

# Embryonic stem cell research and its applications for treating certain human diseases



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## ABSTRACT

Embryonic stem cells, as their name suggests, are derived from embryos. Most embryonic stem cells are derived from embryos that develop from eggs that have been fertilized *in vitro*—in an *in vitro* fertilization clinic—and then donated for research purposes with informed consent of the donors. They are not derived from eggs fertilized in a woman's body.

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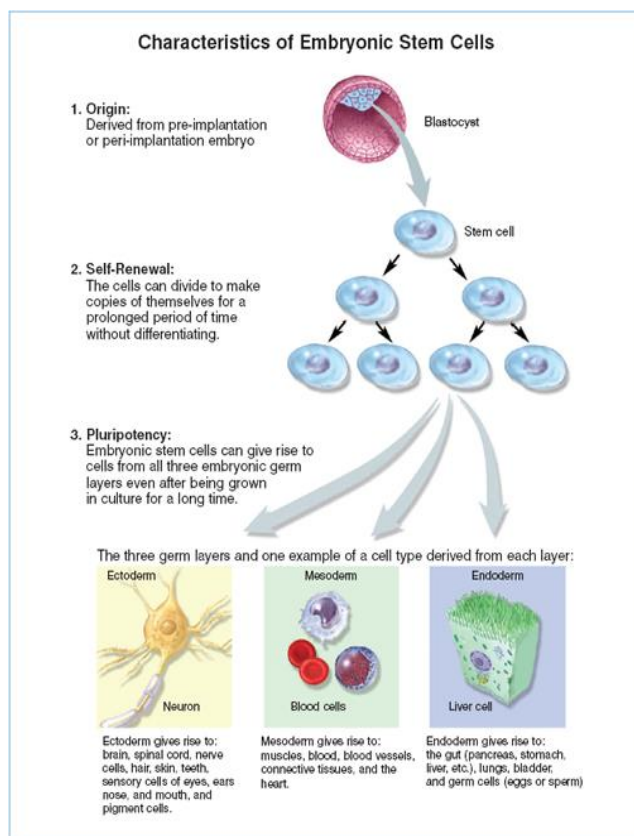
## INTRODUCTION

Human embryonic stem (ES) cells capture the imagination because they are immortal and have an almost unlimited developmental potential (Fig. 1.1: How hESCs are derived). After many months of growth in culture dishes, these remarkable cells maintain the ability to form cells ranging from muscle to nerve to blood—potentially any cell type that makes up the body. The proliferative and developmental potential of human ES cells promises an essentially unlimited supply of specific cell types for basic research and for transplantation therapies for diseases ranging from heart disease to Parkinson's disease to leukemia. Here we discuss the origin and properties of human ES cells, their implications for basic research and human medicine, and recent research progress since August 2001, when President George W. Bush allowed federal funding of this research for the first time. What Are

### Embryonic Stem Cells?

Embryonic stem cells are derived from embryos at a developmental stage before the time that implantation would normally occur in the uterus. Fertilization normally occurs in the oviduct, and during the next few days, a series of cleavage divisions occur as the embryo travels down the oviduct and into the uterus. Each of the cells (blastomeres) of these cleavage-stage embryos are undifferentiated, i.e. they do not look or act like the specialized cells of the adult, and the blastomeres are not yet committed to becoming any particular type of differentiated cell. Indeed, each of these blastomeres has the potential to give rise to any cell of the body. The first differentiation event in humans occurs at approximately five days of development, when an outer layer of cells committed to becoming part of the placenta (the trophoctoderm)

separates from the inner cell mass (ICM). The ICM cells have the potential to generate any cell type of the body, but after implantation, they are quickly depleted as they differentiate to other cell types with more limited developmental potential. However, if the ICM is removed from its normal embryonic environment and cultured under appropriate conditions, the ICM-derived cells can continue to proliferate and replicate themselves indefinitely and still maintain the developmental potential to form any cell type of the body



## Pluripotency of ES Cells

The ability of ES cells to develop into all cell types of the body has fascinated scientists for years, yet remarkably little is known about factors that make one cell pluripotent and another more restricted in

its developmental potential. The transcription factor Oct4 has been used as a key marker for ES cells and for the pluripotent cells of the intact embryo, and its expression must be maintained at a critical level for ES cells to remain undifferentiated.

The Oct4 protein itself, however, is insufficient to maintain ES cells in the undifferentiated state. Recently, two groups identified another transcription factor, Nanog, that is essential for the maintenance of the undifferentiated state of mouse ES cells.

The expression of Nanog decreased rapidly as mouse ES cells differentiated, and when its expression level was maintained by a constitutive promoter, mouse ES cells could remain undifferentiated and proliferate in the absence of either LIF or BMP in serum-free medium. Nanog is also expressed in human ES cells, though at a much lower level compared to that of Oct4, and its function in human ES cells has yet to be examined.

By comparing gene expression patterns between different ES cell lines and between ES cells and other cell types such as adult stem cells and differentiated cells, genes that are enriched in the ES cells have been identified. Using this approach, Esg-1, an uncharacterized ES cell-specific gene, was found to be exclusively associated with pluripotency in the mouse. Another group, however, found 92 genes, including Oct4 and Nanog, enriched in six different human ES cell lines, which showed limited overlap with those in mouse ES cell lines.

Care must be taken to interpret these data, and the considerable differences in the results may arise from the cell lines used in the experiments, methods to prepare and maintain the cells, and the specific methods used to profile gene expression.

## Human embryonic stem cells as models of genetic disorders

Several new studies have started to address this issue. This has been done either by genetically manipulating the cells, or more recently by deriving diseased cell lines identified by prenatal genetic diagnosis (PGD). This approach may very well prove invaluable at studying disorders such as Fragile-X syndrome, Cystic fibrosis, and other genetic maladies that have no reliable model system.

Yury Verlinsky, a Russian-American medical researcher who specialized in embryo and cellular genetics (genetic cytology), developed prenatal diagnosis testing methods to determine genetic and chromosomal disorders a month and a half earlier than standard amniocentesis. The techniques are now used by many pregnant women and prospective parents, especially those couples with a history of genetic abnormalities or where the woman is over the age of 35, when the risk of genetically related disorders is higher. In addition, by allowing parents to select an embryo without genetic disorders, they have the potential of saving the lives of siblings that already had similar disorders and diseases using cells from the disease free offspring

Scientists have discovered a new technique for deriving human embryonic stem cell (ESC). Normal ESC lines from different sources of embryonic material including morula and whole blastocysts have been established. These findings allows researchers to construct ESC lines from embryos that acquire different genetic abnormalities; therefore, allowing for recognition of mechanisms in the molecular level that are possibly blocked that could impede the disease progression. The ESC lines originating from embryos with genetic and chromosomal abnormalities provide the data necessary to understand the pathways of genetic defect

A donor patient acquires one defective gene copy and one normal, and only one of these two copies is used for reproduction. By selecting egg cell derived from embryonic stem cells that have two normal copies, researchers can find variety of treatments for various diseases. To test this theory Dr. McLaughlin and several of his colleagues looked at whether parthenogenetic embryonic stem cells can be used in a mouse model that has thalassemia intermedia. This disease is described as an inherited blood disorder in which there is a lack of hemoglobin leading to anemia. The mouse model used, had one defective gene copy. Embryonic stem cells from an unfertilized egg of the diseased mice were gathered and those stem cells that contained only healthy hemoglobin genes were identified. The healthy embryonic stem cell lines were then converted into cells transplanted into the carrier mice. After five weeks, the test results from the transplant illustrated that these carrier mice now had a normal blood cell count and hemoglobin levels.

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