

Summary

The present volume describes our current knowledge regarding transgenesis and cloning techniques in mammals, their applications for research, and the development of novel therapies. It also reviews the spectacular developments in research on stem cells isolated from different origins and their potential use in regenerative medicine. Numerous therapeutic proteins produced from genetically modified unicellular organisms are routinely used in medicine today.

The development, roughly 15 years ago, of experimental procedures to create genetically modified organisms (or transgenics) by the addition or replacement of genes has created an extraordinary tool to study these organisms. In the mouse, the privileged model for the study of mammalian organisms, these procedures led to the accumulation of an impressive body of results contributing to the improved understanding of molecular mechanisms underlying embryonic development, physiology and pathologies of the nervous system, the immune system, the developing musculature, the reproductive system etc. Transgenesis has also given a remarkable impetus to the development of mouse models for human genetic diseases.

The transfer of somatic nuclei into enucleated oocytes (referred to as cloning), permits the reconstitution of embryos that, upon implantation into a receiving female, can develop to term and be born as physiological normal and fertile animals. In combination with the genetic modification of somatic cells in culture prior being used as nuclei donors, cloning could contribute to the development of transgenesis among non-rodent mammals. The pioneering successes illustrate the potential of this approach for targeted modifications of the genome. Nevertheless the low efficiency and more over the high frequency of fetal and perinatal physiopathologies observed with cloned animals limit the current applications of this technic. This approach has to be used with priority for the better understanding of the fundamental mechanisms that enable the

gain of the full functions of an embryonic nucleus by a nucleus isolated from differentiated cells.

The dramatic lack of human donors for organ transplantation may be solved in the near future by the use of animal organs. Up until the present time, hyperacute rejection and the risk of zoonosis have restrained this new therapeutic strategy. However, the development of organ xenotransplantation may benefit today from gene transfer techniques allowing immuno-modulation and optimized selection and control of the donor animals. These new techniques might be able to minimize the risk of both hyperacute rejection and zoonosis, although it will still be necessary to demonstrate the absence of virus transfer to the general population. Not only would the efficacy of these techniques make organ xenotransplantation in humans possible, but they would also procure more compatible tissues and cells for tissue repair and engineering. Research in these fields must be developed, not only because of their medical interest but also, and more importantly, because they may contribute to improved understanding of tissue compatibility and interspecies infections.

Stem cells open up new therapeutic possibilities, but important questions about their identity and manipulation remain to be resolved. A cell which is multipotent, and has a very considerable proliferative capacity, is considered to be a stem cell. The properties of cells which correspond to this definition, both in the embryo and in adult tissues, are presented. The discussion mainly concerns mammalian cells. Different sources of stem cells are examined in the context of human cell therapy.

The development of biotherapies is largely welcomed as they may provide cures to diverse pathological situations. A concerted effort by different professional groups, including scientists, physicians, industrialists, patient associations, and regulatory authorities, should permit the harmonious development of research programmes from the exploratory phases in experimental animal models through to clinical trials. The object of the present chapter is to illustrate the uniqueness of this coordinated pathway and to pinpoint several key concerns. These include the requirement for a rigorous scientific approach, the importance of physiological studies requiring an ambitious programme of gene inactivation in the mouse, debate about the future of stem cell research, the bottle-neck that represents experimentation in large animals and the need for multidisciplinary hospital structures.

Protein-drugs constitute a specific class of tools within the battery of drugs used for therapeutic treatment. Isolated initially from tissues or body fluids of animal or human origin, their availability and quality are insufficient. The development of genetic engineering procedures and the progress made in biological research permitted the replacement of extracted products by proteins isolated from genetically modified unicel-

lular organisms (e.g. insulin, growth hormone, blood coagulation factors etc). These new approaches also gave rise to the development and marketing of novel protein-drugs unknown previously. In several cases, these novel protein-drugs contributed to significant progress in the treatment of previously incurable diseases. The battery of drugs presently includes about a dozen cytokines, and secreted proteins with diverse biological functions spanning from the stimulation of hemato-poiesis (erythropoietin) to the inhibition of Hepatic Virus C chronic infection (interféron α). A second class includes enzymes or blood coagulation factors. Finally, monoclonal antibodies are used in oncology and diagnostic. The same approach was used for the development of a new generation of safer vaccines against hepatitis A and B viruses.

The Genetically Modified Organisms (GMO) currently used for protein production are cultivated in contained facilities. We also discuss the advantages and inconveniences of producing such drugs in transgenic animals or plants. Finally, gene therapy can also be considered as the administration of GMO-derived drugs and we discuss its potential application.

