CONTENTS

VOLUME XII

TP53 Gene and P53 Protein as Targets in Cancer Management and therapy **1**
Daniela Maurici, *International Agency for Research on Cancer, WHO, France*
Pierre Hainaut, *International Agency for Research on Cancer, WHO, France*

1. Introduction
2. TP53 Mutations and Human Cancer
3. The p53 Protein—A Sensor of Genotoxic Stress
4. Gene Therapy Using TP53
   - 4.1. Replacement Gene Therapy
     - 4.1.1. Viral Delivery
     - 4.1.2. Non-viral Delivery
   - 4.2. E1B-defective Adenoviruses
5. The p53 Pathway as a Target for Pharmacological Intervention
   - 5.1. Restoration of Wild-type p53 Functions
   - 5.2. Modulation of Wild-type p53
     - 5.2.1. Use of Mdm2 Peptides to Stabilize Wild-type p53
     - 5.2.2. Biochemical Modulation of p53 Protein Activity
     - 5.2.3. Inhibiting Wild-type p53: Pifithrin
   - 5.3. Amifostine—A Drug that Targets the p53 Pathway
6. TP53 in Cancer Detection and Monitoring
   - 6.1. Auto Antibodies to p53
   - 6.2. Plasmatic Free TP53 DNA
7. Perspectives and Future Challenges

Plant-Made Vaccines- The Past, Present and Future **27**
Dwayne D. Kirk, *Monash University, Australia*
Amanda M. Walmsley, *Monash University, Australia*

1. Introduction
2. Traditional Vaccines
3. New Generation Vaccines
4. Plant-made Vaccines
5. Plant-made Vaccine History
6. The Successful Plant-made Vaccine
7. The Future
   - 7.1. Plant Expression Systems
   - 7.2. Processing of Plant Materials and Stability of Vaccines
   - 7.3. Intellectual Property, Freedom to Operate and Regulations
   - 7.4. Commercial Feasibility of Plant-made Vaccines

Transgenic Mice in Immunobiology **37**
Harri Alenius, *Finnish Institute of Occupational Health, Finland*

1. Introduction
2. Strategies to Generate Transgenic Mice
   - 2.1. Gene targeting with homologous recombination
   - 2.2. Cre/loxP System in Chromosomal Engineering
   - 2.3. Inducible Gene Expression with Tetracycline Transactivator System
   - 2.4. Gene Targeting by Inducible Activation System
   - 2.5. Tissue Specific Control of Gene Expression

3. Transgenic Mice and the Immune System
   3.1. RAG-Deficient Blastocyst Complementation
   3.2. Transgenic Mice in the Study of Immunological Diseases
      3.2.1. X-Linked SCID
      3.2.2. Type I Diabetes
      3.2.3. Allergic asthma
4. Future Perspectives

Nanomedicine and Medical Nanorobotics **59**
Robert A. Freitas, *Institute for Molecular Manufacturing, USA*

1. Nanotechnology and Nanomedicine
2. Medical Nanomaterials and Nanodevices
   2.1. Nanopores
   2.2. Artificial Binding Sites and Molecular Imprinting
   2.3. Quantum Dots and Nanocrystals
   2.4. Fullerenes and Nanotubes
   2.5. Nanoshells and Magnetic Nanoprobes
   2.6. Targeted Nanoparticles and Smart Drugs
   2.7. Dendrimers and Dendrimer-Based Devices
   2.8. Radio-Controlled Biomolecules
3. Microscale Biological Robots
4. Medical Nanorobotics
   4.1. Early Thinking in Medical Nanorobotics
   4.2. Nanorobot Parts and Components
      4.2.1. Nanobearings and Nanogears
      4.2.2. Nanomotors and Power Sources
      4.2.3. Nanocomputers
   4.3. Self-Assembly and Directed Parts Assembly
      4.3.1. Self-Assembly of Mechanical Parts
      4.3.2. DNA-Directed Assembly
      4.3.3. Protein-Directed Assembly
      4.3.4. Microbe- and Virus-Directed Assembly
   4.4. Positional Assembly and Molecular Manufacturing
      4.4.1. Diamond Mechanosynthesis
      4.4.2. Massively Parallel Manufacturing
   4.5. Medical Nanorobot Designs and Scaling Studies
      4.5.1. Respirocytes
      4.5.2. Microbivores

Role of Xenobiotic Metabolism in Drug Discovery and Development **108**
Rristo Juvonen, *University of Kuopio, Finland*
Paavo Honkakoski, *University of Kuopio, Finland*
Paivi Taavitsainen, *University of Oulu, Finland*
Hannu Raunio, *University of Kuopio, Finland*
Olavi Pelkonen, *University of Oulu, Finland*

1. Introduction
2. General Aspects of Xenobiotic Metabolism
   2.1. Role of Metabolic Studies during Drug Development
   2.2. Overview of Drug Metabolising Enzymes
   2.3. CYP Enzymes involved in Xenobiotic Metabolism
   2.4. CYP3A4
   2.5. CYP Enzymes and Drug Development
3. Methods for Studying in vitro Metabolism
   3.1. Human Liver Microsomes

3.2. Human Hepatocytes
3.3. Permanent Cell Lines and Liver Slices
3.4. DNA-expressed Enzymes
4. Determination of Metabolism in in vitro Systems
4.1. Metabolic Stability of an NCE
4.2. Identification of Metabolites and Metabolic Routes
4.3. Identification of CYPs Metabolising an NCE
4.4. Utilisation of CYP-selective Chemical Inhibitors
4.5. Utilisation of CYP-specific Antibodies
4.6. cDNA-expressed CYPs
4.7. Correlation Analysis
4.8. Measures of Affinities of an NCE for CYPs
4.9. High-throughput Screening in Drug Metabolism
5. In vitro - in vivo Scaling of an NCE
5.1. Apparent Enzyme Kinetic Parameters K_m and V_{max}
5.2. Prediction of the Intrinsic Clearance (Cl_{int})
5.3. Extrapolation of Cl_{int} to in vivo clearance in the whole organism
5.4. Apparent K_i and Type of Inhibition
5.5. Prediction of Drug-drug Interactions
6. Induction of CYP Enzymes
6.1. Mechanisms of Induction for Major Drug-metabolising CYPs
6.2. Species and Inter-individual Differences in Induction
6.3. Assay systems for Induction
7. Modelling of CYP Enzymes
8. In Vitro versus in Vivo
9. Conclusions

From Gene to Clinical Product: An Overview of GMP Requirements Associated to the Development of New Biotherapeutics, in a Multiprocess/Multiproduct Facility **137**
Alex Bollen, *University of Brussels, Belgium*
Jean-Francois Pollet, *Henogen sa, Belgium*

1. Introduction
2. Basic requirements for a State-of-the-Art Biopharmaceutical Development Facility
2.1. The quality management concepts and the current Good Manufacturing Practice (cGMP)
2.1.1. *Quality Assurance [QA]*
2.1.2. *Current Good Manufacturing Practice for medicinal product [cGMP]*
2.1.3. Quality Control [QC]
2.2. Design of building, facilities and equipment
2.3. Organisation and management of documentation for pharmaceutical development and cGMP
2.3.1. Manufacturing formulae and specifications
2.3.2. Procedures
2.3.3. Instructions
2.3.4. Records
2.4. Personnel training requirements
2.5. Validation contingencies in pharmaceutical production
2.5.1. Design Specification [DS]
2.5.2. Installation Qualification [IQ]
2.5.3. Operational Qualification [OQ]
2.5.4. Performance Qualification [PQ]
3. General considerations for a multi-process/multi-product biotech manufacturing facility
3.1. Design of a multi-process/multi-product facility and prevention of cross-contamination
3.2. Personnel, material, product and waste flows
3.3. HVAC system requirements for biotech multi-product facilities
3.4. Biosafety requirements
3.5. Decontamination and cleaning

4. Requirements for manufacture and quality control of investigational medicinal products derived by biotechnological processes
   4.1. Control of starting materials
   4.2. Seed lot and cell bank system
   4.3. Fermentation, or cell culture, and harvesting
   4.4. Extraction, purification and downstream processing
   4.5. Filling/packaging operations, control of final product and batch release
   4.6. Stability considerations and storage
   4.7. Pre-clinical safety evaluation
5. Conclusions

The Impact of Patents on Medical Biotechnology **166**
Jane Nielsen, *University of Tasmania, Australia*
Dianne Nicol, *University of Tasmania, Australia*

1. Introduction
2. Key features of patent law
3. Restrictions on use of gene and research tool patents
4. Increasing complexity of the patent landscape
5. Social policy considerations in the healthcare arena
6. Social policy considerations in the public sector research arena
7. The way forward
8. Conclusion

Human Genetic Data Banks: From Consent to Commercialization - An Overview of Current Concerns and Coundrums **183**
Lori Luther, *University of Toronto, Canada*
Trudo Lemmens, *University of Toronto, Canada*

1. Introduction
2. Types of Biobanks: Population Banks vs. Disease Specific Banks
   2.1. Types of Banks
      2.1.1. Population Biobanks
      2.1.2. Specific Disease Banks
3. Legal and Ethical Issues in the Establishment and Use of Biobanks: How to Reconcile Autonomy with the Existence of Common Interests?
   3.1. Consent
      3.1.1. Types of Consent
         3.1.1.1. General and Specific Consent
         3.1.1.2. Presumed and Prior Informed Consent
         3.1.1.3. Individual and group consent
      3.1.2. Alternatives to Consent
         3.1.2.1. Informed Permission/Authorization
         3.1.2.2. A 2-step process
         3.1.2.3. Co-mingling of broad and specific consent
      3.1.3. Public Consultation as a Middle Ground to Consent
      3.1.4. Exceptions to Consent – Including but not Limited to Research
   3.2. Confidentiality
   3.3. Privacy
   3.4. Duty To Warn Family Members
   3.5. Access
      3.5.1. Participant Access
      3.5.2. Researcher Access
      3.5.3. Third-Party Access
         3.5.3.1. Family Members
         3.5.3.2. Insurers

3.5.3.3. Employers
3.5.3.4. Participants Physicians
3.5.3.5. The State
3.6. Genetic Discrimination
4. Commercialization of Genetic Data: Common Heritage of Humanity vs. Private Interests?
4.1. Commercialization
4.2. Benefit Sharing
4.3. Ownership
4.3.1. Population Banks
4.3.2. Private Banks
4.3.3. Case Law
5. Public Involvement: Can or Should Researchers and Participants be Partners?
6. Conclusion

The Status of the Extracorporal Embryo [Stem Cells] **217**
H. Nys, *Catholic University of Leuven, Belgium*
Brant Hansen, *Catholic University of Leuven, Leuven*

1. The Legal Situation
1.1. The embryo in vitro
1.1.1. Introduction
1.1.2. History of the Embryo Law: European conformity
1.1.3. Definition of the extracorporeal embryo
1.1.4. Research on supernumerary embryos
1.1.5. Creation of embryos solely for research purposes
1.1.6. Prohibitory clauses
1.2. Medically Assisted Procreation
1.3. The embryo in vivo
1.3.1. Termination of pregnancy by a physician
1.3.2. Evaluation of the application of the law
2. Ethical evaluation: The Belgian (federal) Council on Bioethics
2.1. Human reproductive cloning
2.2. Research on human embryos in vitro
2.3. Sex selection
3. Factual Material
3.1. Demographic Structure
3.2. Medically Assisted Reproduction
3.3. Reproductive Tourism
3.4. Termination of pregnancy
3.5. On the limits of biomedicine

Bioterrorism by Biotechnology: Implications for Clinical Medicine **235**
Gifty Immanuel, *Center for AIDS and Antiviral Research, 37 Tenth Street, Tooveypuram, Tuticorin, Tamilnadu, INDIA*

1. Introduction
2. Biotechniques in Bioweaponeering
2.1. Genetic Engineering
2.2. Synthetic Biology
2.3. Nanotechnology
2.4. Dual Agent Fabrication
2.5. Bioregulators Production
2.6. Toxin Synthesis
2.7. Transgenesis
2.8. Genome Sequencing
3. Counter Strategies in Clinical Medicine

3.1. Electron Microscopy
3.2. Genomics, Proteomics and Microarrays
3.3. Biosensors
3.4. Syndromic Surveillance
3.5. Radiation and Chemical Inactivation
3.6. Phage Therapy
3.7. Immunostimulants, Modulators and Enhancers
3.8. Gene Silencing and Gene therapy
3.9. Monoclonal Antibodies and Molecular Decoys
3.10. Nanobiotechnology
3.11. Serum Therapy and Biotherapy
3.12. Vaccines, Antitoxins and Toxoids
3.13. Hemodialysis, Hemofiltration and Plasmapheresis
3.14. Edible Vaccine and Plantibodies
4. Conclusion

HumanF Papillomavirus-Mediated Transformation of The Anogential Tract 253
Renske D.M. Steenbergen, *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*
Jillian de Wilde, *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*
Saskia M. Wilting, *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*
Antoinette A.T.P. Brink, *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*
Peter J.F. Snijders , *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*
Chris J.L.M. Meijer, *Department. Of Pathology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.*

1. HPV in anogenital cancers
2. HPV and cervical cancer development
3. HPV-mediated transformation: additive events
4. Deregulation of E6 and E7 transcription
5. E6 and E7, the viral oncogenes
6. HPV-mediated immortalization
7. Telomerase activation
8. Chromosomal alterations
9. Epigenetic alterations in cervical cancer
10. Concept of multistep process of HPV-mediated carcinogenesis and future perspectives

Index 269

About EOLSS 273