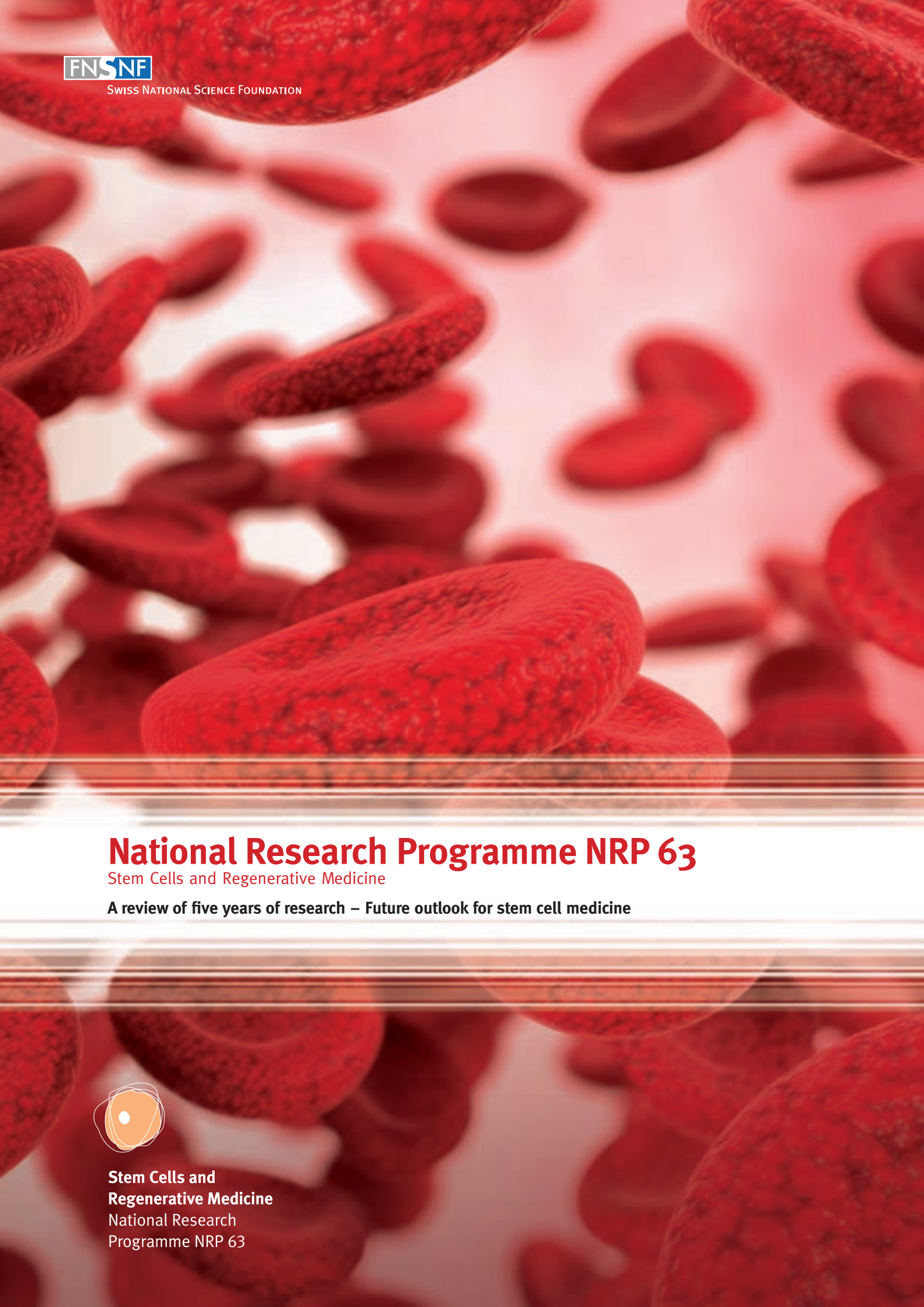

FNSNF
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# National Research Programme NRP 63

## Stem Cells and Regenerative Medicine

**A review of five years of research – Future outlook for stem cell medicine**

**Stem Cells and Regenerative Medicine**
National Research Programme NRP 63

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# Content

# “Step by step, create research that is successful in the long term”

Interview with
**Bernard Thorens**, President of the Steering Committee, National Research Programme “Stem Cells and Regenerative Medicine” (NRP 63)

**What guidelines were followed in NRP 63 in the past five years?**

We focused on basic research for an in-depth understanding of the fundamental mechanisms connected with the development of stem cells and the production of specialised cells – a process called differentiation – through which the tissues and organs of living organisms are formed. With this in mind, we selected the best research projects in order to establish, step by step, a research that would be strong on the long term.

**What are the most important scientific findings of NRP 63?**

Four research groups analysed epigenetic mechanisms, or chemical changes in DNA that activate or deactivate certain genes. This can steer the development of stem cells into certain cell types, such as a liver cell, a red or white blood cell or a nerve cell. The research groups were able to identify new epigenetic mechanisms that play a key role in this process.

Other teams were able to show why stem cells turn into cancer cells. This is making it possible for researchers to consider new ways to hamper this process.

One research team succeeded in characterising stem cell populations in the brain and their recruiting mechanisms. Another team was able to describe for the first time the functions that certain stem cells take on in the olfactory mucosa located in the nasal cavity. Overall, the National Research Programme has produced numerous, extremely interesting findings.

**Did the programme generate medical applications?**

It was not the aim of NRP 63 to launch new clinical studies. Nevertheless, some of the research projects produced findings that could have a medical impact in the future, such as in brain or skin cancer, heart attacks or cystic fibrosis.

Pedro Herrera’s research group at the University of Geneva discovered that cells in the pancreas have a special conversion ability – a new, astounding phenomenon. The pancreas contains clusters of cells called islets of Langerhans that secrete either insulin or glucagon, two hormones that play a key role in regulating blood sugar levels. The researchers discovered that glucagon-producing cells are capable, under certain conditions, to reprogram themselves into insulin-producing cells. In persons with diabetes, the insulin-producing cells no longer function. This discovery could be important in the treatment of diabetes. There are already several patents on this application.

Another research team succeeded in creating a new biomaterial that structurally comes very close to human cartilage. This could help repair deformed ears.

And finally, several of the research groups are already in contact with pharmaceutical and biotech companies to discuss possible clinical applications.

**What were the effects of NRP 63 beyond the scientific community?**

We led very interesting discussions at the ethical and legal levels, such as the use of stem cells in clinical applications. This work has laid the foundation for further development of stem cell donation in Switzerland. Setting up a stem cells bank for the treatment of patients generates questions: to whom do stem cells belong? Do these cells have a market value? May they be sold?

**How did young researchers benefit from NRP 63?**

Each year, a meeting was organised for the research groups, where project leaders, postdocs and doctoral students met; an ideal platform for exchanges. Here, young researchers had an opportunity to discover research topics outside their own areas and thus broaden their horizon.

**What has NRP 63 accomplished for the public?**

The NRP 63 team mounted an exhibition that provides low-threshold access to the topic of stem cells and regenerative medicine. The exhibition informs visitors about possible applications in medicine; it also shows what is scientifically correct or false. The exhibition was held in Lausanne, Zurich and Lucerne and was a great success – especially with schools.

**What will remain of NRP 63 after 2015, after conclusion of the programme?**

NRP 63 funded research projects on stem cells that will be carried on by all the persons who were trained during these five years. In Switzerland, research in this area is of outstanding quality and has a high reputation worldwide. Up to July 2015, the NRP 63 research teams produced 113 publications, some of them in renowned journals like “Nature” and “Science”. More publications are in the making

and will follow. In addition, 24 postdocs and 12 doctoral students were trained in one of the most exciting fields of biology. And it is good to know that almost all of the projects will continue beyond NRP 63.

**What do you wish for the future?**

The public exhibition as well as the ethical and legal discussions gave the NRP 63 research groups the opportunity to see their research area in a larger and interdisciplinary perspective. That is not always the case in research outside an NRP, and I think that this kind of initiative should be supported more often.

# KRAB 'n' KAP:
## An ancient defence system against viruses

**The KRAB gene family and its role in the development of human beings** (2010–2015) → CHF 981,970
**Prof. Didier Trono,** Laboratory of Virology and Genetics, EPF Lausanne

**The genome of higher species, including humans, is sprinkled with millions of virus-like elements, which can multiply, "jump" around from chromosome to chromosome, and profoundly alter the architecture and expression of our genetic material. Maybe up to three quarters of the human DNA derives from these mobile genetic elements, which are powerful motors of evolution but also threats to human life, as they sometimes trigger diseases, including cancer.**

It is thus not surprising that our ancestors developed measures against these genetic invaders. Through the course of evolution, various defence systems came into play to stop their spread or to keep them in check if they had already become integrated into the genome. But what these defence mechanisms look like in detail was unclear for a long time. Under the framework of NRP 63, Didier Trono and his team at the École poytechnique fédérale de Lausanne (EPFL) have now contributed towards uncovering and examining one such mechanism, involved in controlling a vast majority of these elements. They call the system KRAB'n'KAP: "The system arose about 350 million years ago," says Trono, and today it comprises 400 different genes. It is an important factor in ensuring the stability of the genome.

"Our data demonstrate that the selection of these defence mechanisms was not just an arms race", explains the professor in Lausanne, "but rather that evolution capitalised on an elaborate interplay between invaders and defence. Sequences derived from transposable elements, which were once dismissed as 'junk' DNA, actually partner up with the KRAB'n'KAP system to perform regulatory tasks that are essential to multiple aspects of human development and physiology." These results explain why humans and their ancestors have not evolved mechanisms aimed simply at excising transposable elements, but have rather been conducting for hundreds of millions of years a gigantic enterprise of domestication aimed at exploiting their regulatory potential.

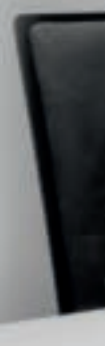
## RESEARCH WILL GO ON

In the past five years, Trono and his team have investigated in detail how the KRAB'n'KAP system works in embryonic stem cells, how it interacts with transposable elements, and what role they jointly play in both embryonic and adult tissues. Trono and his team belong to the top researchers in this area worldwide. The team plans to continue to study this topic after completion of NRP 63.

**Keywords**
KRAB/KAP1, KRAB-Zinc finger protein (ZPF), embryonic stem cells

# Stem cell donation:
## Involving donors more closely

**Legal and ethical challenges of stem cell donation** (2010–2015) → CHF 521,990
**Dr. Jörg Halter,** Department of Haematology, University Hospital Basel; **Dr. Thomas Bart,** Swiss Blood Stem Cells, Berne; **Prof Alberto Bondolfi,** Faculty of Theology and Religious Studies, University of Lausanne; **Yvonne Fischer,** Swiss Blood Stem Cells, Berne; **PD Dr. Urs Schanz,** Division of Haematology, University Hospital Zurich; **Prof. Kurt Seelmann,** Law Faculty, University of Basel



**Interdisciplinarity is often called for and seldom practised. The NRP 63 project on ethical and legal challenges of stem cell donation is one of these rare projects. Here Simone Romagnoli, ethicist, Peter Bürkli, lawyer, and Jörg Halter, medical expert, worked together to develop guidelines for the recruiting and educating of stem cell donors. For in the future, stem cells are likely to be used to treat many different diseases. This will usually involve donations and transplantation.**

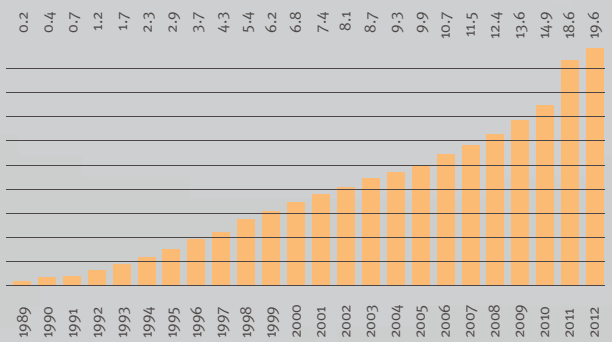
"First, in our team we had to find a common basis," says Halter. Experts working in different research areas also have different ways of thinking. Medical experts' goal is the well-being of the patient; their norms are the guidelines of medicine. And they also want to be able to conduct research. Possible misuse of data collected or new methods developed is inconceivable to many physicians. Lawyers, however, are law oriented. Laws are there to prevent misuse and to protect patients. Ethicists focus mainly on how difficult it is to reconcile the differing values – for example, autonomy, the protection of privacy, the freedom of science. "Views on these values diverge, as can be seen for example in the discussion on appropriate protection in the area of genetics," says Romagnoli.

When it comes to developing guidelines for donors, the difference becomes evident. Ethicists and lawyers favour a staggered model, in which the donors have the opportunity to decide on the use of their donation on several occasions during the course of the donation process. At the time of their initial recruitment and of joining the registry, many questions are not yet relevant for them, as the likelihood that a blood stem cell registry member will actually be called upon to donate stem cells is extremely low. However, in the event that donation is required, donors should be allowed to decide on a number of points: Do I want my donation to be used for research purposes? If something important is discovered in my donor sample that concerns my health, do I wish to receive such information? "This model takes better account of the wishes and the protection of the donor," explains Bürkli.

Physicians see the advantages of the staggered model, but they have doubts concerning its feasibility in everyday use and fear that it would greatly impede research. For this reason, they prefer the route called "general consent", which is practised in some European countries. In the general consent model, donors give their consent (or not) to all possible uses of their donations. This general consent makes things easier for research, because physicians do not have to contact donors again later on to ask for their consent. As Halter explains, "That can quickly become very difficult and can impede research projects." The divergences between physicians and lawyers, but also between the legal and ethical experts, were often large, so that the development of guidelines for stem cell donation was no easy undertaking for the project team.

The results of the research project could be utilised in many ways, including in the revision of the transplantation law, and in the donor consent form that the Swiss Blood Stem Cells (SBSC), the national registry for blood stem cell donors, uses with their registry members. The SBSC changed their practice in past years, and these days recruitment of donors takes place

**Blood stem cell donors worldwide**
in millions




mostly online. But with online registration, it is more difficult to determine if the donor understands what blood stem cell donation is really about. “For this reason, before the donation, extensive information is given to the donor, usually in the form of a discussion,” says Bürkli. “We developed a concept that ensures that this type of donor registration is also legal.” A positive result of the relatively simple online registration in recent years is that many new, young donors have registered.

The research team also founded the Donor Advisory Board. “In the course of the project, it became increasingly clear to us that the donors also needed to be involved more closely in the process,” explains Halter. For there are several issues that concern mainly the donors, such as results of genetic testing, further use of the donations for research purposes, or donor anonymity. The members of the Donor Advisory Board are persons who have already donated blood stem cells. It will be their task to discuss the issues and formulate recommendations. With this advisory group, the work of the research group finds an unlimited continuation beyond the end of the NRP 63 project.

**Keywords**
hematopoietic stem cell transplantation (HSCT), stem cell donors, risk assessment

# Surprising connection between stem cells in the nose and cystic fibrosis

**Nerve stem cells: Control and communication** (2010–2015) → CHF 803,228
**PD Dr. Irene Knüsel; Prof. Jean-Marc Fritschy,** Institute of Pharmacology and Toxicology, University of Zurich

There are stem cells almost everywhere in the human body, including in the nose. Without these stem cells, our sense of smell would quickly deteriorate. This astonishing fact can be explained as follows: we perceive smells thanks to olfactory nerve cells. These neurons line the olfactory epithelium (mucus-coated tissue) in the nasal cavity. Their exposed location puts them in constant contact with viruses, bacteria, and other pathogens. As the neurons of the olfactory epithelium are directly connected to the brain, they are an ideal gateway into the brain for pathogens. For this reason, the cells possess a remarkable defence strategy: they die off if they are infected by pathogens or are injured, are continuously replaced from a pool of stem cells and are integrated into the existing network.

## THOUSANDS OF NEW CELLS EACH DAY

There are different types of stem cells in the olfactory epithelium that produce thousands of new cells each day. It is interesting that the total number of cells in the tissue always remains constant. Only cells that have died are replaced – no more and no fewer. So there is a signal instructing the stem cells when to step up production of new neurons and when to stop. "That process is under the control of microvillar cells," explains Sandra Pfister, who studied this phenomenon in a thesis supported by NRP 63. Microvillar cells in the olfactory epithelium were discovered 35 years ago, but then fell into oblivion. No one knew what the function of these cells was. But this mystery has now been uncovered.

Stem cells in the olfactory epithelium are important in brain research for several reasons: these stem cells divide throughout their lifespan and can be harvested with ease, as the nose is easily accessible; they also regenerate themselves in the laboratory and can develop into many different cell types, such as retinal cells. They have already been used in clinical trials as such. But other medical applications are also conceivable; they could be used to treat neurodegenerative diseases or hearing loss.

The next step in Pfister's doctoral research was to examine how the microvillar cells differ from the olfactory neurons. What genes are active in the microvillar cells that are not active in other cells? "Here, something surprising was found that led us to change the focus of the doctoral research," says Jean-Marc Fritschy, professor at the University of Zurich and co-supervisor of the thesis together with Irene Knüsel. The discovery was that in these microvillar cells, the CFTR gene is active. This gene is connected with the development of cystic fibrosis. In patients with cystic fibrosis, this gene does not work, which causes excessive formation of mucus in the lungs. Why is this gene active in the microvillar cells? What functions does it have there? These questions have not yet been answered in detail. As Irene Knüsel reports, "We found out that when this gene is missing in the microvillar cells, they can no longer perform their regulatory task in keeping the nasal mucous membranes covered with sufficient mucus". If the gene is lacking, the balance between the dying off and the regeneration of olfactory neurons is disturbed.

## BETTER UNDERSTANDING OF CYSTIC FIBROSIS

The research team conducted their experiments with mice. But the results indicate that in humans, there are cells in the lungs that perform a regulatory function similar to the one performed by microvillar cells in the nose. If these cells can be discovered, they could of course be decisive for a better understanding of the origins of cystic fibrosis and possibly also for developing new treatment methods.

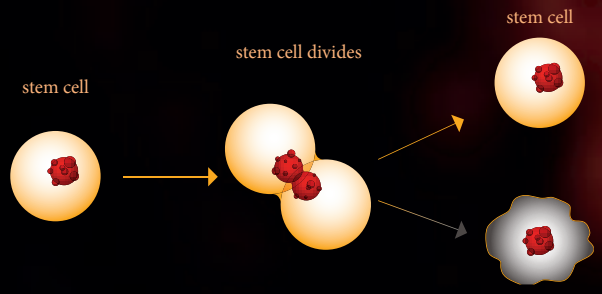
**Keywords**
olfactory stem cells, microvillar cells, cystic fibrosis transmembrane conductance regulator (CFTR)

## Stem cell biology:

# The advances have been breathtaking

**Stem cells are amazing cells with remarkable biological features. Most important among these features is the ability to self-renew and at the same time generate daughter cells that can differentiate into a variety of different cell types. Stem cells exist in early embryos, and these embryonic stem cells can generate all of the lineages of cells that eventually make up the mature body. Stem cells are also present in adult tissues and these adult stem cells can self-renew for long periods of time, indeed in many cases throughout the entire life of an individual, while simultaneously supplying the cells needed for tissue maintenance and regeneration.**

THE SECRET OF STEM CELLS




Differentitation into blood cell, skin cell, cartilage cell, etc.

The promise of harnessing stem cell biology for novel therapy and regeneration in human disease has spurred stem cell research for decades, and significant progress has been made in understanding the fundamental biology of stem cells as well as in utilising these remarkable cells in tissue therapy by transplantation. While there is still much to be learned about stem cell biology before the potential of stem cells for clinical application can be fully realised, conceptual and practical advances made in the last ten years are remarkable, indeed even breathtaking.

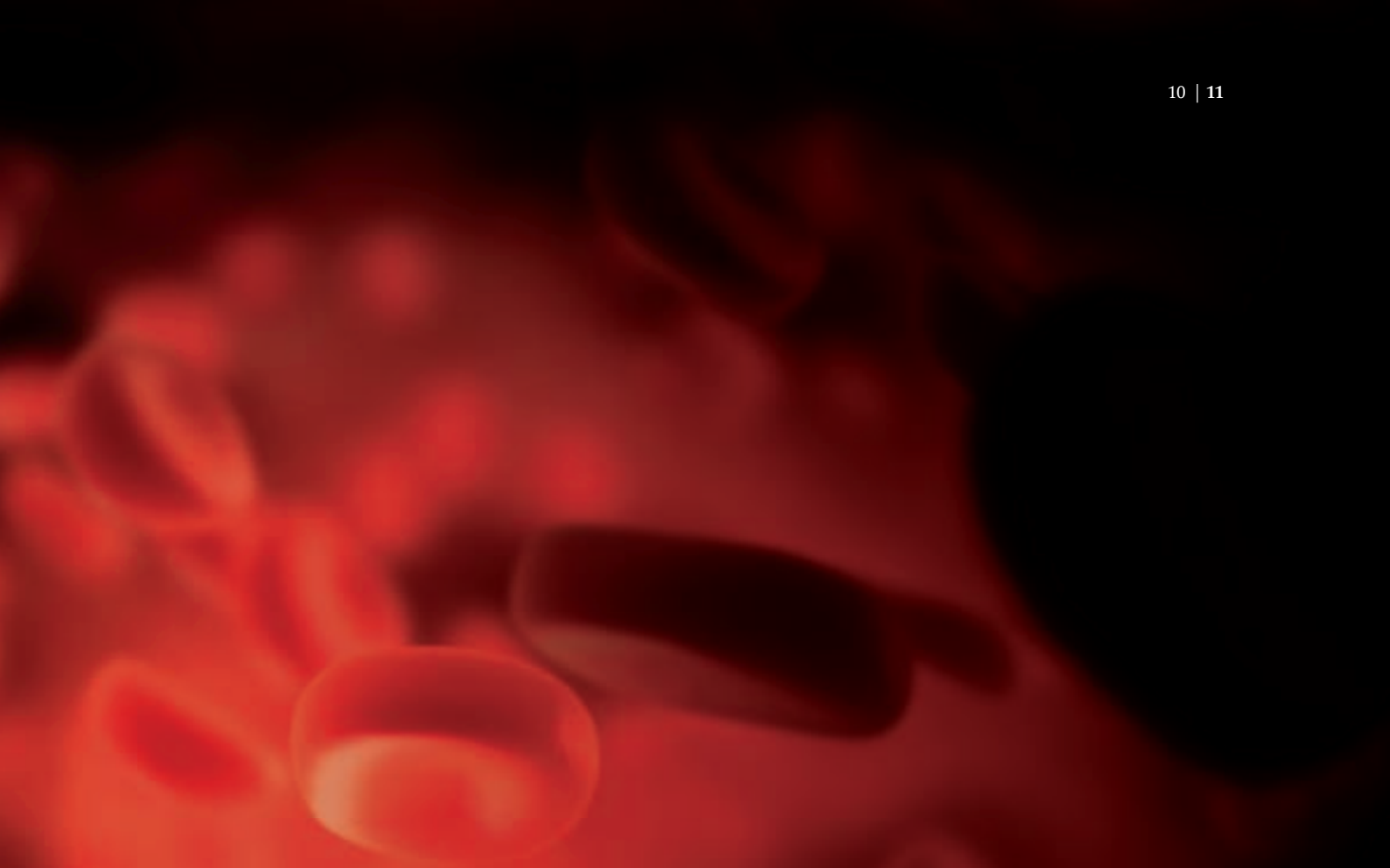
### BIG BANG OF STEM CELL BIOLOGY

In 2006, stem cell research was literally transformed by a "big bang" event when Shinya Yamanaka and his team discovered a simple method to dedifferentiate, or undo a previous differentiation of adult cells into so-called induced pluripotent stem cells (iPSCs) that could generate any type of cell in the body. This type of reprogramming shattered the long-standing biological dogma of the irreversible differentiation of adult cells, and at the same time represented a technological breakthrough that spread through all areas of biomedicine. The award of the Nobel Prize underscores the fact that this discovery has revolutionised our appreciation of stem cell biology and of its potential for biomedical application. The effects of this discovery have been astounding and in the ten years following this discovery, progress in several aspects of stem cell biology has been dramatic.

First, important insight has been gained into the mechanisms that operate during normal stem cell proliferation. Thus, the importance of epigenetics in regulating the proliferation of embryonic stem cells has been established. The control of the asymmetric division mode by which stem cells produce a new stem cell and a differentiated cell has been elucidated. The role of progenitor cells derived from stem cells has been analysed. Moreover, in general terms, the flexibility of cell fate has been recognised and the notion of terminal differentiation of cells has been replaced with that of stable differentiation.

Second, progress has been made in understanding how aberrant proliferation of stem cells can lead to the genesis of tumours. Experimental evidence that stem cells can be the origin of many cancers has been established in the fly, the mouse and other animals. Moreover, the reprogramming of intermediate progenitor cells back to stem cells has also been recognised as having a high potential to produce tumours. Many of the molecular events that force stem cells to become cancer cells have been identified. Importantly, these findings have implications for the safety of potential stem-cell-based therapies.

Third, and perhaps the most directly applicable aspect of the discovery of iPSCs, is the use of these cells in modelling human disease and in drug discovery. iPSCs derived from patients can provide the large numbers of



human cells required for comprehensive analysis of disease mechanisms, thereby avoiding the complexity and ambiguity of using cells from animal disease models. Patient-derived iPSCs can also be used in drug discovery for disease-specific screening of novel pharmaceuticals as well as for more general toxicity testing. Moreover, these cells can be used to engineer patient-specific tissues and organoids as more complex models for disease testing and drug screening.

Finally, significant advances have been made in the area of stem-cell-based regenerative medicine. Cell replacement therapy, in which cell types such as iPSCs are used in transplants to compensate cell loss due to trauma, disease or degeneration, is under investigation for the treatment of several disorders including heart failure, retinal blindness, diabetes type 1, Parkinson's disease and spinal cord injury. Progress has also been made in stimulating resident albeit quiescent adult stem cells to proliferate and generate differentiated cells for cell repair and replacement. Other important issues under investigation in this area are the safety of the cells, their state of maturity as well as their propensity to integrate efficiently into the surrounding tissue.

The paradigm-shifting revolution caused by stem cell biology in recent years is nowhere more apparent than in neuroscience. As late as the 1980s most neuroscientists did not consider neural stem cells to be important players in brain development. The existence of stem cells in the adult brain was not generally accepted before the 1990s. Neural stem cells in the mammalian cortex were only identified after the year 2000. In contrast, once the existence and importance of neural stem cells during neural development and in the adult brain of all animals was recognised, an explosion in advances and applications of neural stem cell biology occurred, fuelled by the availability of iPSC-derived human neural stem cells and neurons.

## ADVANCES IN REGENERATIVE MEDICINE

Currently, the mechanisms that operate in the proliferation of neural stem cells and the generation of their more differentiated cells are being elucidated in mammalian models. Human stem cells are being used as a source of neurons and glial cells in the development of transplantation therapy for neurodegenerative diseases. The self-assembly of complex sensory and neural tissues and organoids from stem-cell-derived neuronal cells is being investigated. Patient-derived iPSCs are being used to model neurological diseases and, combined with targeted genome modification methods, to investigate the molecular genetic bases of these diseases. Indeed, the impact of neural stem cell biology on the field is so extensive that it is difficult to appreciate and relate the full extent of the changes that have occurred in just a few years.

It will be very exciting to see what the next ten years hold in store for stem cell biology in neuroscience and in biomedical sciences in general.

**Heinrich Reichert**, Professor at the University of Basel

# “It is more complicated than we thought”

**Stopping stem cells from becoming brain tumours** (2010–2015) → CHF 470,122
**Prof. Heinrich Reichert,** Biozentrum, University of Basel; **Prof. Jürgen Knoblich,** Institute of Molecular Biotechnology, Vienna, A

**In the future, stem cells are expected to be used to treat a variety of diseases, including neuronal diseases such as Parkinson’s or multiple sclerosis, by replacing dead nerve cells with new ones. But before this dream can become a reality in hospitals, there is a long way to go. Probably the biggest obstacle is that stem cells can sometimes form tumours; if they are used in the brain, brain tumours could result. For the past five years, Professor Heinrich Reichert and his team at the University of Basel have studied in the fly Drosophila how brain tumours can develop from stem cells – in order to prevent this from happening.**

**Prof. Reichert, how are you studying how brain tumours can form from stem cells in the fly?**

Using the fly has the advantage that you can switch off every single gene relatively easily. We can then observe in the living animal whether turning off a gene has an effect on the formation of brain tumours. We can examine whether this intervention leads to more or fewer brain tumours.

**What have you learned from your experiments?**

We discovered a total of about 800 genes that have an effect on neuronal stem cells, and some of these genes can affect the formation of brain tumours. Only about one half of these genes were previously known to have this effect and were described in the literature. So we discovered many new genes, and proceeded to examine their effect more closely.

**What did you find?**

From any given stem cell, different types of nerve cells can be produced. The development from the stem cell to the mature nerve cell is a process that occurs in several steps and is controlled by several genes. But more than that – and this is new: not only genes decide, but also epigenetic factors.

**How do epigenetic factors work?**

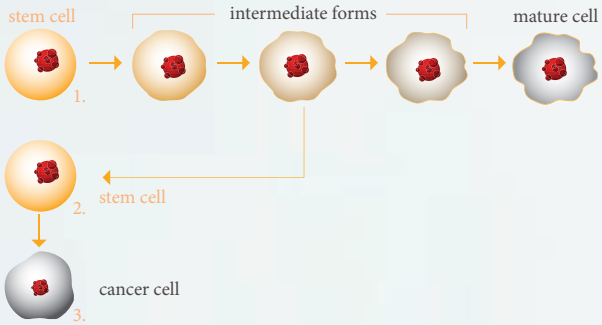
Epigenetic factors are like a higher control level that can switch several genes on and off.

**What does this mean in view of possible medical applications?**

It means that when developing drugs, this level has to be taken into account as well. It is more complicated than we thought.

**What else have you found?**

That a high risk of brain tumour formation does not come from the stem cells themselves, as we had originally thought, but rather from cells that are intermediate forms between stem cells and mature nerve cells. The process from stem cell to mature nerve cell is not linear; a reversal developmental is possible, resulting in an intermediate cell becoming a stem cell again, and then turning into a cancer cell.




**What are the consequences with regard to the development of therapies?**

There is a high probability that processes like those we have observed in the fly can also be found in humans. This means that for now, we strongly advise against using stem cells or intermediate cells directly, for regenerative medicine, as the risk that these cells can form tumours is unpredictable. In our opinion, at the present time, only mature cells should be considered for use in regenerative medicine.

**Have you considered how these new findings could be used to prevent the formation of tumours?**

Yes, and we have also conducted some initial experiments. With no success as yet. In some cases, it was possible to delay the formation of tumours for long periods. But sooner or later all of the flies developed tumours. Here, collaboration with pharmaceutical companies is needed, to look for and analyse new substances. My colleague Jürgen Knoblich in Vienna, with whom we had an excellent collaboration, will work on this in the future.

**Keywords**
brain tumour, Drosophila, tumour stem cells

## The essential ability to distinguish between

# "self" and "non-self"

**Analysis of thymus development** (2010–2015) → CHF 567,816
**Prof. Georg Holländer,** Department of Biomedicine, University of Basel

**The thymus is a strange organ. If the organs of the body were likened to a school class, the thymus would be the oddball that no one really knows and that most people think would not be missed.**

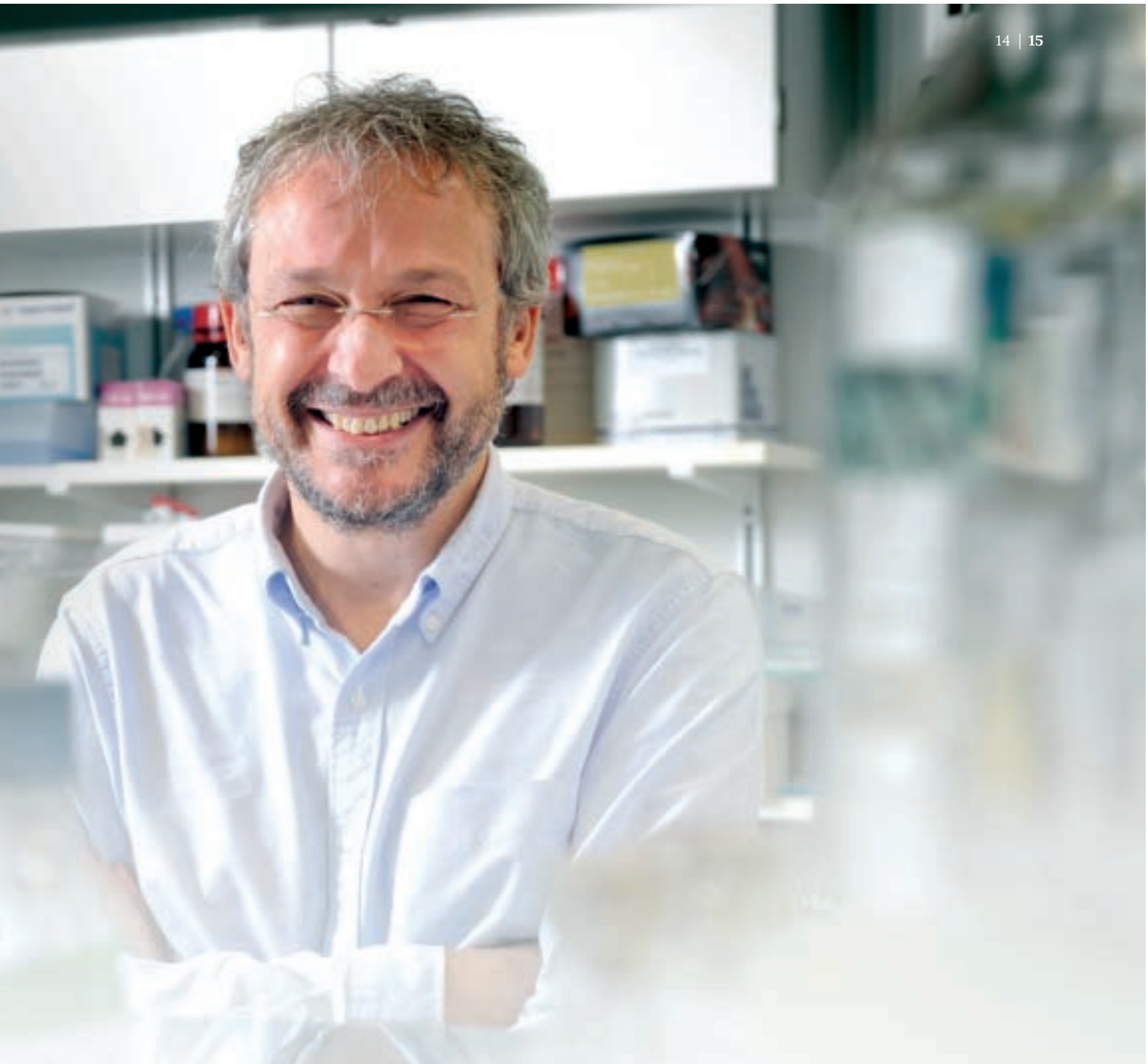
There are a number of reasons for this. For example, when people think of "organs", heart, lungs, and brain come to mind first. The thymus gland comes last, if at all. The thymus is thought to be "dispensable", like the gall bladder. In the past, paediatric surgeons performing heart surgery used to simply remove the thymus, as it is located in front of the heart. The notion that the thymus is dispensable may possibly go back to Nobel laureate Sir Peter Medawar, who in 1963 called the thymus "an evolutionary accident". But it may also have something to do with the fact that over a person's lifetime, the thymus shrinks from the size of a pear to the size of half a pea.

### NOT COMPLETELY UNNECESSARY

But in fact the thymus fulfils its most important function already in infancy: the production of all T lymphocytes, which are an essential component of the immune system. "But this does not mean that the thymus is thereafter completely unnecessary," emphasises Georg Holländer, a professor at the University of Basel and a researcher who has studied the thymus intensively for many years.

"Surgeons have since stopped to simply remove the thymus, as long-term side effects of this intervention are more serious than was originally thought." The thymus plays a key role in teaching the immune system to distinguish between "self" and "non-self". This is a vital distinction, for how does the immune system recognise whether a certain cell in the body is one of the body's own cells or a foreign pathogen? If the immune system mistakes self for non-self, the result is called an autoimmune disease: the immune system attacks the body's own cells or tissues. There are hundreds of autoimmune diseases, including diabetes, rheumatism, and multiple sclerosis.

In his NRP 63 project, Holländer's research team focuses mainly on the development of thymic epithelial cells. How do the mature thymic epithelial cells finally



develop from stem cells via several stages? Holländer likens this process to a train journey from Basel to Chur. The cells mature via several stations, and when they reach Chur, they are ready for their function, which is their unique ability to control the maturation of T lymphocytes. "To be able to recreate thymic epithelial cells in the laboratory, we have to know precisely what stations we need to travel through," explains Holländer, so that the production does not end up on a railway siding. But research has not yet reached that point. The departure station and the destination station are now known, and thanks to the research work of Holländer and his team, we now have a better knowledge on some of the intermediate stations on the line from Basel to Chur. But there are still gaps in our knowledge.

A further goal of the research group is to recreate not only the individual thymic epithelial cells in the laboratory but also the entire thymus, so that patients such as children born with thymus defects can be treated. "Five years from now, research will have advanced to the point where a more or less functioning thymus can be recreated in the mouse," Holländer believes. Technical advances are making experiments possible today that were considered unfeasible just a few years ago. "However, it will take considerably longer than that before a thymus can be recreated in humans."

**Keywords**
epigenetic regulation, thymic epithelial cells, polycomb repressive complex (PRC)

# The unexpected conversion of cells

**New understanding in the regeneration of insulin-producing cells** (2010–2015) → CHF 992,845
**Prof. Pedro Herrera,** Faculty of Medicine, University of Geneva

Pedro Herrera's stem cell journey had a bumpy start. At the turn of this century, his research group worked on the biology of the pancreas. Like many other research groups around the world, he worked with embryonic stem cells (ES cells), in the hope that someday these cells could be used to treat diabetes as insulin-producing cells, called beta cells. For a number of reasons, the team decided to abandon that course. Another route looked more promising: "We wanted to explore a different approach to reconstitute the missing insulin cells. We wanted to study the capacity of regeneration of the pancreas, in living animals."

Through intensive efforts the team subsequently produced mice in which beta cells can be destroyed practically at the touch of a button. The mice are then

kept alive with insulin therapy, similar to the treatment used for human patients with diabetes. What happens in the pancreas of these mice? "Our first surprise was that within a short time, the cells that had been removed were being replaced; new beta cells were produced," says Herrera. After a few months, the mice survived without insulin treatment.

The second surprise was that other pancreatic cells, called alpha cells, which secrete the hormone glucagon, spontaneously reprogrammed to become insulin producers. Like maple trees converting into beech trees – a process that biology textbooks say is impossible.

## OLD MICE HAVE SAME POTENTIAL

The team then wanted to find out whether this reprogramming ability is dependent on age. Is the effect found only in young adult mice? That could well have been the case, for it is known that the regeneration potential basically decreases as age increases. Interestingly, the experiment showed that old mice maintain the same regeneration potential. The process is robust and long-lived – an important finding with potential therapeutic implications.

Next, the team became interested in the study of pancreas regeneration in juvenile mice: "We found that several weeks after injury, the pancreas in these mice had plenty of regenerated beta cells and, accordingly, all animals were cured," reports Herrera. In addition, the team discovered a different reprogramming process. In fact, the new beta cells in juveniles were generated from delta cells, which normally produce the hormone somatostatin. Here, delta cells dedifferentiate back to a more original state, and then produce new cells. "Not only new delta cells, but also beta cells!" says Herrera.

All of this is very interesting with regard to medical applications for patients with diabetes, even if there is still a long road ahead. Instead of administering insulin to patients with diabetes, it may someday be possible to reconstitute new beta cells from alpha or delta cells. These would then produce the body's own insulin. A number of pharmaceutical companies have also recognised this potential, which is why Herrera is in contact with them. He has also patented some of his discoveries.

Today, it is clear that Pedro Herrera's research effort has added a new chapter to biology. It looks like biology textbooks will have to be revised.

**Keywords**
beta cells, plasticity, pancreas

# Summary of all projects

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**The KRAB gene family and its role in the development of human beings** (2010–2015)

- Prof. **Didier Trono**

BUDGET: **CHF 981,970**

KEYWORDS: KRAB/KAP1, KRAB-Zinc finger protein (ZPF), embryonic stem cells

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**Legal and ethical challenges of stem cell donation** (2010–2015)

- Dr. **Jörg Halter**
- Dr. **Thomas Bart**
- Prof. **Alberto Bondolfi**
- **Yvonne Fischer**
- PD Dr. **Urs Schanz**
- Prof. **Kurt Seelmann**

BUDGET: **CHF 521,990**

KEYWORDS: hematopoietic stem cell transplantation (HSCT), stem cell donors, risk assessment

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**Nerve stem cells: Control and communication** (2010–2015)

- PD Dr. **Irene Knüsel**
- Prof. **Jean-Marc Fritschy**

BUDGET: **CHF 803,228**

KEYWORDS: olfactory stem cells, microvillar cells, cystic fibrosis transmembrane conductance regulator (CFTR)

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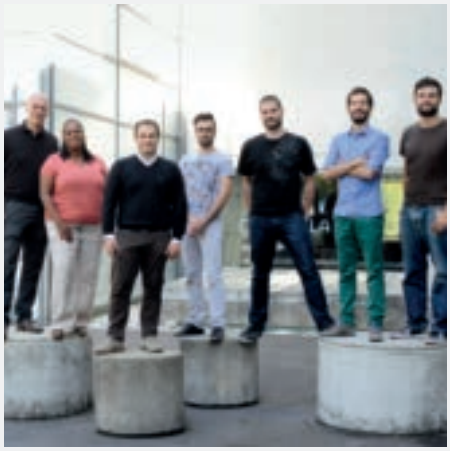

**How does heart tissue regenerate?** (2010–2015)

- Prof. **Thierry Pedrazzini**
- Prof. **Daniel Schorderet**
- Prof. **Dario Diviani**

BUDGET: **CHF 940,139**

KEYWORDS: miRNA/lncRNAs, zebrafish, heart regeneration

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**Mapping stem cell diversity in the adult brain** (2010–2015)

- Dr. **Olivier Raineteau**

BUDGET: **CHF 807,834**

KEYWORDS: subventricular zone, neural progenitor cells, topographical mapping

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**A new biomaterial for ear reconstruction** (2010–2013)

- Prof. **Ralph Müller**
- Prof. **Paul Gatenholm**
- Prof. **Nicole Rotter**
- Prof. **Gerjo van Osch**
- **Jens Riesle**
- **Anette Jork**

BUDGET: **CHF 143,080**

KEYWORDS: ear tissue regeneration, nanocellulose, biomaterial

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**Stopping stem cells from becoming brain tumours** (2010–2015)

· Prof. **Heinrich Reichert**
· Prof. **Jürgen Knoblich**

BUDGET: **CHF 470,122**

KEYWORDS: brain tumor, Drosophila, tumour stem cells

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**Analysis of thymus development** (2010–2015)

· Prof. **Georg Holländer**

BUDGET: **CHF 567,816**

KEYWORDS: epigenetic regulation, thymic epithelial cells, polycomb repressive complex (PRC)

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**New understanding in the regeneration of insulin-producing cells** (2010–2015)

· Prof. **Pedro Herrera**

BUDGET: **CHF 992,845**

KEYWORDS: beta cells, plasticity, pancreas

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**Boosting the healing of wounds** (2010–2015)

· Prof. **Lukas Sommer**

BUDGET: **CHF 1,046,046**

KEYWORDS: neural crest-derived stem cells (NCSCs), melanoma, epigenetic regulators

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**A novel approach to generate blood vessels** (2010–2014)

· Dr. **Stefano Di Santo**
· Prof. **Hans Rudolf Widmer**
· Dr. **Robert Hans Andres**

BUDGET: **CHF 276,064**

KEYWORDS: paracrine factors, precursors of endothelial cells, cell-free medium

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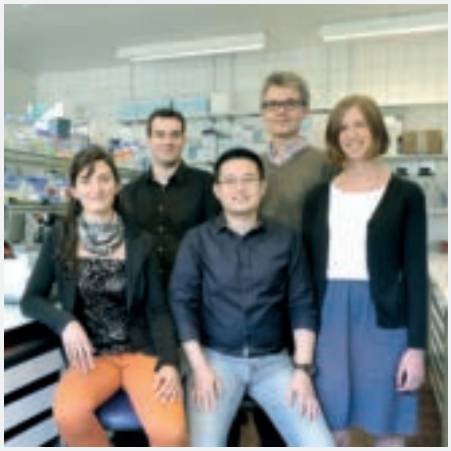


**How an embryo develops from a sperm and an egg** (2010–2015)

· Prof. Dr. **Antoine Peters**

BUDGET: **CHF 767,536**

KEYWORDS: polycomb group proteins (PcG), epigenetic inheritance, embryogenesis

# Heart regeneration: Moving away from the hype

**How does heart tissue regenerate?** (2010–2015) → CHF 940,139
**Prof. Thierry Pedrazzini,** Department of Medicine, University of Lausanne; **Prof. Daniel Schorderet,** Institute for Research in Ophthalmology, Sion; **Prof. Dario Diviani,** Faculty of Biology and Medicine, University of Lausanne

**Up to ten years ago, researchers were convinced that the heart had no capacity to regenerate after a heart attack. The dying tissue caused by the injury was considered to be irremediably lost, and subsequent reduced pumping ability was thought to be irreversible.**

"Today we know that this is not entirely true," explains Thierry Pedrazzini, who is a professor at the University of Lausanne Medical School. It is estimated that approximately one per cent of the heart muscle can be renewed each year. "There is a constant regenerative process in the heart but with its slow turnover, it does not allow for compensation of the loss of myocardium after infarction."

## HEART REGENERATES EVERY 100 YEARS

Theoretically, the heart would regenerate itself only every 100 years but could we possibly accelerate this naturally occurring regeneration, and, in this way, help cardiac patients? Originally, many research teams worldwide started looking for cardiac stem cells in the heart. However, if these cells exist, it is in very low numbers, not sufficient to make a difference in the damaged muscle. This led to the idea that one could supplement the heart with another source of stem cells, specifically stem cells from the bone marrow. Hundreds of clinical studies were conducted to evaluate the potential of bone marrow cells in cell replacement therapy for heart disease without consistent results. True regeneration was never demonstrated.

Researchers became sceptical. "In my opinion, there are no genuine stem cells in the heart that can produce new heart muscle cells," says Thierry Pedrazzini. In the past years, this idea was inappropriately hyped. Now, the question is: if cardiac stem cells do not exist, where does the regeneration come from? One of the answers is "precursor cells". Precursor cells are not "true" stem cells because they are already geared to produce a given cell type. The laboratory of Thierry Pedrazzini has in fact been able to isolate precursor cells from the heart of human cardiac patients. Interestingly, cardiac precursor cells give rise predominantly to smooth muscle cells, which are components of the blood vessels. The fact that precursor cells do not produce cardiomyocytes – the heart muscle cells – might explain in part why the heart does not significantly regenerate.

Importantly, in a subsequent step, the Lausanne team succeeded in reprogramming precursor cells in such a way that they no longer produced smooth muscle cells but instead the desired heart muscle cells (the manipulation targets long non-coding RNAs). The reprogrammed cells represent therefore a promising source of cells to be used in cell therapy in humans.

Alternatively, new heart muscle cells could also be obtained from another source – namely, from the heart muscle cells themselves. This can work if one can force these cells to start dividing. "Interestingly, we and others were able to accomplish this successfully," reports Thierry Pedrazzini. In this case, the regeneration rate in the mouse heart could be increased from one to three per cent. "This is just the beginning of a very interesting approach we are going to pursue."

## COLLABORATION WITH BIOTECH COMPANY

Thierry Pedrazzini has already obtained a patent covering the therapeutic use of long non-coding RNAs in heart disease. The laboratory is currently collaborating with a biotech company to elaborate diagnostic tools.

It is no wonder that he is pleased with the support received from the NRP 63 programme over the past five years: "Our project investigated a completely novel approach, which meant starting practically from scratch. At the end of the funding period, we are extremely satisfied with the progress."

**Keywords**
miRNA / lncRNAs, zebrafish, heart regeneration

# A stem cell map of the brain

**Mapping stem cell diversity in the adult brain** (2010–2015) → CHF 807,834
**Dr. Olivier Raineteau,** Brain Research Institute, University of Zurich/ETH Zurich

**"We are very pleased with the results of our research project," reports Olivier Raineteau, currently a professor at the University of Lyon, who goes on to mention a crucial factor in the success of the project: "Under NRP 63 we were able to pursue our research project for five years." He says that such long-term funding is not often found nowadays. Today, successes have to be produced rapidly, even though many know that good research takes time. "In a shorter-term framework, our project would probably have not been successful."**

Raineteau's research group focused on stem cells in the brain. Until recently, experts believed that the adult brain was no longer able to produce new neurons. "Today we know that that is not true," says Raineteau, who is a professor in neuroscience. The hope now is that this plasticity of the brain can be used to generate new neurons in diseases or after accidents involving head trauma.

In the human brain, there are two main regions with stem cells which contribute to the small-scale but continuous production of new neurons. One of these is the subventricular zone (SVZ). Raineteau's team studied this region of the brain in detail, made a three-dimensional map of the zone – and an astonishing discovery.

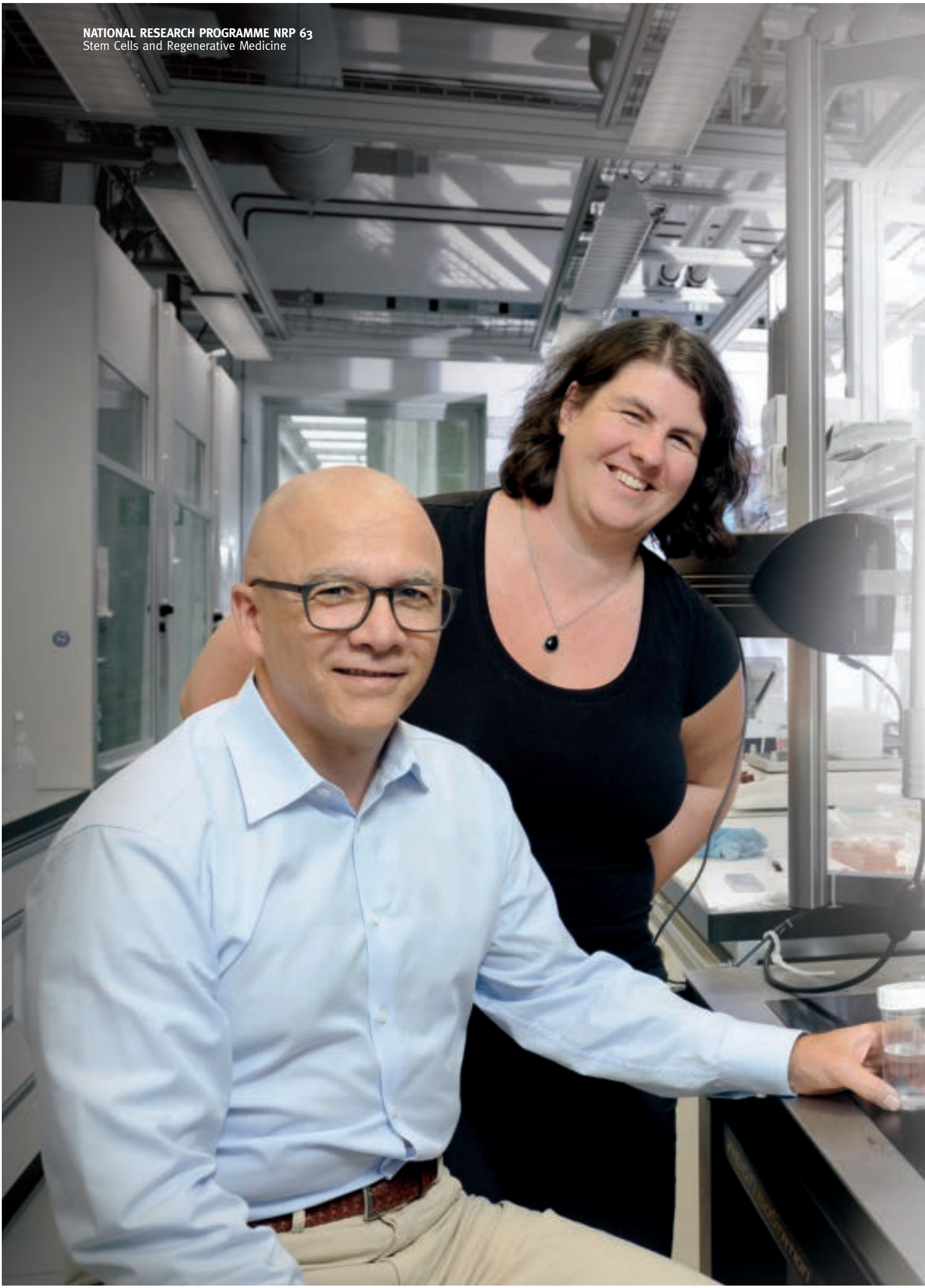
In the SVZ, there are different populations of stem cells. They differ in that each population can produce only a specific type of brain cells. No population possesses the ability to generate all types of neurons. Interestingly, which stem cells produce which neurons depends on the exact location of the stem cells within the SVZ: "There are spatial rules, a topographical code that tells the stem cells what cells they may produce," Raineteau explains. The team then made a three-dimensional map of the brain showing the locations of the different populations of stem cells. "Overall, the map shows that the SVZ is a complex region. More complex than what was once thought."

In a next step the researchers mapped this region of the brain not only in mice but also in monkeys and found that there are great differences between the two animal species. The team then used the maps to isolate populations of stem cells and to conduct a genetic analysis of the different cells. "This step worked very well", Raineteau says, "we can clearly distinguish between the different type of cells, and we know what steps are necessary for neuron A or B to be produced."

The last and most difficult step of the project is progressing to the medical application. Here, the researchers are focusing mainly on brain injuries, for example on areas of the brain that were damaged by a lack of oxygen. Using small biomolecules, the team will try to stimulate division of the appropriate stem cells in the affected brain region: "In the last five years we have acquired a lot of information that allows us to take a very targeted approach to this process." The research team can now stimulate very specific populations of cells to divide, while leaving other populations unaffected. This is an important step towards future medical interventions with as few side effects as possible.

**Keywords**
subventricular zone, neural progenitor cells, topographical mapping

**NATIONAL RESEARCH PROGRAMME NRP 63**
Stem Cells and Regenerative Medicine



# A new material to rebuild ears

**A new biomaterial for ear reconstruction** (2010–2013) → CHF 143,080
**Prof. Ralph Müller,** Institute for Biomechanics, ETH Zurich; **Prof. Paul Gatenholm,** Chalmers University of Technology, Gothenburg, SE; **Prof. Nicole Rotter,** Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Ulm University Medical Centre, DE; **Prof. Gerjo van Osch,** Departments of Orthopaedics and Otorhinolaryngology, Erasmus Medical Centre, Rotterdam, NL; **Jens Riesle,** CellCoTec, Bilthoven, NL; **Anette Jork,** CellMed AG, Alzenau, DE

**Kenneth Toe was born with a malformed ear. The young boy, who lived in Bremen, and loved playing soccer found this more and more difficult to deal with as he grew older. Our ears are exposed; when they are malformed, it is not easy to simply hide them. At the age of six, Kenneth was teased by other children, and what is more, he had trouble hearing with that ear. His mother decided to take him to an ear surgeon at Klinikum Bremen. The surgeon constructed a new ear for Kenneth out of a plastic mould, which was then implanted under the skin. The procedure worked. And Kenneth is happy with his new ear.**

There are many possible causes of ear malformation; some children are born with it, other malformations are caused by injuries. The standard procedure today for ear reconstruction is the autologous method, where rib cartilage is used to make a scaffold, which is then transplanted under the skin. Surgeons have many years of experience with this method. But rib cartilage ear reconstruction has disadvantages: the procedure is long and painful, and with this material, the reconstructed ear is hardly an exact reconstruction of the patient's auricle. A synthetic scaffolding can also be used to cre is the optimal solution in the long term.

## NEW MATERIAL: NOT TO STIFF, NOT TO SOFT

For these reasons, a number of researchers worldwide are looking for better solutions. Two of these researchers are Ralph Müller and Kathryn Stok at the ETH Zurich. They both believe that they have found a promising solution: nanocellulose, a novel material that offers distinct advantages. One is that it has practically the same material characteristics as natural cartilage. It is not too stiff, which would cause discomfort or pain when wearing a helmet or lying on the ear during sleep. It is not too soft, for it would otherwise lose its shape. Stok reports that "In our study we found nanocellulose to be well suited for use in ear reconstructions". The material is strong, stable, and a good substitute for cartilage, and most of all, it can be enriched with the patient's own cells. It can support a developing living tissue – in contrast to a plastic implant.

The researchers also think that nanocellulose could be used for other body parts made of cartilage, actually "anywhere where cartilage needs to be replaced", says Stok. It will be some years yet before the new material can be used in patients; up to now it has only been tested in animals.

The development of new materials is enormously important: "Tissue engineers have worked with the same set of materials for too long," says Stok. This is also the reason why tissue engineering has not advanced as it should have after 20 years of research: "At the moment, research teams base their work on existing, familiar materials in order to understand cell behaviour, and then try to filter out what could be right for medical use." Stok believes that the process should work in the opposite direction: "First we should ask what characteristics the material must have to satisfy a medical purpose. Then we should develop that material." Stok hopes that in this way tissue engineering will get to where it is urgently needed: in everyday hospital practice.

The nanocellulose project is now moving into the next phase. The research team is developing a production method that will ensure that laboratories all over the world will be able to produce the material in sufficient quantities. This is important to ensure comparability of the results. The Swiss company regenHU is involved in this step; they are developing their 3D bioprinters and bioinks to print patient-specific ear shapes along with cells for tissue growth.

**Keywords**
ear tissue regeneration, nanocellulose, biomaterial

# “I hope this is not real blood!”

A school class in the stem cell exhibition
“Stem Cells – The Origin of Life”

# “Stem Cells – The Origin of Life”

It’s a Thursday morning in June. Students from the Freies Gymnasium Zürich have already gathered in front of the Zoological Museum of the University of Zurich. Their biology class will be held here today, at the exhibition “Stem Cells – The Origin of Life”. They listen with obvious interest to the last instructions given by their biology teacher, Mr. Müller, before entering the exhibition: “We haven’t had stem cells in class yet. And you don’t have to try and understand everything down to the last detail. Just keep an open mind and allow for surprises.” At the entrance, the group is welcomed by Tobias Alther, who will guide the students through the exhibition.

**STUDENTS SHUDDER**

It quickly becomes apparent that the students are not so clueless after all. Already at the start, hands go up when Tobias asks if anyone can explain what stem cells are. “They are special cells that divide and produce new cells,” one of the girls calls out. And when it comes to the terms “totipotent” and “pluripotent”, the students show that they have paid attention in Latin class. “Totus means whole and pluri must come from plus and means more,” says one of the students. “And potentia is power or ability,” says another.

While some of the students hog the stem cell scanner, Tobias shows the others everything that stem cells can do. Using various parts of the exhibit, he explains the ability of plants, animals, and humans to regenerate. The students ask questions: whether it is true that both parts of a severed earthworm can survive. Or how often a lizard can shed its tail. Or how long it takes for an axolotl to grow a new leg.

In the background, a boy is still busy with the stem cell scanner. He wants to find out more about the age of his cells. But he is only half as tall as the scanner and simply cannot reach the knob on the monitor that says “How old are my cells?” “That’s tough,” says a girl who is watching, she gives it a try herself – and succeeds. Together they read the information on the monitor, and the girl calls out, “What? Some of my cells are younger than I am!”

Tobias leads the group into the stem cell lab. In front of a giant projection screen on which blood cells are pictured, he explains how blood stem cells from bone marrow are removed from donors and given to patients. Some of the students shudder when they are shown the long needle that is used to draw marrow out of a donor’s pelvic (hip) bone. The students prefer to look at the blood bag that is lying in the silver cool box, which is designed for transporting stem cells. The bag is filled with a rust-coloured liquid. “What do you think is in there? I hope it is not real blood!”

The class moves on and Tobias explains that stem cells were discovered thanks to a tragic event. When the Americans dropped the atomic bomb on Hiroshima in 1945,

many people died due to the effects of the atomic radiation. As doctors found out, the stem cells were destroyed, and no new blood cells could be made. “Why do you die if the body no longer produces blood?” asks a student. Tobias explains that blood cells generally live for only three months and then die. If they are not replaced, death follows.

Next, the students move on to look at a three-dimensional model of the skin that illustrates three primary types of burns, first-, second- and third-degree, and explains why in third-degree burns, the skin can no longer regenerate itself, since the skin stem cells are destroyed. One of the students is struck by an idea: “But if we never get burned and our stem cells produced new cells over and over again, wouldn’t we be immortal?” “That only happens in a fantasy world. For example, with Wolverine,” says Tobias, pointing to a glass case containing a display of the comic book superhero in action. Thanks to his super powers of regeneration, Wolverine is invincible. If he is injured, his wounds heal in seconds. “In human beings, however, stem cells lose something of their power with each division, until at some point, they can no longer divide. Then the person dies. Do you guys want to live forever?” There is a mixed chorus of “Yes!” and “No!”. “At the end of the exhibition you can think some more about what you would decide if you had the choice between immortal life or finite life. But first, let’s watch the film about Jens.”

Jens Müller survived leukaemia thanks to blood stem cell transplantation; the film tells his story. Things get quiet in the exhibition space. The students put on headphones and watch the film. Jens’ words makes them thoughtful. Afterwards, they exchange their thoughts: “I find it amazing that someone would just simply donate stem cells without knowing who they are for. Would you do that?” asks one student. “I would want to know who will receive my cells,” says another. “I’ve never even thought about it. Can I donate? How old do you have to be to be a donor?”

The students slowly leave the exhibition taking with them a lot of thoughts and images to their next class. “That was a great biology class,” says one of the girls. “Now I know that I came from one single super cell!”

# How wound healing and skin cancer are connected

**Boosting the healing of wounds** (2010–2015) → CHF 1,046,046
**Prof. Lukas Sommer,** Institute of Anatomy, University of Zurich

**Ow! It can happen so quickly! – you cut a finger with a kitchen knife and blood wells up immediately. But then, within minutes, the bleeding stops. And after a few weeks, the wound is completely healed. This is a normal and natural process, but an extremely complex one. First, the injured blood vessels are closed, then a secretion cleanses the wound, and finally the wound is filled with new tissue. Many different substances are involved in the healing process as well as several types of stem cells, which produce new cells.**

For five years, Lukas Sommer and his team at the University of Zurich have closely studied one type of these stem cells, neural crest stem cells (NCSC). NCSC offer an especially broad potential. They can develop into different cell types – skin, cartilage and bone cells but also smooth muscle cells in the heart. This is unusual, because most stem cells in adult bodies have lost this ability.

But what is the role of these cells in wound healing? "We were able to show, for the first time, that these cells are needed for efficient wound healing," says Sommer. The researchers found that the greater the number of these cells in the wound, the faster the wound healed. "It goes without saying that, theoretically, using these cells could accelerate wound healing," Sommer says. However, it is not exactly clear yet how stem cells affect wound healing. Directly through the production of new cells? "We will study this further." There is also an interesting connection with other processes in the body for which there are indications that they proceed in a similar way to skin wound healing, such as the healing of tissue after a heart attack.

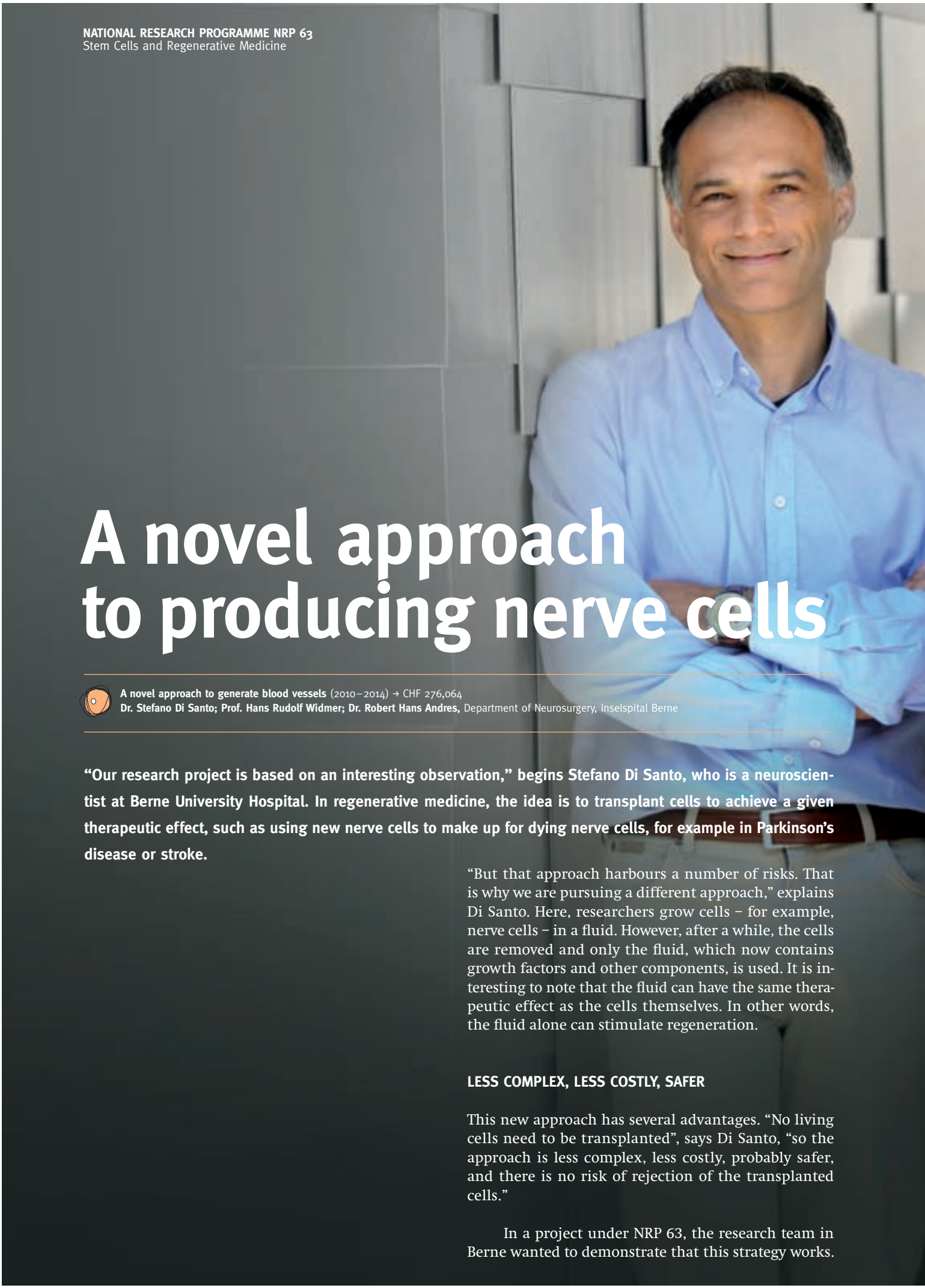
Another part of Sommer's research was investigating how in rare cases, stem cells can also degenerate and develop tumours. The research team undertook comparisons: how do stem cells behave when they work normally? And how do they behave when they become cancer cells? "Knowing the difference between benign and malignant growth is important. Stem cells can only be used in medicine if their growth can be controlled," explains Sommer. The team has achieved interesting findings in this area and was able to clarify the difference in detail, which is an important foundation for medical applications.

It is interesting to note that Sommer's research project is not the only project under NRP 63 that investigated this question. Heinrich Reichert's research also focused on the development of tumours (in the brain, however). Both research teams came to the same conclusion: the theory of cancer stem cell is supported.

There has been a focus on cancer stem cells for some years now. According to this theory, stem cells are responsible, when a cancer recurs years after a successful cancer treatment. Conventional cancer drugs often attack rapidly dividing cells, to which cancer cells belong. But cancer stem cells divide slowly and for this reason are resistant to conventional cancer therapies. They fly under the radar of those cancer drugs, staying around for years in the tissue and then suddenly start to form new tumours. Sommer's research team has also discovered that there is a second possible way for cancer stem cells to develop: they can develop from not completely matured skin cells that revert to stem cells.

To prevent the development of cancer stem cells, Sommer has already conducted collaborations with pharmaceutical companies to develop chemical substances counteracting stem cell growth. "The challenge here is that we do not want to kill naturally occurring, healthy stem cells as well." This, too, is a research topic that the research team will study in the next few years.

**Keywords**
neural crest-derived stem cells (NCSCs), melanoma, epigenetic regulators



# A novel approach to producing nerve cells

**A novel approach to generate blood vessels** (2010–2014) → CHF 276,064
**Dr. Stefano Di Santo; Prof. Hans Rudolf Widmer; Dr. Robert Hans Andres,** Department of Neurosurgery, Inselspital Berne

**"Our research project is based on an interesting observation," begins Stefano Di Santo, who is a neuroscientist at Berne University Hospital. In regenerative medicine, the idea is to transplant cells to achieve a given therapeutic effect, such as using new nerve cells to make up for dying nerve cells, for example in Parkinson's disease or stroke.**

"But that approach harbours a number of risks. That is why we are pursuing a different approach," explains Di Santo. Here, researchers grow cells – for example, nerve cells – in a fluid. However, after a while, the cells are removed and only the fluid, which now contains growth factors and other components, is used. It is interesting to note that the fluid can have the same therapeutic effect as the cells themselves. In other words, the fluid alone can stimulate regeneration.

## LESS COMPLEX, LESS COSTLY, SAFER

This new approach has several advantages. "No living cells need to be transplanted", says Di Santo, "so the approach is less complex, less costly, probably safer, and there is no risk of rejection of the transplanted cells."

In a project under NRP 63, the research team in Berne wanted to demonstrate that this strategy works.

"No easy task, for we had to start virtually from scratch," says Hans Rudolf Widmer, head of the research laboratory and professor of neurosciences at University Hospital Berne. Using rats, the team first studied the effect of the fluid on nerve cells in the brain: does simply injecting the fluid lead to the production of new nerve cells? In living animals, the team found that the fluid did in fact stimulate stem cell division.

## THOUSANDS OF DIFFERENT COMPONENTS

Second, the team wanted to find out how this cell-free process works. What components in the fluid are responsible for the effect? How do they work? "To answer this question, we tried to limit the number of components. However, exactly the opposite occurred." To examine what components of the fluid are involved in the effect, the team conducted numerous experiments. They very soon discovered that there are over a thousand different components in the fluid – many of them known, including growth factors and cytokines, but many not yet known. Rather surprisingly, lipids (fatty acids) are also involved. And to make things even more complicated, it quickly became apparent that it is not individual substances that cause the effect but rather, many substances linked together and, in addition, the effect is also dose dependent. "This complexity is the reason why we have not yet been able to find out what exactly causes the effect and what components are responsible," explains Di Santo.

## FOCUS ON PARKINSON'S DISEASE

However, in recent years, there has been an increasing number of publications dealing with this phenomenon. Work in Berne continues, and will be combined with an ongoing project on Parkinson's disease. In Parkinson's, certain nerve cells die off and the brain cannot replace them. "Theoretically, our cell-free approach could also be used in patients with Parkinson's to allow transplanted nerve cells to grow better," says Widmer. The researchers in Berne have a lot of experience in this area. The first ever transplantation of cells in a patient with Parkinson's disease in Switzerland was carried out at the University Hospital in Berne. Now it remains to be seen whether Berne will also be the first to use cell-free therapy on a patient with Parkinson's.

**Keywords**
paracrine factors, precursors of endothelial cells, cell-free medium

# Studying the origin of human beings

**How an embryo develops from a sperm and an egg** (2010 – 2015) → CHF 767,536
**Prof. Dr. Antoine Peters,** Friedrich Miescher Institute for Biomedical Research, Basel

The start of a human life is fascinating. Two cells, an egg and a sperm, converge to form a new cell that has the unique ability to develop into a human being. In contrast to egg and sperm, the early embryonic cell is totipotent, an all-rounder cell. The process is complex, and today it is unclear whether science will ever understand it in its entire breadth and depth. This does, however, not deter Antoine Peters and his team to study the process.

We inherited much of what we are from our parents and grandparents. It is known that mother and father pass on not only eye colour and body size to the child but also many other characteristics, such as the risk for certain types of cancer. Information flows on two levels: much is transmitted on the "classic" route via genes, some on the "new" route via epigenetics. Epigenetic is a relatively new research area. Epigenetic regulators are overarching factors that possess the ability to turn entire sets of genes on and off. What is important is that not only genes but also epigenetic information is in part inherited.

## FROM PARENTS TO CHILDREN

Antoine Peters and his research group are mainly interested in how epigenetic information passes from parents to children: Studies in humans and in rodents show that nutritional intake during embryonic development or adulthood can affect metabolic processes in children and even grandchildren. There are also indications that severe psychological experiences can be passed on to a person's children and grandchildren. Thus, epigenetics in mammals goes further than was once thought. Nonetheless, experts are cautious about the mechanisms of inheritance, which can be diverse.

Looking at thousands of mouse genes, Peters examined which are turned on or off in egg cells that develop in mothers, turned on or off during the development of sperms in fathers, and then turned on or off in embryonic cells of children. There is no simple answer. In any case, it is not so that a gene is turned on in the child if it is turned on in the mother and father: "We have discovered various interesting patterns, but overall, regulation is complex."

In his experiments with mice, Peters has focused mainly on a particular group of proteins called polycomb group proteins, or PcG proteins, because they are critical when it comes to turning genes on or off. Over the last five years, Peters' team has made important findings that contribute towards understanding how they do this. In addition, Peters discovered that the PcG proteins are important not only during the formation of early embryos but also later in life, during the development of germ cells in the embryo and in adult mice.

**Keywords**
polycomb group proteins (PcG), epigenetic inheritance, embryogenesis

# Milestones

3
papers

17
papers

## 2007

**November**
The Federal Council commissions the Swiss National Science Foundation to conduct NRP 63.

## 2008

## 2009

**February**
Call for proposals begins.

## 2010

**February**
Research work begins. The Steering Committee approves 11 projects out of 58 proposals submitted. One project from the ERA-NET scheme is added (Ralph Müller's project).

**May**
Kick-off meeting in Berne

## 2011

**May**
First meeting of all NRP 63 researchers held in Nottwil. The research teams present information on their projects.

# 113

**Papers total** (as of August 2015)
More papers will follow.

**Open Access**
The NRP 63 project leaders advocate the making of all papers published under the NRP 63 available to other research groups worldwide.

More than 90 % of all NRP 63 publications are deposited in open access repositories of Swiss universities.

**31** papers

**20** papers

**22** papers

**20** papers

## 2012

### May
Second meeting of all research groups held in Berne. The research teams report on initial progress.

## 2013

### July
The Stem Cell School Tool goes online. The tool gives pupils at the baccalaureate level an up-to-date look at stem cell research and regenerative medicine.

### September
Third meeting of all NRP 63 research groups held in Berne. The doctoral students and postdocs present their findings in the form of posters.

## 2014

### September
The exhibition "Stem Cells – The Origin of Life" opens at the Musée de la main, Unil-CHUV in Lausanne.

## 2015

### March
The Stem Cells exhibition moves to the Zoological Museum of the University of Zurich.

### March
The research projects are completed and the groups prepare their final project reports.

### June
The Stem Cells exhibition moves to the Lucerne Natur-Museum.

## 2016

### Spring
The NRP 63 final brochure is presented: Under NRP 63, 113 papers were published (as of August 2015), and 24 postdocs and 12 doctoral students were trained. Several of the research teams are already in contact with biotech or pharmacological companies.

# National Research Programme NRP 63

The Federal Council commissioned the Swiss National Science Foundation (SNSF) to carry out the National Research Programme "Stem cells and regenerative medicine" (NRP 63) in order to boost Swiss research in this cutting-edge technology. Between 2010 and 2015 twelve groups from Basel, Berne, Geneva, Lausanne and Zurich worked on this research area, with a budget of 10 million Swiss francs.


**Publisher**

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Swiss National Science Foundation

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