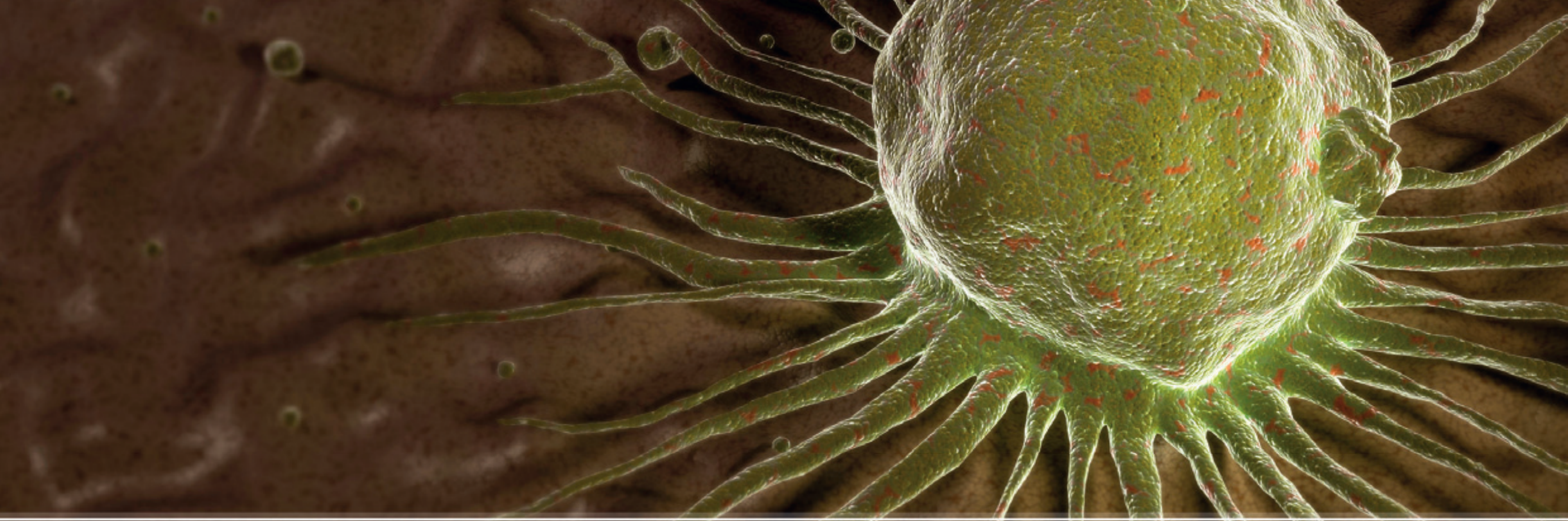

National Research Programme Portrait (NRP 63)

Stem Cells and Regenerative Medicine

FNSNF
Swiss National Science Foundation

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www.nrp63.ch
You can subscribe to the electronic newsletter on the website.

What is an NRP?
The National Research Programmes (NRP) contribute scientifically substantiated solutions to urgent problems of national significance. They are approved by the Federal Council, last from 4 to 5 years and are funded with CHF 5 to 20 million. The NRPs are problem-oriented; inter- and transdisciplinary; dedicated to achieving a defined, overall goal through co-ordination of individual research projects and groups and focused on the knowledge transfer of the results.

A fundamental question

The human body is tremendously complex. It is composed of various tissues and organs that are in turn made up of different cell types. All of these cells with their various functions develop from a single cell, the fertilized egg cell, a stem cell. During the development of this cell into an embryo, the cells split off into various cell lines through division. How can a single cell produce such a wealth? Thousands of researchers around the globe are occupied with this fundamental question. Thanks to stem cell biology, today this question can be explored from a new angle.

In the laboratory researchers can study how a stem cell develops into a new cell type, which external signals and internal changes it needs in order to become a heart muscle cell, nerve cell, or insulin-producing cell. Researching this transformation process is fascinating for at least two reasons: first, it allows one to observe the underlying mechanism that enables an organism to develop and second, mastery of this mechanism can

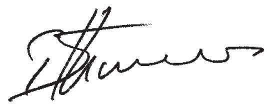
Prof. Bernard Thorens

be used in order to develop new therapies, in other words, to produce 'spare parts' for sick or damaged organs. But before these therapeutic dreams can come true, considerable work is necessary to enlarge our understanding of stem cells.

The goal of the National Research Programme NRP 63 is to give Swiss stem cell research an additional boost, because stem cells have the potential to revolutionise medicine in the next few decades.

The goal of the National Research Programme "Stem Cells and Regenerative Medicine" (NRP 63) is to give Swiss stem cell research an additional boost. More specifically, its aim is to attract Swiss scientists with a demonstrated expertise in molecular and cell biology, as well as to train young scientists in this field. The NRP 63 focuses on the underlying mechanisms of stem cell biology with the goal of making this knowledge accessible for future therapies.

Stem cells have the potential to revolutionise medicine in the next few decades. However, because stem cell research is still a relatively young field, it is uncertain whether or not this potential will be realised. Nobody can say where this journey will lead. Today's achievements may already be outdated tomorrow. The developments related to so-called iPS cells (induced pluripotent stem cells, see page 5) demonstrate exactly that. Just a few years ago, few scientists would have thought it possible to programme adult stem cells back to a state that resembles that of embryonic stem cells. Within a few years, the focus shifted: today, embryonic stem cells are somewhat eclipsed by iPS cells. However, it is not yet clear which cell types are best suited for regenerative medicine.



Prof. Bernard Thorens
President of the NRP 63 Steering committee
University of Lausanne

Great expectations for stem cells

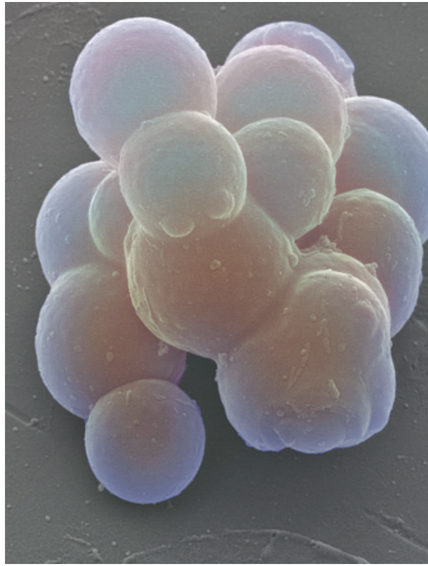
How stem cells function is still unclear. The NRP 63 will thus serve to pave the way for stem cells' future medical applications.

Without stem cells, wounds would not heal, and blood, skin and other tissues would not regenerate. Without these biological all-rounders, living things would neither develop nor survive. The study of these cells is one of the most fascinating field in biology.

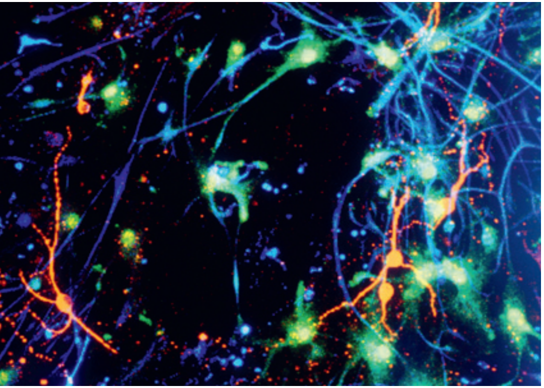
There are great hopes for these cells: stem cells should not only explain how human beings, animals and plants grow; they should also help cure diseases such as Parkinson's or Type 1 diabetes. This is the distant goal of regenerative medicine – to renew damaged, diseased or old tissue with the help of stem cells. But we have a long way to go until this is possible.

To renew damaged, diseased or old tissue – this is the distant goal of stem cell medicine.

The United States, Great Britain, Israel, South Korea, Japan, Germany and other countries have recognised stem cells' potential for the treatment of vari-



Picture showing stem cells from blood from the umbilical cord. All blood cell types derive from them.



Stem cells seen through a microscope: the coloured lines show the projections that these cell produce when growing.

ous illnesses and support research in the field. Recently, the state of California alone has invested three billion dollars over ten years.

The pressure on the research community to constantly stretch therapeutic limits also carries certain risks, such as performing clinical trials prematurely without understanding exactly what kind of effect stem cells have on the human body. Against this background, the NRP 63 was launched with the goal of better understanding how stem cells function. The NRP 63 will contribute to establishing a solid basis for future medical applications. In addition, Swiss stem cell research will be promoted and young scientists will be trained in this field.

The current situation in the field of stem cell research is comparable to that of genetic research at the beginning of this century. After the human genetic code was decoded, many thought that new medicines could be produced quickly based on the discovery. This is no longer merely a dream, but because of unanticipated complexities, it took longer than expected.

Three different types of stem cells

Adult stem cells

Adult stem cells (AS cells) probably exist in every human and animal tissue. Their main function is to constantly replenish damaged or dead cells in the body. They deliver peak performances in the human body every day, producing billions of new cells, mainly blood, intestinal and skin cells.

AS cells are limited, or multipotent, in their potential. For example, “only” blood system cells, and not nerve or muscle cells, can develop from a blood stem cell.

Embryonic stem cells

Any of the over 200 types of human body cells can develop from an embryonic stem cell (ES cell). When ES cells are stimulated by the proper growth factors, they can become skin, brain or muscle cells. In comparison with AS cells, they are not only multipotent, but pluripotent.

ES cells are extracted from the embryo during the so-called blastocyst stage. The embryo is destroyed when ES cells are extracted; research involving these cells is thus ethically controversial.

iPS cells

AS cells can be reprogrammed by changing four genes in their genetic make-up. It is as if the clock in the cell is turned back to zero. Cells similar to ES cells arise and are called iPS cells (induced, pluripotent stem cells). The advantage of iPS cells is that their creation is ethically acceptable. However, it is not yet clear whether they are at all suited to application in the field of regenerative medicine.

From wound healing to brain tumours

The NRP 63 comprises 12 projects that span the field of stem cell biology. Research will be conducted with human adult stem cells as well as with animal embryonic and adult stem cells.

Research groups from Basel (4 projects), Bern (1), Geneva (1), Lausanne (2) and Zurich (4) are involved in the NRP 63. One research team is examining stem cells in order to better understand how they can contribute to wound healing, another team is analysing whether it is possible to prevent brain tumours from arising from stem cells after stem cell transplantation. Others are trying to compile a type of catalogue of the different stem cell types in the brain or develop a new biomaterial for ear reconstruction.

Below is a brief overview of the 12 projects:

Project 1: A novel approach to regenerate blood vessels

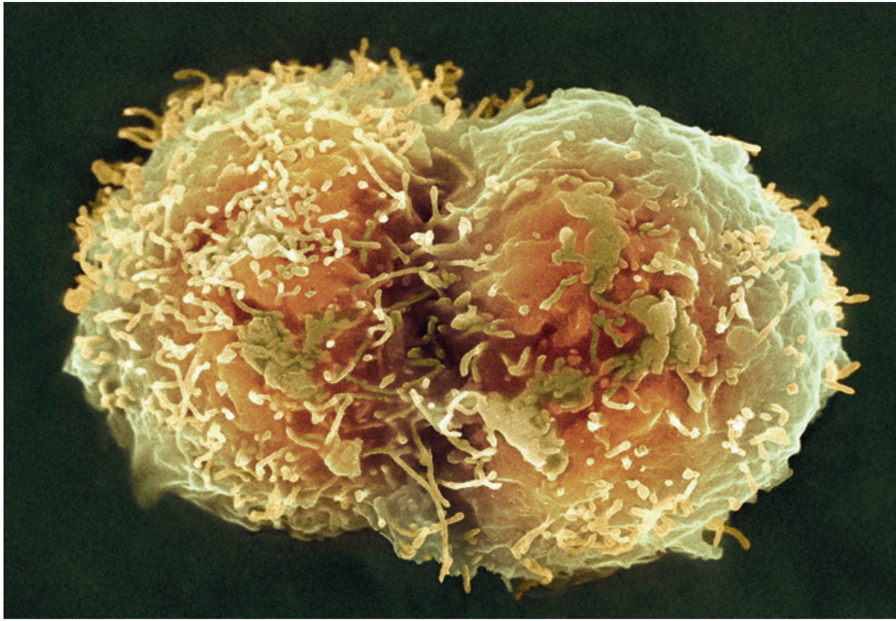
Ischemia is the inadequate supply of blood to an organ. As a result the affected organ suffers from a lack of oxygen and nutrients and can die. If the heart muscle is affected, it can lead to a heart attack. If arms and legs are affected, it leads to a condition known as arterial occlusion. To treat these diseases, different approaches have been suggested including the idea of helping new blood vessels to grow by stem cell transplantation. Such an approach is fraught with obstacles, such as tissue rejection. Also, the appropriate stem cells are difficult to retrieve and they don't multiply easily in the laboratory.

The research team of Stefano Di Santo pursues a new approach. Instead of treating damaged tissue through transplantation, the researchers are trying to stimulate the organ's own stem cells to divide. In Switzerland alone, hundred of thousands of patients could potentially benefit – patients suffering from a heart attack, stroke or arteriosclerosis.

Project 2: Nerve stem cells: Control and communication

The human nose contains anything from 10 to 30 million receptor cells which can recognize thousands of different smells. In the olfactory epithelium located in the nasal cavity, smell receptor cells are constantly regenerated over a person's lifetime. Olfactory stem cells are responsible for this.

These nerve stem cells could be used against a variety of ailments such as the loss of hearing and sight, Parkinson's and stroke. However one of the challenges is that stem cells transplanted in the brain do not assimilate very well. To overcome this obstacle, this research project tries to get a better understanding of the stem cells' direct surroundings because only in the right surroundings can stem cells perform their work as desired. The project of Rebecca Elsässer aims at understanding how nerve cells could be used for transplantation.



Stem cells are responsible for tissue regeneration and healing in humans. The cells represented here are in the process of becoming blood cells.

The twelve NRP 63 projects at a glance

More information about the projects is available at www.nrp63.ch

1 **A novel approach to regenerate blood vessels**
Dr. Stefano Di Santo, Universitätsklinik für Neurochirurgie, Inselspital Bern

2 **Nerve stem cells: control and communication**
Dr. Rebecca Elsässer, Institut für Pharmakologie und Toxikologie, Universität Zürich

3 **Legal and ethical challenges of stem cell donation**
Dr. Jörg Halter, Departement Innere Medizin, Universitätsspital Basel

4 **New understanding in the regeneration of insulin-producing cells**
Prof. Pedro Herrera, Faculté de Médecine, Université de Genève

5 **Analysis of thymus development**
Prof. Georg Holländer, Department Biomedizin, Universität Basel

6 **A new biomaterial for ear reconstruction**
Prof. Ralph Müller, Institut für Biomechanik, ETH Zürich

7 **How does heart tissue regenerate?**
Prof. Thierry Pedrazzini, Département de médecine, Université de Lausanne

8 **How an embryo develops from a sperm and an egg**
Dr. Antoine Peters, Friedrich Miescher Institut, Basel

9 **Mapping stem cell diversity in the adult brain**
Dr. Olivier Raineteau, Institut für Hirnforschung, Universität Zürich/ETH Zürich

10 **Stopping stem cells from becoming brain tumours**
Prof. Heinrich Reichert, Biozentrum, Universität Basel

11 **Boosting the healing of wounds**
Prof. Lukas Sommer, Anatomisches Institut, Universität Zürich

12 **The KRAB gene family and its role in the development of human beings**
Prof. Didier Trono, Laboratoire de virologie et de génétique, EPF Lausanne

Project 3: Legal and ethical challenges of stem cell donation

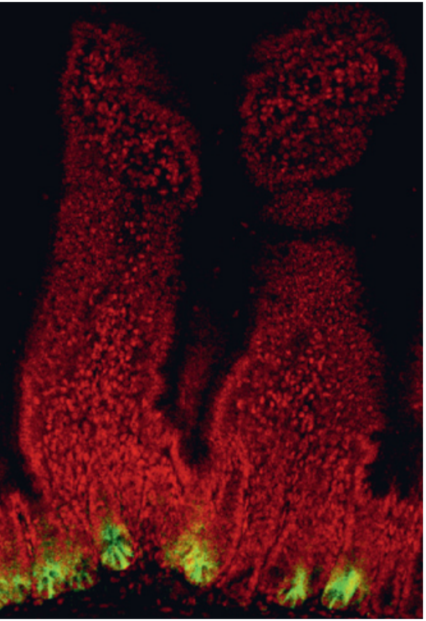
The transplantation of blood stem cells has already saved many lives. If a patient needs new blood cells, relatives are one option. Another is to find a match among the almost 14 million people who have volunteered to donate blood stem cells. Now it appears this pool of donors is no longer sufficient. The pressure is growing to find new donors. But how should one proceed? What rights do donors have? Should donors know who get their stem cells? Does it matter to donors if patients are responsible for their illnesses? Can donors withdraw their donations in such cases? These are just some of the countless ethical and legal questions which arise. The aim of this project by Jörg Halter is to find answers to these questions and develop recommendations and guidelines for all parties involved.

Project 4: New understanding in the regeneration of insulin-producing cells

About 20,000 people suffer from type 1 diabetes in Switzerland. Even if this disease can be treated with insulin injections, new therapeutic options are important.

Mice have the astounding capacity of generating new insulin producing cells. Is this a way to a new treatment against diabetes?

Beta-cells, which are part of the pancreas, are responsible for the regulation of blood sugar. They measure blood sugar constantly and pour out insulin if necessary. In type 1 diabetes patients, these beta-cells are completely or almost completely lost. The hope is that these beta-cells can be regenerated in adult diabetics. The research project by Pedro Herrera is based on an astonishing observation: Af-



The stem cells in green on the picture continually produce new bowel cells.

ter the destruction of more than 99 percent of all beta-cells, the mouse pancreas has the ability to regenerate up to ten percent of these cells. How does this happen? Pedro Herrera and his team noticed that other cells of the pancreas, so-called non beta-cells, can be reprogrammed to become new beta-cells. With the help of genetically modified mice, the researchers will examine this process.

Project 5: Analysis of thymus development

Every day the human immune system is confronted umpteen times with a crucial question: Is a newly discovered object, like this cell, part of the body or is it a pathogen which must be destroyed? Wrong or incomplete answers to these questions can have far-reaching consequences for the person concerned, leading for example to autoimmune diseases like multiple sclerosis.

T-lymphocytes are key to the defence against all kinds of pathogens. These defence cells are produced throughout our lifetime in the thymus, an organ which lies in the chest above the heart. These T-cells need a scaffold of tissue cells, notably thymic epithelial cells (TEC). Tissue cells must be replaced regularly since they die off after a few weeks. Tissue stem cells are responsible for this regeneration. However, many questions are still unresolved about the development of these cells and that is what the research team of Georg Holländer is investigating.

Fresh insights into the development of tissue cells in the thymus as well as the T-lymphocytes are a prerequisite for the development of new therapies. Patients whose thymus is absent or damaged cannot be adequately treated today.

Project 6: A new biomaterial for ear reconstruction

In about one in 10,000 births, the visible outer part of the ear, the auricle, is severely malformed or absent. Furthermore, tumours and injuries can damage or disfigure the auricle. For such patients it is important for their psychological and emotional well-being to have as normal an appearance as possible. This particularly applies to children.

Current approaches to ear reconstruction are still inadequate. The project by Ralph Müller focuses on the development of a novel biomaterial called bacterial cellulose, a biomaterial that can be used for ear reconstruction.

Project 7: How does heart tissue regenerate?

Cardiovascular diseases are responsible for 40 percent of deaths in Switzerland, making them the main cause of mortality. The heart can be damaged either acutely as in myocardial infarction or gradually because of work overload, for instance in people suffering from hypertension. The human heart has only a limited capacity to regenerate spontaneously, however, several recent lines of investigation suggest that regeneration in the human heart could be possible. These investigations indicate that recruitment of stem cells could be used to produce new heart muscle tissue in the mammalian heart. The aim of the project of Thierry Pedrazzini is to identify the function of so called miRNAs and their role in this regeneration process (miRNA = micro ribonucleic acid).

Project 8: How an embryo develops from a sperm and an egg

The start of a human life is stunning. Two cells, a sperm and an egg, converge to form a new cell which is now in a position to become a human being. The original cells could not achieve that on their own.

We are all a product of a stem cell: the fertilized ovule with a diameter of a tenth of a millimetre.

The creation of this cell is extremely complicated and dependent on various factors. The genetic material, the DNA, is involved of course. In addition, proteins which surround the DNA are important. The Polycomb group (PcG) proteins play a critical role in this process. These proteins are master regulators of embryo development. They carry out their work by modifying the complex of DNA and proteins, known as chromatin, and by steering the activity of genes. However, the exact mode of action is largely unknown and will be analysed by Antoine Peters.

Project 9: Mapping stem cell diversity in the adult brain

Contrary to what was once thought, stem cells exist in the adult brain but they differ in their ability to give birth to new brain cells.

Recent work indicates that nerve stem cells in the adult brain can only produce specific types of brain cells rather than all of them. The capabilities are dictated by the exact location of the nerve stem cell in the adult brain. This new information raises a number of important questions: How does this "topographic coding" work? How many different sorts of brain cells can those particular stem cell populations generate? Olivier Raineteau and his research team propose to make three-dimensional maps showing the distribution of distinct nerve stem cell populations (focusing on the adult subventricular zone). This map will provide crucial information of nerve stem cells from the adult brain and on their true potential to participate in brain repair.

Project 10: Stopping stem cells from becoming brain tumors

One of the goals of regenerative medicine is to treat damaged brain tissue (for example after a stroke) using stem cell transplantation. Normal stem cells produce the right number of healthy nerve cells. However, if they become abnormal, stem cells create uncontrolled numbers of new cells and a tumor develops. This is especially devastating if such cancer cells form in the brain because they are difficult to access and brain damage cannot be reversed. Before stem cells can be used to treat brain damage, it is vital to understand why nerve stem cells suddenly start growing out of control.

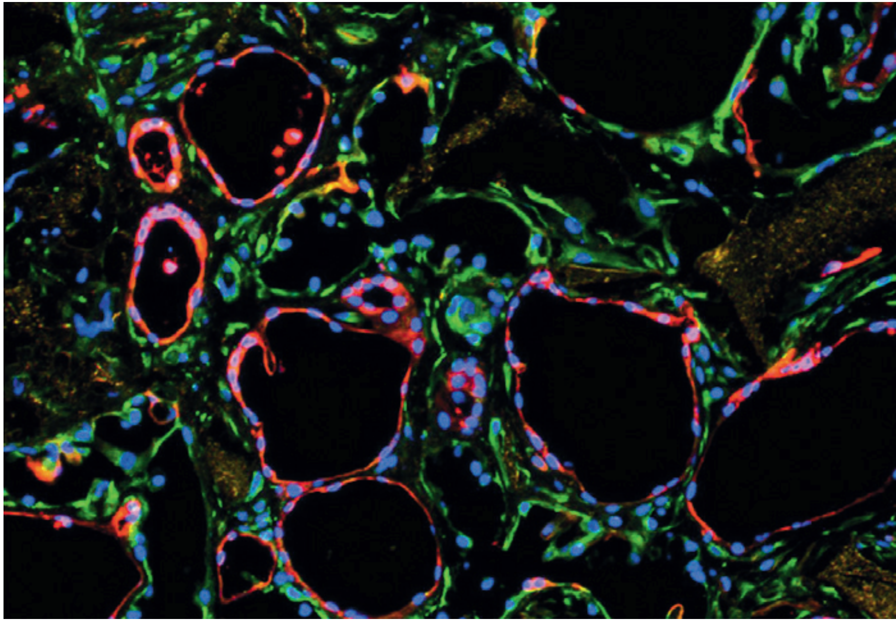
Heinrich Reichert's research group will initially investigate these mechanisms in the fruit fly, by examining the fruit fly's roughly 18,000 genes to see which ones are involved in this mechanism. They will then pursue the most promising gene candidates from this investigation.

It is necessary to check that stem cells do not change into tumour cells before they can be used in medicine.

Project 11: Boosting the healing of wounds

The existence of skin stem cells, responsible for the daily replacement of dead skin cells, has been known for a long time. But in the skin, there is another special kind of stem cells, which derives from the neural crest, an embryonic structure. These cells are called Neural Crest Stem Cells (NCSCs). Researchers have discovered that they can develop into many different cell types and occur in mice as well as in humans. NCSCs are not directly responsible for the renewal of skin cells but exactly what they do is unclear.

Because stem cells are mostly involved in healing or regenerative processes, the assumption is that the NCSCs perform a similar task and for example participate in skin pigmentation and wound healing processes. That is what Lukas Sommer and his team will be looking at. If there is a connection, this project may provide ways to speed up wound healing.

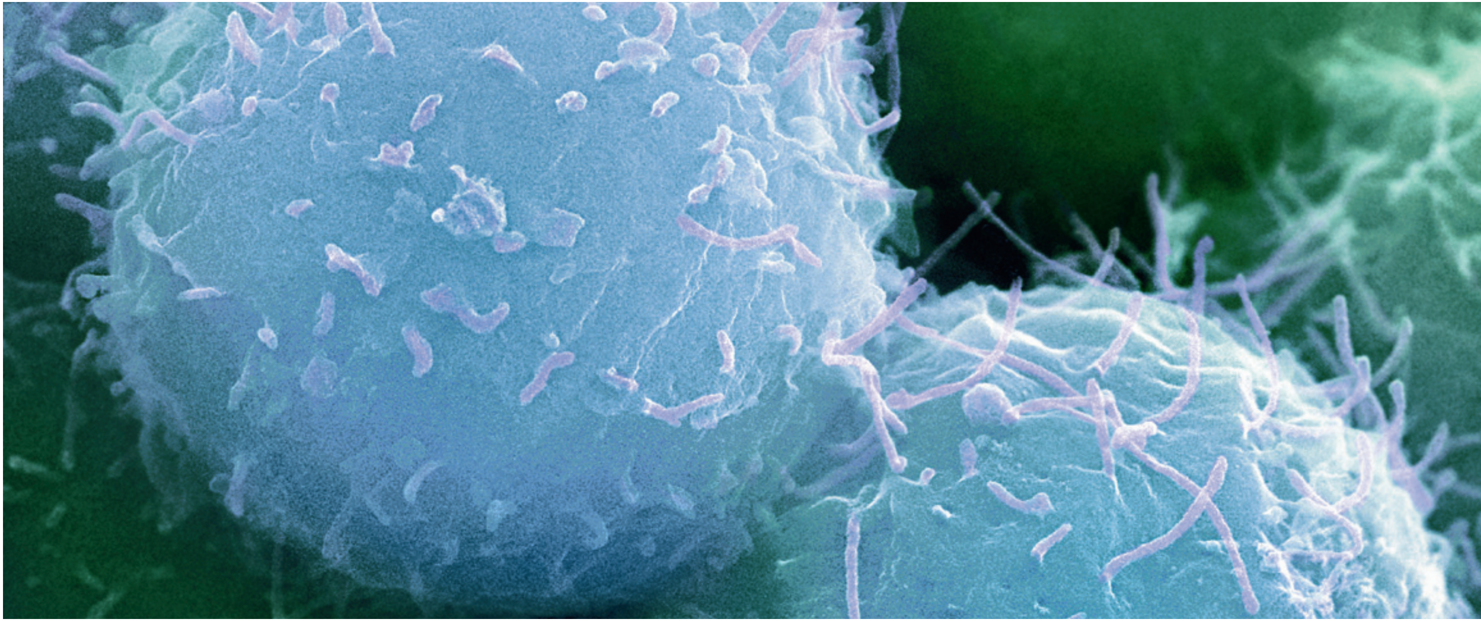


Since stem cells biology is a relatively young discipline, there are still many things that remain unexplored.

Project 12: The KRAB gene family and its role in the development of human beings

Human beings and other higher mammals possess approximately 20,000 genes. These genes can be grouped in gene families which inherit different tasks. About 400 genes belong to the so-called KRAB-ZFP family. This gene family has a leading role because it can stop other genes from becoming active. They control other genes and guarantee that they are only activated at the right time in the development of mammals. They also play an important role in the development of embryonic stem cells.

But to date it remains unclear how exactly they do their work – how do they get into contact with other genes and which messengers they use? Didier Trono and colleagues from the EPF Lausanne will try to answer these questions within the next few years.



Blood stem cells can save lives. One of the projects of NRP 63 investigates the ethical and legal aspects of their use in medical applications.

Stem cell research between hype and hope

The NRP 63 should lead to new findings about the way stem cells function, but not to new treatments or medicines. Pointing out opportunities without providing false hope is the trickiest task involved in stem cell research.

For several years now, the internet has been rife with offers of various wondrous stem cell treatments – for example, therapies for diabetes or cancer and anti-aging treatments. Such offers are generally suspect, especially when expensive treatments whose effectiveness has not been proved in clinical trials are presented with no research to support them. Stem cells are not a path to eternal youth, nor are they a new type of rejuvenation therapy. In the medical field, stem cells have so far mainly been used in treating leukaemia and lymphoma patients, for in vitro fertilisations and for skin transplants.

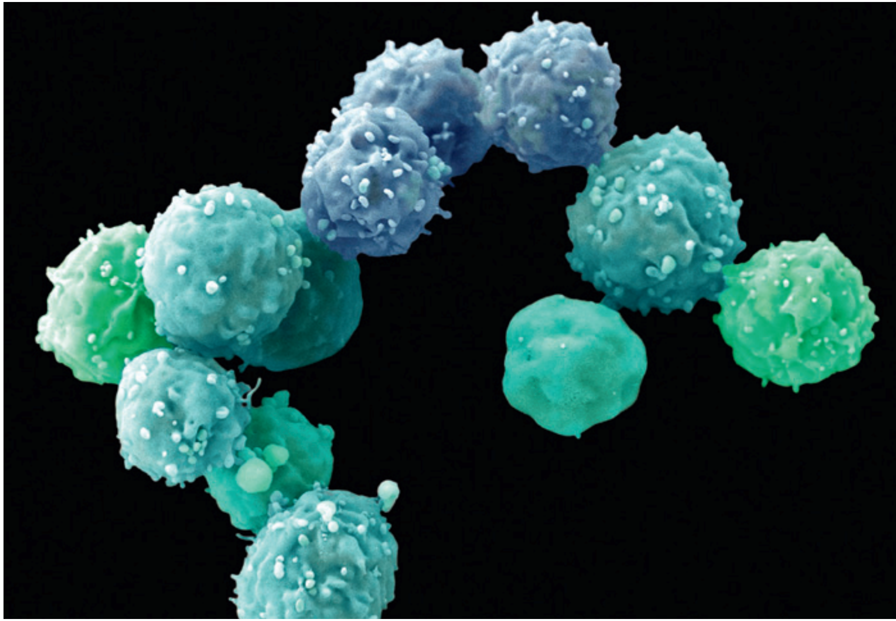
No clinical trials planned

There are no clinical trials on patients planned within the framework of the NRP 63. The goal is not to develop new stem cell treatments, but rather to pave the way for them. A major problem for regenerative medicine is that the stem cells used to heal diseases can become abnormal and mutate into cancer cells. Therefore, it is important to analyse how these processes take place in order to prevent them.

Transferring know-how

National Research Programmes focus on the knowledge transfer of results. Knowledge transfer means transferring the know-how collected through the NRP 63 to other interested groups. Results from the NRP 63 could be of interest to clinically active doctors and biotech and pharmaceutical companies as a base for launching subsequent projects. In addition, transferring knowledge to the public and to the fields of bioethics and politics is important in order to keep these groups informed about current developments in stem cell research.

The programme also aims to recruit highly qualified scientists from universities, university clinics and other academic institutions. It is important for young researchers to have the possibility to be trained at top laboratories around the world so that they can subsequently return to Switzerland with their newly acquired expertise.



Picture of embryonic stem cells. All cell types of the human body derive from them.

November 2007:
The Federal Council commissions the Swiss National Science Foundation to carry out the NRP 63.

February 2009:
Call for pre-proposals begins: Swiss research teams can apply to take part in the NRP 63 with a short project outline (submission deadline April 2009).

July 2009:
The Steering Committee selects 28 projects from the 58 outlines submitted. Chosen researchers are invited to submit a comprehensive research proposal.

February 2010:
Research begins: The Steering Committee approves 11 projects following an intensive evaluation process. One project from the ERA NET joins the list (Ralph Müller project). A total of 12 projects thus receive funding; initial project funding amounts to 4.9 million Swiss francs.

Participants

Steering Committee

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Davor Solter,
Senior Principal Investigator at the Institute of Medical Biology and Professor at the Duke-National University of Singapore Graduate Medical School, Singapore

March 2015:
Projected end of research.

September 2015:
End of the Programme:
The Steering Committee
presents the final report.

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The Swiss National Science Foundation
The Swiss National Science Foundation (SNSF) is Switzerland's leading provider of scientific research funding. Commissioned by the federal government, it supports research work in all academic fields, from philosophy and nanoscience to biology and medicine.

The focus of its activities is the scientific endorsement of projects submitted by researchers. Yearly, approximately 3000 projects including around 7000 scientists are funded by the SNSF with an annual total amount of approximately CHF 700 million.

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www.nrp63.ch

The NRP 63 in brief

The NRP 63 is a Programme supporting stem cell research in Switzerland. It has a budget of 10 million Swiss francs and will extend through 2015. A total of 12 research teams from Basel, Berne, Geneva, Lausanne and Zurich are involved.

The NRP 63 has the following goals:

- Support basic research on stem cells and regenerative medicine
- Encourage scientists with an excellent track record in developmental and cell biology to engage in this field
- Recruit and train young scientists in this field
- Overall, the programme should enhance the international visibility of Swiss research in stem cell biology and regenerative medicine.