki Kitada, Yasumasa Kuroda, and Mari Dezawa*  

9 Generation and Hepatic Differentiation of Human iPS Cells ................ 103  
*Tetsuya Ishikawa, Keitaro Hagiwara, and Takahiro Ochiya*  

10 Efficient Hepatic Differentiation from Human iPS Cells by Gene Transfer ................................................................. 115  
*Kenji Kawabata, Mitsuru Inamura, and Hiroyuki Mizuguchi*
11 “Tet-On” System Toward Hepatic Differentiation of Human Mesenchymal Stem Cells by Hepatocyte Nuclear Factor ................................. 125
Goshi Shiota and Yoko Yoshida

12 SAMe and HuR in Liver Physiology ....................................................... 133
Laura Gomez-Santos, Mercedes Vazquez-Chantada, Jose Maria Mato, and Maria Luz Martinez-Chantar

PART III BD FORMATION FROM STEM CELLS

13 Transdifferentiation of Mature Hepatocytes into Bile Duct/ductule Cells Within a Collagen Gel Matrix .................................................. 153
Yuji Nishikawa

PART IV LIVER STEM CELLS AND HEPATOCARCINOGENESIS

14 Identification of Cancer Stem Cell-Related MicroRNAs in Hepatocellular Carcinoma ................................................................. 163
Junfang Ji and Xin Wei Wang

PART V APPLICATION OF LIVER STEM CELLS FOR CELL THERAPY

15 Intravenous Human Mesenchymal Stem Cells Transplantation in NOD/SCID Mice Preserve Liver Integrity of Irradiation Damage ...... 179
Moubarak Mouiseddine, Sabine François, Maâmar Souidi, and Alain Chapel

16 Engineering of Implantable Liver Tissues ............................................. 189

17 Mesenchymal Stem Cell Therapy on Murine Model of Nonalcoholic Steatohepatitis ................................................................. 217
Yoshio Sakai and Shuichi Kaneko

Index ........................................................................................................... 225
Contributors

AGNIESZKA BANAS • Laboratory of Molecular Biology, Institute of Obstetrics and Medical Rescue, University of Rzeszów, Faculty of Medicine, Rzeszow, Poland

ALAIN CHAPEL • IRSN, DRPH/SRBE/LTCRA, CEDEX 92262, France

YOCK YOUNG DAN • Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

MARI DEZAWA • Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan

F. EVENOU • Laboratoire Matière et Systèmes Complexes (MSC), Bâtiment Condorcet, Université Paris Diderot, Paris 7, France

SABINE FRANÇOIS • IRSN, DRPH/SRBE/LTCRA, CEDEX 92262, France

T. FUJII • Institute of Industrial Science, University of Tokyo, Tokyo, Japan

LUC GAILHOUSTE • Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan

LAURA GOMEZ-SANTOS • Metabolomics Unit, CIC bioGUNE, Technology Park of Bizkaia, Bizkaia, Basque Country, Spain

KEITARO HAGIWARA • Division of Molecular and Cellular Medicine, National cancer Center Research Institute, Tokyo, Japan

M. HAMON • Department of Mechanical Engineering, Auburn University, Auburn, AL, USA

SURADEJ HONGENG • Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

H. HUANG • Okami Chemical Industry Co. Ltd, Kyoto, Japan

NORIHISA ICHINOHE • Department of Tissue Development and Regeneration, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

MITSURU INAMURA • Department of Biochemistry and Molecular Biology, Graduate School of Pharmaceutical Science, Osaka University, Osaka, Japan

TETSUYA ISHIKAWA • Core Facilities for Research and Innovative Medicine, National cancer Center Research Institute, Tokyo, Japan

JUNFANG JI • Laboratory of Human Carcinogenesis, Bethesda, MD, USA

SHUICHI KANeko • Center for Liver Diseases, Kanazawa University Hospital, Kanazawa, Japan; Department of Gastroenterology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

KENJI KAWABATA • Laboratory of Stem Cell Regulation, National Institute of Biomedical Innovation, Osaka, Japan

MASAAKI KITADA • Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan

JUNKO KON • Department of Tissue Development and Regeneration, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

N. KOJIMA • Institute of Industrial Science, University of Tokyo, Tokyo, Japan
YASUMASA KURODA • Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan
JOSE MARIA MATO • CIC bioGUNE, Technology Park of Bizkaia, Bizkaia, Basque Country, Spain
MARIA LUZ MARTINEZ-CHANTAR • CICbioGUNE, Metabolomics Unit, Bizkaia, Basque Country, Spain
TOSHIHIRO MITAKA • Department of Tissue Development and Regeneration, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan
ATSUSHI MIYAJIMA • Laboratory of Cell Growth and Differentiation, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan
K.P. MONTAGNE • Institute of Industrial Science, University of Tokyo, Tokyo, Japan
HIROYUKI MIZUGUCHI • Department of Biochemistry and Molecular Biology, Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan
MOUBARAK MOUISEDDINE • IRSN, DRPH/SRBE/LTCRA, CEDEX 92262, France
YUJI NISHIKAWA • Division of Tumor Pathology, Department of Pathology, Asahikawa Medical University, Asahikawa, Japan
T. NIINO • Institute of Industrial Science, University of Tokyo, Tokyo, Japan
M. NISHIKAWA • Renal Regeneration Laboratory, VAGLAHS at Sepulveda & UCLA David Geffen School of Medicine, Los Angeles, CA, USA
MIHO NITOU • Department of Biology, Faculty of Science, Shizuoka University, Shizuoka, Japan
TAKAHIRO OCHIYA • Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan
K.H. SA-NGIAMSUNTORN • Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
NOBUYOSHI SHIOJIRI • Department of Biology, Faculty of Science, Shizuoka University, Shizuoka, Japan
GOSHI SHIOTA • Division of Molecular and Genetic Medicine, Department of Genetic Medicine and Regenerative Therapeutics, Graduate School of Medicine, Tottori University, Tonnag, Japan
MAâMAR SOUIDI • IRSN, DRPH/SRBE/LTCRA, CEDEX 92262, France
MINORU TANAKA • Laboratory of Cell Growth and Differentiation, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan
MERCEDES VAZQUEZ-CHANTADA • CIC bioGUNE, Technology Park of Bizkaia, Bizkaia, Basque Country, Spain
XIN WEI WANG • Laboratory of Human Carcinogenesis, Bethesda, MD, USA
SHOHEI WAKAO • Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan
ADISAK WONGKAJORNSILP • Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
YOKO YOSHIDA • Department of Molecular Neuropathology, Tokyo Metropolitan Institute for Neuroscience, Tokyo, Japan