

Stem Cell – Principle –

Rationale

Research on human stem cells and their use for applications to regenerate tissues and organs can play an important role in developing novel therapies for various diseases. Research in this field needs careful evaluation of ethical and legal concerns and requires a clear framework within the Merck KGaA, Darmstadt, Germany Group. To provide clarity, Merck KGaA, Darmstadt, Germany has developed the following company Principle.

Objective

This company Principle provides all Merck KGaA, Darmstadt, Germany employees with background information on Stem Cells and with the current position of the company on the use of human stem cells. The Principle also provides a clear statement about the company's guiding values towards research and application as well as on cloning of human beings.

As the Stem Cell field is rapidly progressing this Principle undergoes regular review by the Stem Cell Research Oversight Committee (SCROC). Merck KGaA's, Darmstadt, Germany SCROC is working under the guidance of the Merck KGaA, Darmstadt, Germany Bioethics Advisory Panel (MBAP) to help ensure alignment in regards with Merck KGaA's, Darmstadt, Germany overall bioethical guidelines and principles.



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1. Background

Stem cells have the ability to self-renew themselves indefinitely through mitotic cell division and to give rise to various specialized cell types that form tissues and organs

In a developing embryo, stem cells can differentiate into the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells but also maintaining the normal turnover of regenerative organs such as blood, skin and intestinal tissue.

There are several different types of stem cells described exhibiting different "potencies", which specifies their differentiation potential.

- Human embryonic stem cells (hESCs) are cells of the inner cell mass of a blastocyst, an early-stage embryo. hESC produced by the first few divisions of the fertilized egg are totipotent and distinguished by their ability to differentiate into any cell type of an embryo.
- Induced pluripotent stem cells (iPSCs) are a type of pluripotent stem cell that can be generated from adult cells by re-programming. Since iPSCs can be derived directly from tissue, they bypass the need for embryos.
- Adult stem cells, also called somatic stem cells, are stem cells which maintain and repair the tissue in which they are found. Most adult stem cells are lineage-restricted (multipotent) and are generally referred to by their tissue origin (mesenchymal stem cell, adipose-derived stem cell, endothelial stem cell, dental pulp stem cell, etc.).

Stem cells derived from nuclear transfer: Somatic cell nuclear transplantation has become a focus of study in stem cell research and aims to obtain pluripotent cells from a cloned embryo. These cells genetically match the donor organism from which they come. This gives them the ability to create patient specific pluripotent stem cells, which could be used in therapies or disease research.

Many countries including Germany have legal frameworks regulating the use of hESCs and implementing approval processes for the use of certain types of stem cells.

In addition, in oncology a different type of stem cells has been discovered, which are termed 'Cancer Stem Cells' (CSCs). CSCs exist at low frequency within the bulk of a tumor. CSCs as a sub-population of cancer cells possess characteristics which are associated with normal tissue stem cells i.e. self-renewal and the ability to differentiate into multiple cell types. Due to their nature, research in the CSC



field as such does not raise ethical objections. In this setting, the therapeutic intent is the inhibition or elimination of the CSCs through specific drugs with the aim to avoid progression or re-occurrence of the disease.

2. Merck KGaA's, Darmstadt, Germany Position

Merck KGaA, Darmstadt, Germany recognizes the potential benefits of conducting properly defined research with stem cells because of the breakthrough therapeutic potential for the treatment of degenerative diseases, various conditions and injuries. Therefore, research with human stem cells is allowed with careful consideration of ethical and legal standards. Merck KGaA, Darmstadt, Germany has established the SCROC to provide oversight and guidance on any research Merck KGaA, Darmstadt, Germany conducts involving stem cells.

Merck KGaA, Darmstadt, Germany, through internal research as well as in collaboration with external partners, develops new stem cell research tools, products and therapeutic production processes. Merck KGaA, Darmstadt, Germany acknowledges the ethical controversy surrounding the derivation and use of stem cells. In doing so, Merck KGaA, Darmstadt, Germany complies with the following framework:

- Wherever possible Merck KGaA, Darmstadt, Germany uses animal stem cells, human iPSCs or human adult stem cells rather than hESCs.
- Merck KGaA, Darmstadt, Germany uses hESC cell lines compliant with the legal framework of the respective country regulations in which the research is conducted.
- Merck KGaA, Darmstadt, Germany opposes reproductive cloning of human beings and does not contribute to such activities in any way.
- Merck KGaA, Darmstadt, Germany will not engage in the production of human embryos for research purposes and will not engage in any activity of deriving hESCs (in accordance with the German Embryo Protection Act).
- At present, Merck KGaA, Darmstadt, Germany is not engaged in the creation and use of human artificial gametes for reproductive purposes.
- Merck KGaA, Darmstadt, Germany conducts research with CSCs as they are sub-populations of cancer cells and a promising target for cancer treatment.



- For any stem cell research with animals, careful ethical and legal assessments are also made in accordance with Merck KGaA's, Darmstadt, Germany Policy on Animal Welfare.
- Any use of human stem cells within the Merck KGaA, Darmstadt, Germany group has to go through the SCROC for advice and review. This includes any collaborations or grants involving such research.
- The review process by the SCROC is mandatory. There is a separate Work Instruction dealing with the Merck KGaA, Darmstadt, Germany internal approval processes in place.
- In accordance with the SCROC charter, the SCROC reviews stem cell research proposals and, if needed, commercial strategies for compliance with Merck KGaA's, Darmstadt, Germany ethical and legal guidelines as well as this Principle.

3. Current Engagement

Healthcare research programs:

Merck KGaA, Darmstadt, Germany is regularly investigating the use of stem cells as tools in its research programs directed towards the fields of disease target identification and drug screening as well as drug safety, predictive toxicology and metabolism.

The healthcare business of Merck KGaA, Darmstadt, Germany continues to observe ongoing research utilizing stem cells for therapeutic purposes and collaborates with external partners (i.e. academic institutions and companies) focusing on research programs with stem cells. These collaborations follow this Principle as well.

Merck KGaA, Darmstadt, Germany is actively engaged in research of the biology of CSCs with the aim of targeting their selective inhibition or elimination *in vivo* to generate new treatment modalities for cancer patients. For this purpose, Merck KGaA, Darmstadt, Germany will collaborate, if necessary, with leading scientists in the field.



Life Science products for stem cell research and manufacturing:

As a global supplier for the life science market, Merck KGaA, Darmstadt, Germany develops and markets research tools, reagents, cell lines, and technologies in the field of stem cell biology. Life Science products are developed within Merck KGaA, Darmstadt, Germany or in collaboration with academic and industrial partners. The product portfolio ranges from re-programming and cultivation to characterization and separation of stem cells.

Prior to signing any agreement with a partner, Merck KGaA, Darmstadt, Germany will review and comply with ethical, regulatory and legal requirements related to and contained within this Principle. Merck KGaA, Darmstadt, Germany will make this Stem Cell Principle public, and expect our customers and partners to comply with it.

Merck KGaA, Darmstadt, Germany will not deliver any of its stem cell products and services, if Merck KGaA, Darmstadt, Germany becomes aware of any projects by customers, partners or institutes directed at the creation of human embryos or the cloning of human beings.

All Merck KGaA, Darmstadt, Germany scientists and researchers using, or otherwise working with, human stem cells are responsible for understanding and abiding by this Stem Cell Principle. In addition, given the high level of scientific sophistication of Third Parties, we expect that such Third Parties are up-to-date with respect to the on-going conversation around stem cells and capable of making informed decisions regarding their own stem cell usage.

4. Outlook

Merck KGaA, Darmstadt, Germany has installed the SCROC in order to ensure the internal assessment of the stem cell position for Merck KGaA, Darmstadt, Germany and to constantly review this position according to latest scientific, legal and ethical insights. This committee advises on a regular basis on important topics with ethical and legal impact, focusing on stem cell research.



5. Glossary

Abbreviation	Definition
CSC	Cancer Stem Cell
hESC	human Embryonic Stem Cell
hPSC	human Pluripotent Stem Cell
iPSC	induced Pluripotent Stem Cell
MBAP	Merck KGaA, Darmstadt, Germany Bioethics Advisory Panel
SCROC	Stem Cell Research Oversight Committee

- **“Principle”: Corporate definition**

A Principle specifies the basic rules for Corporate Governance which needs to be complied with by all subsidiaries of Merck KGaA, Darmstadt, Germany (“Subsidiaries”). Its purpose is to ensure a consistent corporate governance framework for all Subsidiaries worldwide. A Principle defines corporate governance structures and corporate governance responsibilities. It does not address organizational responsibilities.

For reference, the link to other Merck KGaA, Darmstadt, Germany policies:

http://biopharma.merckgroup.com/en/research_development/positions_policies/positions_policies.html

