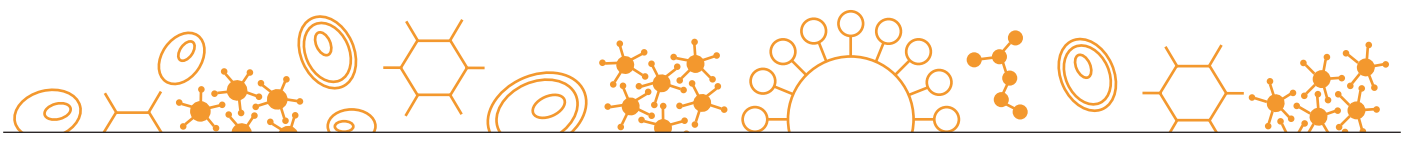
Understanding Stem Cells The Conference

1 Basics



1 Basics

In this module, the students work on the basics of stem cell research. As participants in a scientific conference, they prepare a keynote presentation and a session as a kick-off.

90 minutes

Tasks:
Keynote presentation, session

Material:
Keynote
Session A
Session B
Session C

Introduction

Nothing else in the world is so powerful as an idea whose time has come.
Victor Hugo, French writer

"All improvement is progress, but not all progress is an improvement."
Sigmund Graff, German writer and playwright

Keynote presentation

The conference begins with a keynote presentation on the types of stem cell. Initially, the students individually develop an overview of stem cell types. A keynote speaker then presents their overview.

30 minutes

Individual work
Keynote exercise sheet
Keynote material sheet

Session

Three groups of students each develop a session topic and think about which questions the visitors might ask in their session. They specify a session speaker to introduce the topic. Questions from session visitors are answered jointly by the group.

The session topics can be introduced and discussed in sequence. Or the groups may send their own participants to other groups to ask questions. In this case, all topics may run simultaneously.

60 minutes

Group work
Session exercise sheet
Session A material sheet
Session B material sheet
Session C material sheet

Outlook

"Our conference continues. In the next module, we look at the opportunities and limitations of stem cell research and explore the ethical pros and cons in panels."

Keynote presentation

Keynote presentations are important talks launching large conferences. They are delivered by particularly recognized scientists. A keynote presentation deals with the central conference topics.

TASK Develop an overview of stem cell types. Present your overview as a keynote presentation

OBJECTIVE **The differences between the stem cell types should be clear in your overview at a glance. The overview serves as the basis for a keynote presentation.**

TIP For example, you could create a table or a diagram. First decide on categories to sort by.

Examples of categories:
Select one or more, or define your own categories:

NATURAL
POTENTIAL
PLURIPOTENT
MULTIPOTENT
DIFFERENTIATION OPTIONS
SPECIAL FEATURE
ARTIFICIAL
TIME
TOTIPOTENT

Session

Sessions are presentation series in a conference. In sessions, several presentations dealing with aspects of a specific topic are delivered. They are presented in smaller groups. When the presentations are over, the session participants ask questions and discuss. At large conferences, several sessions may be held simultaneously (parallel sessions).

TASK You will receive scientific material on your topic. Working together with your session group, work through the essential facts. Prepare for the session.

OBJECTIVE **Your group speaker should be able to introduce your topic briefly. As a group, you should be able to answer questions from other conference participants.**

TIP Gather possible questions and answers on flash cards.

Session Topics
Session A: Blood stem cells
Session B: Reprogramming
Session C: Induced pluripotent stem cells

Stem cell types

Body cells that can make copies of themselves and differentiate into different cell types or tissues are generally referred to as stem cells. Depending on the type of stem cell and its influence, they have the potential to develop into any tissue (embryonic stem cells) or certain specified tissue types (adult stem cells). Stem cells are able to generate daughter cells, which themselves possess stem cell properties.

Embryonic Stem Cells (ES) are isolated from the blastocyst, an early embryonic stage in mammals. In human embryonic development, the blastocyst develops five to six days after fertilization. Embryonic stem cells are isolated from the internal cell mass (embryoblast), from which the whole organism develops during natural embryonic development. The blastocysts are destroyed to produce embryonic stem cells. Transferred to a cell culture dish, embryonic stem cells are considered to be pluripotent, so they can form many or almost all cell types of the adult, but not an entire organism.

Fetal stem cells are isolated from older embryos or fetuses (five to nine weeks old) that have miscarried, or they are harvested after termination of pregnancy. These stem cells have a potential that in the transition between embryonic and tissue stem cells. They can no longer differentiate into almost all cells as embryonic stem cells can. However, they still grow faster than tissue stem cells, which are already defined as cell types of a particular tissue.

Tissue stem cells are specific dividable cells in already mature tissues. These adult stem cells serve self-renewal and the development of specialized tissue cell types. Their differentiation potential is limited to the maturation of genetically determined tissues in the environment of which (niches) they are found, for example, in the skin, the liver, the intestine or the hematopoietic system. They are therefore referred to as multipotent, not pluripotent.

Human embryonic stem cells (hES cells) are cultivated from early embryonic cells. For research purposes, embryonic stem cells from surplus, artificially inseminated embryos (in vitro fertilization) are currently being harvested in various countries, for example in Belgium and the United Kingdom. The removal of the hES cells leads to loss of the embryo. The production of hES cells in this manner is considered ethically unacceptable in Germany and is prohibited (Embryo Protection Act). Importing hES cells for research purposes is also generally prohibited but may be allowed under certain conditions. The permits are issued by the Robert Koch Institute (RKI).

Induced pluripotent stem cells (iPS cells) are stem cells that are created by artificial reprogramming of human body cells. In 2006, the Japanese scientist Shinya Yamanaka used viruses to introduce the genes Oct4, Sox2, cMyc and Klf4 into mouse body cells for the first time, activating quiescent developmental genes. In this manner, body cells were programed back into an embryonic state, i.e. reprogrammed (Takahashi and Yamanaka, 2006). One year later, the same was achieved in human cells.

Germ cells are cells that form the germ line and are already predetermined for development of the next cell generation in the early embryo. They alter only slightly during embryonic and later development. Only from the primordial germ cells of the gonadal

ridge (progenitor cells of egg and sperm cells) can pluripotent stem cells be cultivated under laboratory conditions. In the body, the haploid gametes, i.e. the sperm and oocytes, which form a diploid zygote after fertilization, emerge from them. It is already possible today to artificially produce sperm and oocytes from induced pluripotent stem cells of the mouse and to use them for fertilization. If this also becomes possible in the future with reprogrammed human stem cells, it may be possible to generate a human embryo without the need for natural germ cells. This may be useful to some couples who cannot otherwise have children. However, they raise many new ethical issues that require discussion in society as well as legal regulations.

Mesenchymal stem cells (MSC) are tissue stem cells originating in the mesoderm germ layer. They can be isolated from bone marrow, adipose tissue and umbilical cord tissue. They are also called stromal cells and are very similar to connective tissue cells, the fibroblasts. It has been demonstrated that MSC can differentiate into chondrocytes (cartilage-forming cells), osteoblasts (bone-forming cells) and adipocytes (adipose tissue cells). Differentiation of these cells into muscle cells and heart muscle cells is the subject of controversial debate in scientific circles. The terms adult stem cells (tissue stem cells) and MSC are often used synonymously. However, the MSCs of various tissues represent only one of many types of adult stem cells, because skin stem cells, intestinal stem cells, blood stem cells and the stem cells of all tissues belong to the adult stem cells. MSCs are extremely important in the development of therapeutic approaches using stem cells and are frequently used in clinical studies. In many cases, the effect of the cells is not attributed to differentiation into tissue cells but to the support of endogenous stem cell repair processes. Here, the cells release factors that positively influence regeneration.

Multipotent stem cells (*multipotent*, from the Latin *multus* (many) and *potentia* (capacity, power)) have limited differentiation potential and, in the various tissue types, replace dead cells and aid regeneration following injuries.

Pluripotent stem cells (*pluripotent*, from the Latin *plus* (more) and *potentia* (capacity, power)) can form all cell types of the three germ layers (endoderm, mesoderm and ectoderm) and the germ line by differentiation. However, they cannot form extraembryonic tissue (trophoblast) and thus no viable organism.

Totipotent stem cells (*totipotent*, from *totus* (whole) and *potentia* (capacity, power)) are able to develop a complete autonomous organism through cell division. The cells are only totipotent at a very early embryonic stage from the fertilized egg cell to the 8-cell stage.

BLOOD STEM CELLS:

The pioneers of stem cell research

By Christèle Gonneau for EuroStemCell

Blood stem cells are also known as haematopoietic stem cells. Like other stem cells, they can self-renew, or copy themselves. They also produce the different types of specialized cells found in the blood: both red blood cells and the many kinds of white blood cells needed by the body's immune system.

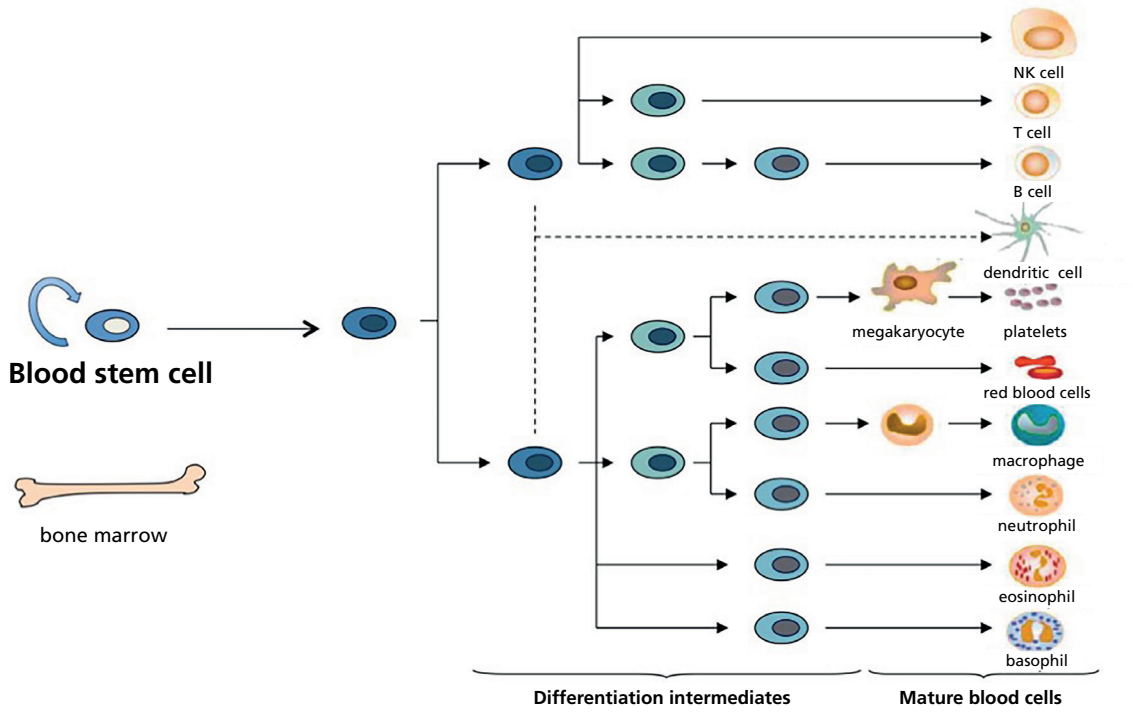


Image 1: The tree of blood: Blood stem cells are at the origin of all blood cell types. Once a blood stem cell divides, its daughter cells take various differentiation routes to produce different types of specialized blood cells.

Blood stem cells

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Specialized blood cells do not live very long, so the body needs to replace them continuously. Blood

stem cells do this job. They are found in the bone marrow of long bones such as the femurs (thigh bones), and in the hips or pelvis, the vertebrae (backbones) and the rib cage. They can also be obtained from the umbilical cord blood and the placenta at birth.

Blood stem cells and disease

Blood stem cells need to make just the right number of each type of blood cell to keep the body healthy. This is a carefully controlled process. When it goes wrong, the result may be a blood disease such as leukaemia or anaemia.

Blood stem cells are already widely used to treat such diseases. A survey in 2008 showed that more than 26,000 patients are treated with blood stem cells in Europe each year - their own (autologous) or from others (allogeneic). These blood stem cells come from three different sources – bone marrow, the bloodstream of an adult or umbilical cord blood.

1. Bone marrow transplants are in fact blood stem cell transplants. Such transplants can be used to treat patients with blood diseases like leukaemias, lymphoma or multiple myeloma. After high doses of chemotherapy or radiation therapy, the patient's own blood stem cells are destroyed. Bone marrow containing healthy blood stem cells is taken from a donor and transplanted into the patient. The donor blood stem cells can then take over the job of making blood cells in the patient's body.

2. Blood stem cells can also be obtained from the **bloodstream.** Certain proteins are used to stimulate stem cells from the bone marrow to move into the bloodstream so that enough cells can be isolated for a transplant. These stem cells are most commonly used for treating cancers like leukaemias and lymphomas.

3. Blood stem cells can be isolated from **umbilical cord blood** after birth. The cells can then be used to treat children with some kinds of blood diseases, such as leukaemia, congenital immunodeficiencies, anaemias or sickle cell disease. Researchers are looking for ways to increase the number of stem cells that can be obtained from cord blood, so that they can be used routinely to treat adults too.

Current Research

Scientists are still learning about how blood stem cells develop in the embryo, how they are controlled in the adult body and what goes wrong in certain blood diseases. But they are also using today's understanding of blood stem cells to investigate new ways to treat patients. A bone marrow transplant is only possible if a compatible donor is available. The patient and donor must be very carefully matched to avoid immune rejection of the transplant. Even when a suitable donor can be found, there is still a small risk of rejection. Umbilical cord blood does not need to be matched quite so precisely to the patient, but there are not enough stem cells in an umbilical cord to treat an adult. So we need to find alternatives. Researchers are investigating ways to produce large numbers of blood stem cells in the laboratory. They are also developing methods for growing specialized blood cells from blood stem cells, for example to produce red blood cells for blood transfusions.

The future

Red blood cells from pluripotent stem cells

Red blood cells carry oxygen around the body. Patients who lose a lot of blood need to have it replaced

straight away by a blood transfusion. There are not enough blood donors to meet patient needs, so researchers are looking for an alternative solution. Since pluripotent stem cells have the potential to make any cell type of the body, they could potentially provide an unlimited supply of red blood cells. It is already possible to make small numbers of red blood cells from pluripotent stem cells in the lab. Now the real challenge is to develop techniques for producing the large numbers of red blood cells that are needed for transfusion.

Growing blood stem cells in the lab

Red blood cells, like other mature blood cells, are short-lived and specialized for a particular job. To cure disease in the long-term, doctors need to transplant something that can keep producing new blood cells throughout the patient's life: blood stem cells. Scientists are searching for ways to grow a limitless supply of blood stem cells. One possibility might be to collect stem cells from the bone marrow then grow and multiply them in the lab. Researchers are also trying to make blood stem cells from embryonic stem cells or induced pluripotent stem (iPS) cells. iPS cells could be made from a patient's own skin and then used to produce blood stem cells. This would overcome the problem of immune rejection.

Source
https://www.eurostemcell.org/blood-stem-cells-pioneers-stem-cell-research
2016

IPS CELLS AND REPROGRAMMING:

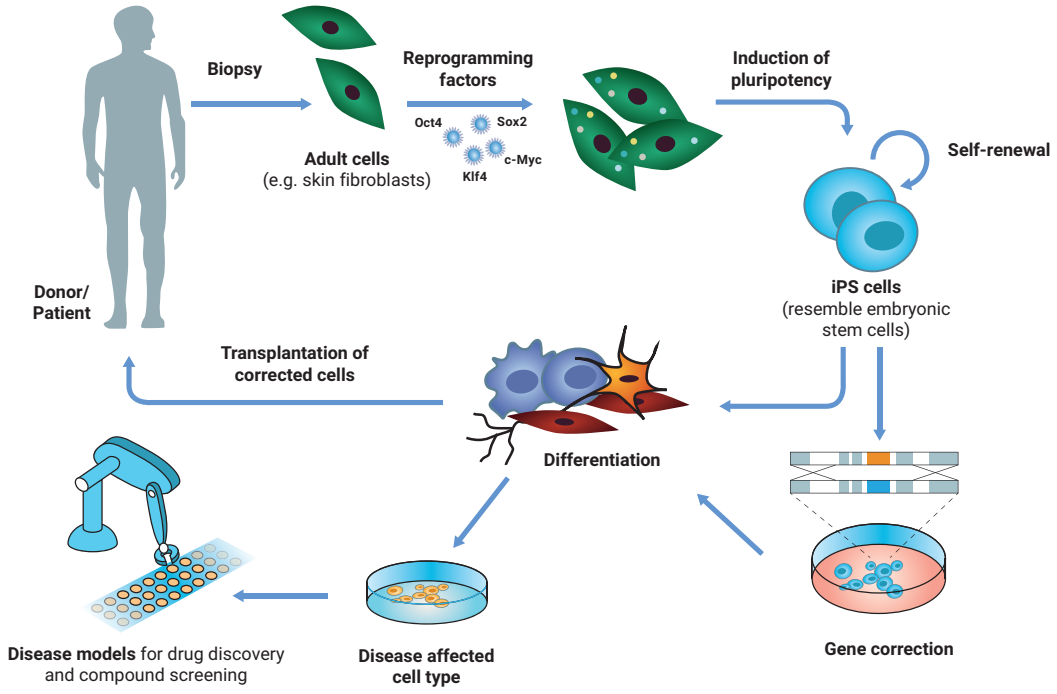
Turn any cell of the body into a stem cell

By Manal Hadenfeld and Michael Peitz for EuroStemCell

Reprogramming allows the nucleus of any cell in the body to be returned to an early stage of embryonic development. In 1962, the British researcher John Gordon was able to show that a cell nucleus from a body cell of a full-grown clawed frog can be restored to an early embryonic state by transferring it to a depleted fertilized egg cell (zygote). The zygote developed with the genetic information from the nucleus of the body cell into a tadpole and further into a frog. The experiment shows that factors in the cytoplasm of the oocyte restore the genetic information of the transferred nucleus to its original state, i.e. reprogramm it. Such experiments are called somatic cell nuclear transfer (SCNT). The clone sheep Dolly was created by the British Ian Wilmut in 1997 in this way, although it was still largely unclear which factors in the egg cell regulate the reprogramming.

The Discovery of iPS Cells

In 2006, a Japanese researcher, Shinya Yamanaka, showed in mouse cells that four transcription factors are sufficient to restore differentiated body cells and the genetic information in their nucleus to the state of embryonic stem cells: Oct4, Sox2, Klf4, and c-Myc. This discovery surprised many scientists and changed our understanding of how cells work. Meanwhile, it has also been shown that with different combinations of defined factors, not only pluripotent cells from body cells arise, but cells of a germline can be transferred directly into another germline. For example, mesodermal fibroblasts can be directly transformed into ectodermal neurons. Researchers refer to this process as direct reprogramming. Reprogramming technologies are opening up new possibilities for the study and treatment of diseases today.



adapted from M. Rossbach

iPS and Embryonic Stem Cells

IPS cells and embryonic stem cells are very similar. They are self-renewing, meaning they can divide and produce copies of themselves indefinitely. Both types of stem cell can be used to derive nearly any kind of specialized cell under precisely controlled conditions in the laboratory. Both iPS cells and embryonic stem cells can help us understand how specialized cells develop from pluripotent cells. In the future, they might also provide an unlimited supply of replacement cells and tissues for many patients with currently untreatable diseases.

In contrast to embryonic stem cells, making iPS cells doesn't depend on the use of cells from an early embryo. Are there any other differences? Current research indicates that some genes in iPS cells behave in a different way to those in embryonic stem cells. This is caused by incomplete reprogramming of the cells and/or genetic changes acquired by the iPS cells as they grow and multiply. Scientists are studying this in more detail to find out how such differences may affect the use of iPS cells in basic research and clinical applications. More research is also needed to understand just how reprogramming works inside the cell. So at the moment, most scientists believe we can't replace ES cells with iPS cells in basic research.

iPS Cells and Disease

An important step in developing a therapy for a given disease is understanding exactly how the disease works: what exactly goes wrong in the body? To do

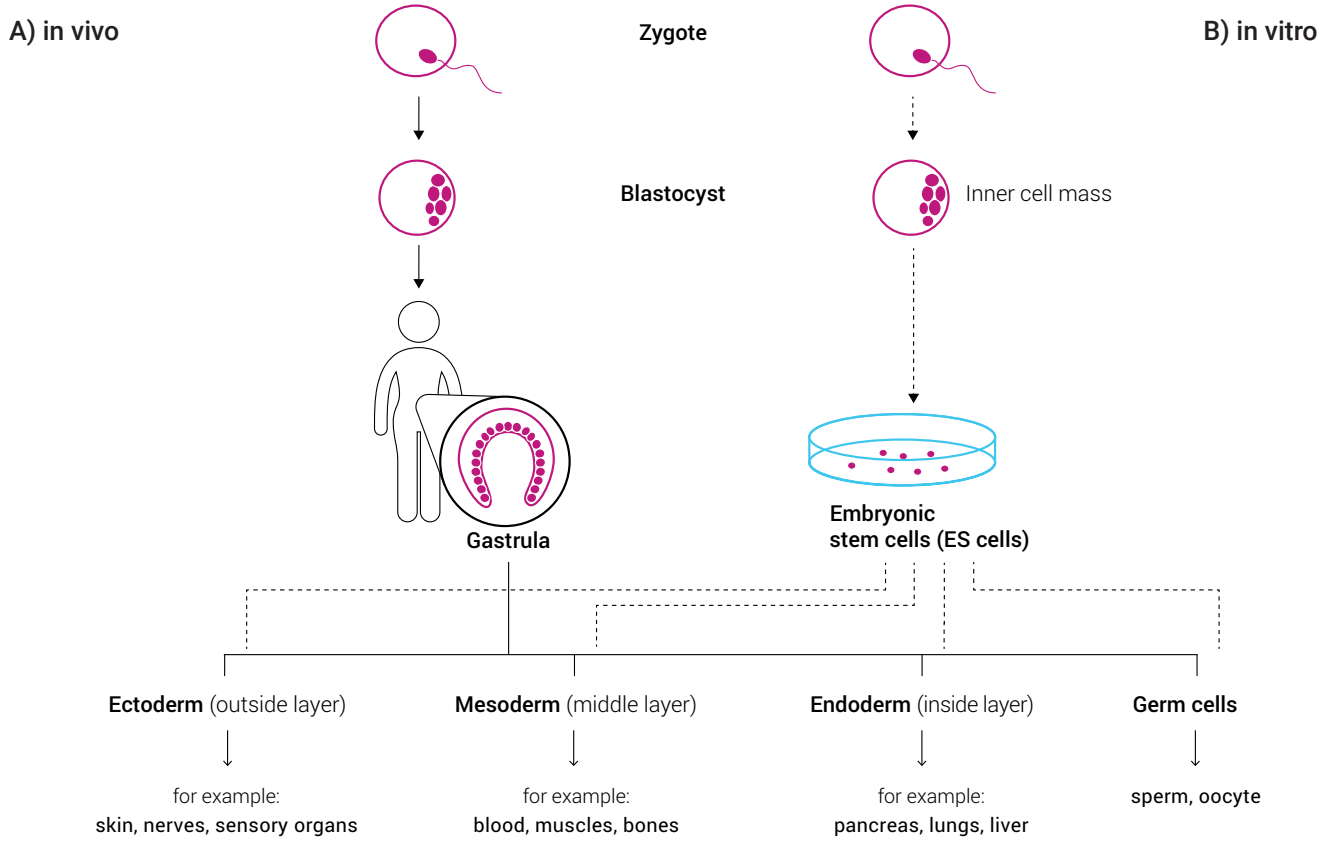
this, researchers need to study the cells or tissues affected by the disease, but this is not always as simple as it sounds. For example, it's almost impossible to obtain genuine brain cells from patients with Parkinson's disease, especially in the early stages of the disease before the patient is aware of any symptoms. Reprogramming means scientists can now get access to large numbers of the particular type of neurons (brain cells) that are affected by Parkinson's disease. Researchers first make iPS cells from, for example, skin biopsies from Parkinson's patients. They then use these iPS cells to produce neurons in the laboratory. The neurons have the same genetic background (the same basic genetic make-up) as the patients' own cells. Thus scientist can directly work with neurons affected by Parkinson's disease in a dish. They can use these cells to learn more about what goes wrong inside the cells and why. Cellular 'disease models' like these can also be used to search for and test new drugs to treat or protect patients against the disease.

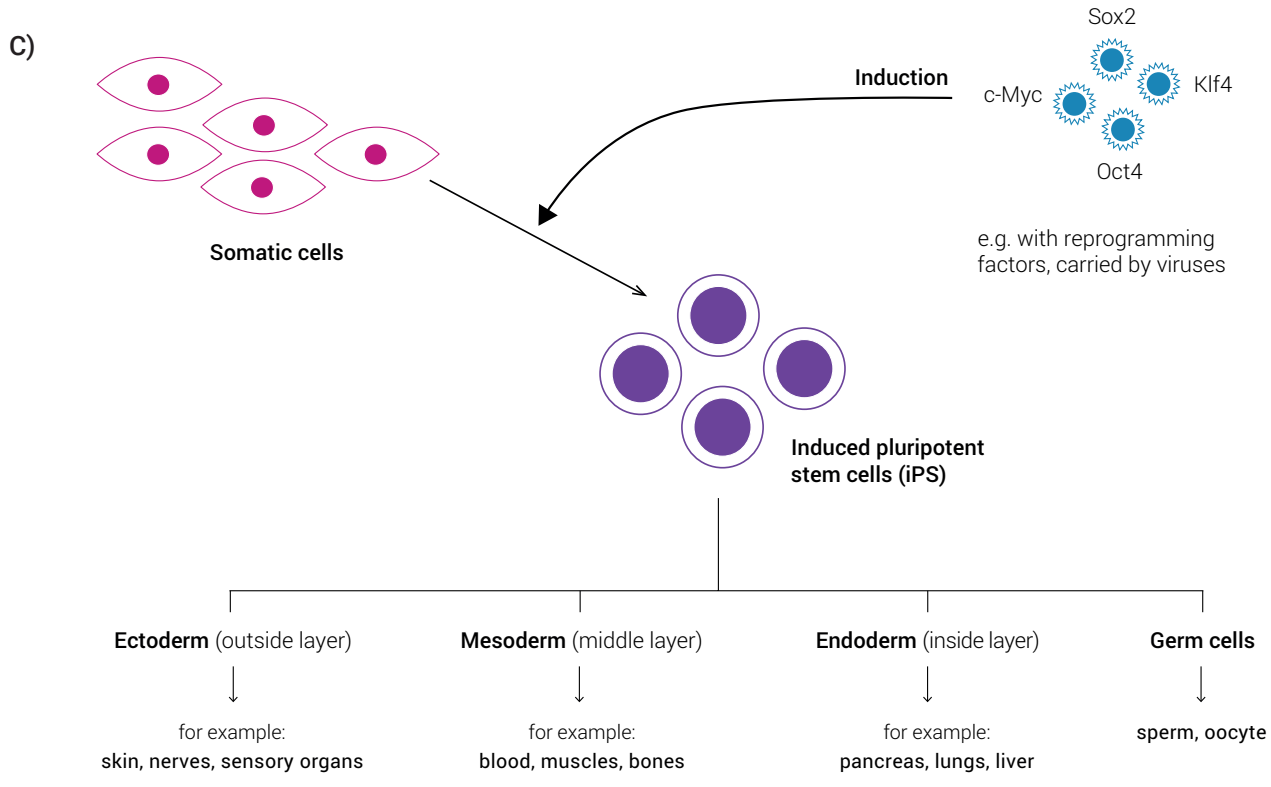
Future Applications and Challenges

Reprogramming holds great potential for new medical applications, such as cell replacement therapies. Since iPS cells can be made from a patient's own skin, they could be used to grow specialized cells that exactly match the patient and would not be rejected by the immune system. If the patient has a genetic disease, the genetic problem could be corrected in their iPS cells in the laboratory, and these repaired iPS cells used to produce a patient-specific batch of healthy specialized cells for transplantation. But this benefit remains theoretical for now.
Until recently, making iPS cells involved permanent genetic changes inside the cell, which can cause tumours to form. Scientists have now developed methods for making iPS cells without this genetic modification. These new techniques are an important step towards making iPS-derived specialized cells that would be safe for use in patients. Further research is now needed to understand fully how reprogramming works and how iPS cells can be controlled and produced consistently enough to meet the high quality and safety requirements for use in the clinic.

Source:
https://www.eurostemcell.org/ips-cells-and-reprogramming-turn-any-cell-body-stem-cell
2016

How do pluripotent cells develop?





About the lesson series "Understanding Stem Cells - The Conference for Schools"

In this four-part series of lessons, the German Stem Cell Network and the Ernst Schering Foundation provide teachers with fact-checked knowledge about stem cells. The freely usable material allows students from 14 years onwards to actively immerse themselves in current research. The scientific experts at the German Stem Cell Network ensure the technical and professional quality of the material.The Schering Foundation uses its experience in science education to introduce young adults to current research topics using new methods and to encourage their interest in science. This material is available online at: http://www.understanding-stemcells.info

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