Preface

A new era of developmental and molecular biology has grown from the successful derivation of undifferentiated embryonic stem (ES) cells from mouse embryos by Evans and Kaufmann [1981] and Martin [1981], and the application of gene targeting technology to ES cells by Thomas and Capecchi [1987]. As a direct consequence of these advances, hundreds of mutant mouse ('knock-out' and 'knock-in') strains have been established that pass genetic modifications to their offspring through germ-line transmission. ES cells not only give rise to all cell types in a mouse, but they differentiate in vitro into cells of endodermal, ectodermal and mesodermal lineages when cultured in three-dimensional aggregates called embryoid bodies. By using different methods to generate embryoid bodies, protocols have been established to differentiate ES cells into cardiogenic, myogenic, neurogenic, adipogenic, vascular and hematopoietic cells; consequently, more complex processes of cell differentiation, like vasculogenesis and angiogenesis, or neuromuscular interaction and synaptogenesis can be analyzed in culture. The use of ES cells for studying in vitro the regulation of cellular differentiation during early embryonic development by 'gain of function' and 'loss of function' analyses, the establishment of routine assays for pharmacological and toxicological screening procedures and, more recently, the selective differentiation of ES cells into specific somatic cell lineages are fields where ES cells have become more widely employed and accepted. Differentiation of ES cells in culture thus has developed into one of the most important cellular systems for the study of developmental biology.

The idea of a Special Issue to summarize our present knowledge of ES cell biology and their developmental

potential in vitro arose at a Stem Cell Workshop held at an International Meeting of the European Tissue Culture Society in Mainz, October 1997. It seemed everyone was aware that it was only a matter of time until pluripotent stem cells of human origin would become available, and we discussed the potential prospects and problems of employing technologies with human ES cells at this meeting. In November 1998, the successful derivation of pluripotent embryo and primordial germ cell-derived cell lines originating from human embryonic and fetal tissue was reported by Thomson and Gearhart and their coworkers. The use of human ES cells for molecular and developmental biology and the exciting prospect of using these cells for human therapy seemed within grasp. It was only reasonable to assume that the techniques of in vitro differentiation which were established for mouse ES cells – together with the nuclear transfer technology described by Campbell and Wilmut [1997] – would be applied to pluripotent stem cells of human origin. Although some recent reviews devoted to specific fields like cardiogenesis are available [see Hescheler et al., 1997; Metzger et al., 1997; Wobus and Guan, 1998], a more comprehensive review of current uses and strategies with mouse ES cells was not. In this context, a Special Issue devoted to Embryonic Stem Cells as Developmental Model in vitro was envisioned.

Leading experts working with ES cells were contacted and invited to submit articles for this issue. Although not everyone could submit a manuscript within the designated time frame, this issue is a compilation of their and our efforts to present a comprehensive overview of the uses of ES cells in vitro. The first two chapters are dedicated to

molecular mechanisms regulating self-renewal and differentiation of ES cells (Burdon et al.) and the expression pattern of Oct-4, a key regulator of totipotency during the mammalian life cycle (Pesce et al.). The following articles review the present knowledge of ES cell-derived neurogenesis (Gottlieb and Huettner), adipogenesis (Dani) and hematopoiesis (Hole) on tissue-restricted gene and protein expression. To study developmental aspects of ion channel formation and signalling cascades during early developmental stages, one chapter is devoted to confocal imaging and patch clamp analyses of differentiated cells derived from ES cells (Hescheler et al.). The use of differentiation factors and signalling molecules for selective differentiation of ES cells will become more and more important; therefore, the effects of retinoic acid on stage-dependent differentiation of ES cells is summarized (Rohwedel et al.). Another article describes the use of ES cells in an in vitro embryotoxicity screening system, which is already part of a validation study of the European Union (Scholz et al.). Two chapters summarize the attempts to establish pluripotent cell lines from species other than mouse (Pain et al.), including the most recent strategies to introduce genetic modifications into livestock by nuclear transfer (Prelle et al.). The results of the nuclear transfer technology employed by Campbell and Wilmut [1997] led us to use the terms 'totipotent' for zygotes and blastomeres of early cleavage stage embryos, and 'pluripotent' for cells and cell lines derived from either the inner cell mass or primordial germ cells. As already mentioned, one of the most exciting areas of ES cell research is the isolation and exploitation of pluripotent stem cells of human origin and their possible use in tissue transplantations, a topic addressed in the final chapter of this issue (Boheler and Fiszman).

We are aware that the application of ES cell technology to pluripotent human ES cell lines has enormous ethical implications. International regulations for the use of stem cells and nuclear transfer techniques with human cells are needed to prevent abuse and overcome legal problems within and between countries. Perhaps the scientific information contained within this Special Issue will serve to inform and educate those interested parties involved in the debate on the uses and limitations of ES cells.

Finally, we are deeply grateful to the contributing authors for their participation and significant contributions to this issue. Although it was not possible to include all the interesting features of in vitro differentiated ES cells, it is hoped that this issue and the references included within will be valued by cell biologists working with pluripotent ES cells, both in vivo and in vitro, and those researchers who may wish to employ this highly versatile system in their studies in biotechnology and pharmacotoxicology, as well as in the establishment of techniques for tissue repair and cell therapy.

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