
Stem Cells and Regenerative Medicine

Implementation Plan of the National Research Programme NRP 63

Berne, 9 February 2009

Contents

1.	Summary	4
2.	Introduction	5
2.1	Background	5
2.2	National and international context	6
3.	Goals of the research programme	7
4.	Main research topics	7
4.1	Stem cells and organ development	7
4.2	Defining stemness, cell plasticity and stem cell niches	8
4.3	Role of stem cells in repair and regeneration	8
4.4	Comparison and functional analysis of normal and abnormal stem cells	8
4.5	Legal and ethical research on stem cells and regenerative medicine	9
5.	Career Development	9
5.1	Fellowships for prospective researchers	9
5.2	Fellowships for advanced researchers	10
6.	Practical significance and target audience	10
7.	Submission procedure	11
7.1	Basic procedures	11
7.2	Pre-proposals	11
7.3	Full proposals	12
7.4	Selection criteria	13
7.5	Research authorisation	13
7.6	Schedule and budget	14
8.	Organisation and Management	15

What are National Research Programmes (NRP)?

The research carried out by National Research Programmes consists of targeted research that contributes to the solution of contemporary problems of national importance. Under the provisions of Article 6, paragraph 2, of the Law on Research of 7 October 1983 (as of 25. February 2008) the Federal Council selects the topics and foci to be researched in NRPs and mandates full responsibility for implementing the Programmes to the Swiss National Science Foundation (SNSF, Division IV).

Article 4 of the Federal Ordinance on the Law on Research of 10 June 1985 (as of 1 April 2008) describes the purposes and contents of NRPs as follows:

«¹ National Research Programmes are a means to direct and support coordinated research projects that have a common goal. Where needed, National Research Programmes should strengthen scientific research capacities.

² Topics of research are appropriate for National Research Programmes if, in general,

- a. scientific research on the problem is of national importance;*
- b. Swiss research can make a significant contribution to the resolution of the problem;*
- c. solutions require research contributions from multiple disciplines;*
- d. the research goals cannot be met exclusively through basic research, through research within a specific section of the administration, or through industrial applications research;*
- e. research on the problem can be expected to produce research results that have practical applications within a five-year time period.*

³ The following criteria should be taken into consideration in setting forth the topics of National Research Programmes:

- a. the programmes can provide the scientific basis for decision-making by government and the administration;*
- b. the programmes can be conducted with international collaboration and are also of great interest to Switzerland.»*

1. Summary

Stem cell biology is an area of research with a high potential impact on the therapy of diseases that are still incurable, such as Parkinson's disease or type 1 diabetes.

The National Research programme «Stem Cells and Regenerative Medicine» (NRP 63) aims to boost research in the field of stem cell biology. One goal of the proposed programme is the support of original research. The research projects will focus on basic themes such as stem cell and organ development; the definition of “stemness”, cell plasticity and stem cell niches; the comparison and functional analysis of normal and abnormal stem cells and the role of stem cells in repair and regeneration. Since the ultimate intent of this research is to provide applications in regenerative medicine, each grant proposal should describe the perspectives for therapeutic use. Furthermore, legal and ethical aspects of stem cell research and regenerative medicine will be investigated with a focus on future opportunities and impacts.

Another major goal of this NRP is to recruit promising young scientists to this field. Two types of post-doctoral fellowships will be supported within this programme: young researchers, with little or no experience in stem cell biology are invited to submit proposals for a two year stay abroad with follow-up funding for a year in Switzerland; senior post-doctoral scientists with experience in stem cell biology are invited to submit proposals for a junior investigator position at a Swiss research institution.

NRP 63 is financed with CHF 10 million for a duration of five years research.

2. Introduction

2.1 Background

Stem cells are pluripotent or multipotent cells possessing the ability to develop into specialized cells that ensure proper organ function. Because of their promise in regenerative medicine, over the past few years stem cells and so-called progenitor cells have been studied extensively as potential tools for the repair or replacement of defective organs in disease. Examples of these attempts include treatment of specific diseases of the nervous system, haematopoietic disorders, diabetes, skin replacement, ophthalmologic diseases, and treatment of cardiovascular diseases. The spectrum of scientific studies involving stem cells in basic, translational and clinical research is very large. In some fields it has already brought success, while practical perspectives for treatment of disease are still lacking in others.

The enormous pressure on the academic community to open new therapeutic frontiers as quickly as possible has also led to the underestimation of risks, to clinical trials that are partially disputed with respect to their basic scientific background and interpretation, and in rare instances, to misconduct. Even in cases where stem cell therapies are successful, the applications are largely empirical and the molecular mechanisms are not always understood. As a consequence, emphasis still needs to be put on gathering basic knowledge about the nature of stemness of any cell type, cell differentiation, organ and tissue development and stem cell/host tissue interactions, before major breakthroughs in therapeutic concepts are possible.

Research on human embryonic stem cells (hESC) represents a special case, being – for ethical reasons – regulated by strict laws that vary from country to country. In countries like the UK and Sweden a liberal policy prevails, whereas the policy in Germany is considerably more restrictive. The legal position taken by Switzerland can be considered mid-way within Europe. The new law on research with hESC in Switzerland, which came into force in 2005, regulates the conditions under which stem cells can be isolated from human embryos and also defines the criteria allowing human embryonic stem cells to be imported from abroad. In terms of peer-reviewed publications, the country currently dominating research with hESC is the USA, followed by Israel and the UK. Israel and Switzerland have similar sized populations; thus a small country has the potential to make a major impact on this field of research.

At the international level, organisations with the specific task of carrying out stem cell research have been founded in several countries. This reflects the large, albeit partially disputed, expectations for this type of research in our society. In many countries with reputations as leaders in biomedical research, stem cell research is carried out in a highly competitive environment, and partially supported by the medical and pharmaceutical industry.

At present, Swiss stem cell research as a whole is weakly visible in an international context. However, the high calibre research in cell and development biology in Switzerland should be a sound basis for performing internationally recognised research in stem cell biology. The aim of this research programme is therefore to foster basic research and to recruit promising young scientists to this field.

On November 28, 2007, the Federal Council approved the launch of the National Research Programme 63 (NRP 63) “Stem Cells and Regenerative Medicine” and entrusted the Swiss National Science Foundation (SNSF) with its implementation.

A total sum of CHF 10 million was allocated to NRP 63 for its five year research duration. The National Research Council then selected a Steering Committee and assigned it the task of writing this Implementation Plan based on the Programme Outline and Feasibility Study. The Implementation Plan was approved by the Federal Department of Home Affairs, on the 9.2.2009.

2.2 National and international context

There are no obvious clues why Swiss science, which has an excellent reputation in the fields of cell and development biology, has been less competitive in the field of stem cell research. One reason might be that the legal situation with regard to hESC was unclear, until the new legislation for human embryonic stem cells came into force in 2005. Scientists may have been discouraged from embarking on this type of research, but this is unlikely to be the only factor.

In the field of regenerative medicine the National Research Programme 46 «Implants and Transplants» supported 40 projects with a budget of 15 Mio CHF. These included 16 projects on stem cells and 7 projects on tissue repair. Most of these projects were carried out in the period from 2000 to 2005. Systems biology, with many links to developmental biology, is strongly supported by the Swiss government (Swiss Initiative in Systems Biology – SystemsX.ch) with a budget of CHF 100 Million for the period 2008–2011.

At an international level, the fields of stem cell biology and regenerative medicine are developing rapidly. Various industrialised nations have recognised their significance, and are actively promoting research within special programmes or institutes, such as EuroStemCell, an integrated project funded with € 11.9 Million under the EU's Sixth Framework Programme (2004–2008), or the California Institute for Regenerative Medicine established in 2005 by the state of California with a budget of US\$ 3 Billion for 10 years.

The frame of reference for NRP 63 is therefore mainly international. A current list of the main initiatives and research programmes with links to web sites is available at the NRP 63 web site (www.nrp63.ch).

3. Goals of the research programme

The three aims of this programme are: first, to support basic research on stem cells and regenerative medicine, second, to encourage scientists with an excellent track record in developmental and cell biology to engage in this field, and third, to recruit and train young scientists in this field. It should be realised that the ultimate goal of this research is to provide applications in regenerative medicine. Each grant proposal should therefore explain the long-term perspectives and the potential for therapeutic use. For research on legal and ethical questions in stem cell biology, current concepts and existing laws should be scrutinised and future developments should be anticipated and discussed.

In general, the programme should enhance the international visibility of Swiss research in stem cell and regenerative medicine.

4. Main research topics

The stem cells now being used, or being considered for use, in treating human disease must be pluripotent or multipotent, such that they can develop into different tissues. For this reason, the research foci listed below are organised according to basic concepts, with a main emphasis on understanding the mechanisms involved, rather than concentrating on the phenomenology of development and repair of specific organs. Importantly however, projects supported by the programme, although focusing on basic mechanisms, need to be embedded into a perspective of future application for prevention or therapy of diseases.

For research proposals requiring hESC, applicants must prove that suitable cell lines are available for the project. The derivation of human embryonic stem cell lines will not be covered by this programme. The reasons are that (1) the rate of derivation is too low, (2) the supply of surplus embryos in CH is unpredictable, and (3) there are several hundred hESC lines worldwide that fulfil Swiss legal criteria. Therefore, it should be possible for appropriate stem cell lines to be imported if necessary. At present, the Federal Office of Health has twenty-seven hESC lines licensed for use in Switzerland.

4.1 Stem cells and organ development

Stem cells are found in all multi-cellular organisms. Some principles and mechanisms of organ development can be considered to be universal, while others will pertain to specific organisms and tissues. The emphasis of this module will be on the role of stem cells in developmental biology, focusing on the following topics:

- Mechanisms responsible for differentiation of embryonic stem cells.
- Mechanisms, signalling pathways and molecules responsible for regulating cell fate during development
- Analyses of the transcriptome and proteome of stem cells and correlation with changes of phenotype during development

- Common fate denominators in different organs at different stages of development

4.2 Defining stemness, cell plasticity and stem cell niches

A somatic or adult stem cell has the ability to undergo asymmetric division, resulting in self-renewal of the stem cell itself and generation of a second cell type that is committed to a differentiation pathway. The immediate environment of the stem cell (stem cell niche) contributes both to the maintenance of the stem cell and the cell types that develop. This module places emphasis on:

- Characterization of progenitors of adult stem cells
- Mechanisms and signalling pathways determining maintenance of stemness in adult stem cells
- Mechanism and signalling pathways inducing proliferation and differentiation of adult stem cells
- Mechanisms responsible for plasticity and reprogramming of adult stem cells

4.3 Role of stem cells in repair and regeneration

In many respects, the major goal of stem cell research is to facilitate replacement or repair of damaged or defective tissue. Tissue dysfunction may result from external or internal factors (or a combination thereof) leading to direct tissue damage or to maladaptive remodelling in disease. In some instances, genetic mutations or polymorphisms may underlie or contribute to these processes. This research module concentrates on the following topics:

- Molecular basis of the interactions between stem cells and host tissue (cell-cell interactions, paracrine signalling, cell-to-cell diffusion of regulatory molecules). Factors influencing the survival of donor cells after engraftment
- Genetic engineering to manipulate stem cell differentiation and function, to improve engraftment and/or to modulate target organ function
- Methods and mechanisms of application and integration of stem cells into host tissue

4.4 Comparison and functional analysis of normal and abnormal stem cells

The properties of stem cells that make them so promising for regenerative medicine (longevity, ability to proliferate and differentiate) can also be potentially hazardous, if they give rise to pathogenic cell types. Importantly, an outcome that needs to be prevented is the acquisition of a tumorigenic phenotype that may lead to neoplastic disease in the recipient. Topics covered in this module include:

- Extrinsic factors, including genetic manipulation, as a cause of pathologic differentiation and tumorigenicity of stem cells
- Intrinsic factors and processes leading to tumorigenic stem cell development within the host environment
- Identification of prognostic markers for tumorigenicity

4.5 Legal and ethical research on stem cells and regenerative medicine

The rapid pace of stem cell research means that current concepts and existing laws need to be reviewed periodically and possibly modified. In addition, the impact of scientific advances should be anticipated and legal and ethical implications discussed with a focus on future opportunities and consequences.

5. Career Development

A central goal of the NRP should be to attract young scientists. The first objective is to train young scientists with little or no experience in stem cell research and regenerative medicine. Within this programme, they should spend at least two years at a leading institution abroad. The funding includes a third year, to continue their project at a host institution in Switzerland. The second objective is to recruit young, promising scientists with an excellent track record in stem cell biology. The intent is to allow them to achieve independence within a Swiss research institution.

These two approaches should have a sustained effect on the programme development far beyond the five-year period envisioned for an NRP: first, it expands the methodological repertoire currently available in Swiss laboratories in this field; secondly, it establishes personal relationships between young investigators and foreign scientists that may be mutually beneficial for many years to come; thirdly, it promotes international networking in this highly competitive field.

5.1 Fellowships for prospective researchers

Fellowships for prospective researchers offer young scientists who are at the point of starting their research career, the possibility of training at a research institution abroad. Research topics should fit into the categories defined in sections 4.1–4.4. These fellowships should not bypass or compete with existing postdoctoral fellowship programmes of the SNSF. They should be strictly project related and include a minimum 2 year stay abroad, with follow-up funding for a year at a Swiss research institution. Where justified, the follow-up year can be postponed, but must take place within the 5 year research period of NRP 63.

Funding includes personal maintenance, a fixed sum for travel expenses and may include a contribution towards research and conference expenses. The size of the fellowship is based on family status, family obligations and cost of living in the host country. Written proof of support by the research institution abroad can accompany the pre-proposal, but is only compulsory for the full proposal. Applicants should name the Swiss research institution to which they intend to return. Access to infrastructure at this institution does not need to be guaranteed at this stage, however, it must be provided before the 3rd year of funding is made available.

The requirements for the fellowships are as follows: the prospective researchers must start the fellowship at latest 3 years after obtaining their doctorate. Applicants

should either have Swiss nationality or hold a degree from a Swiss University or have carried out research in Switzerland for at least two years at the point at which the full proposal is submitted.

5.2 Fellowships for advanced researchers

Fellowships for advanced researchers will create new opportunities for promising young scientists to make the transition to independent junior group leaders. Post-doctoral scientists with experience in stem cell research or regenerative medicine, who are able to carry out work of high scientific quality, will be encouraged to submit research projects to NRP 63. Research topics should fit into the categories defined in sections 4.1–4.4. The proposed research projects must be limited to a maximum of 36 months. During the course of the programme and based on the interim reports, the Steering Committee will decide whether individual projects should be extended for a maximum of 24 months. This programme does not overlap with the existing SNSF programme SNSF professorship, because it is designed for more junior candidates with the aim of specifically promoting the research covered by the NRP 63. The SNSF professorship is more selective and not linked to a particular theme.

In their research proposals, the applicants can apply for their own salary, consumables, and where justified, for a technician and / or a PhD student. The applicant needs to document that she / he will be hosted by an institution for the duration of the project and that the availability of the necessary scientific infrastructure is guaranteed. Written proof of support by the host institution can accompany the pre-proposal, but is only compulsory for the full proposal. The conditions favouring long-term integration of the applicant in the home institution need to be described. The salary of the applicant is based on the standard salaries for corresponding positions at the home institution.

The requirements for the fellowships are as follows: The advanced researchers must start the fellowship at the latest 5 years after obtaining their doctorate. The research must be executed in Switzerland. Applicants should either have Swiss nationality or hold a degree from a Swiss University or have carried out research in Switzerland for at least two years at the point at which the full proposal is submitted.

6. Practical significance and target audience

Switzerland needs to establish itself internationally in the field of stem cell research. Therefore, the programme is primarily addressed to recruiting high calibre scientists at universities, university hospitals and other academic institutions. Great importance is attached to giving young scientists the opportunity to be trained in the top laboratories abroad and to return to Switzerland with their newly acquired expertise. The results from basic research will provide the badly needed foundations for Swiss translational research, which is likely to involve biotechnology companies and the pharmaceutical industry, before new therapies can finally be used in the clinics. At the Federal level, the development of novel stem cell therapies may also require the drafting of new guidelines or changes in the law.

7. Submission procedure

7.1 Basic procedures

The Implementation Plan as well as forms, rules of procedure and instructions for the submission on the portal *mySNF* can be found on the following website: www.snf.ch.

There is a two-stage submission procedure for NRP 63: Pre-proposals are submitted first, followed by invited full proposals. This procedure allows projects to be better coordinated and priorities to be established. Both the pre- and the full proposals must be written in English for evaluation by external referees.

Pre- and full proposals have to be submitted online on the portal *mySNF*. For the use of *mySNF* prior user-registration on the homepage of <https://www.mysnf.ch> is required. For a submission on schedule, a user account has to be applied for two weeks before the submission date at the latest. The submission of the documents by postal delivery is only accepted in exceptional cases after consultation with the Swiss National Science Foundation.

The proposed research projects must follow SNSF guidelines, conform to Swiss law and be limited to a maximum of 36 months. During the course of the programme, and based on the interim reports, the Steering Committee will decide whether individual projects should be extended for a maximum of 24 months. An exception to this rule is the fellowship for prospective researchers, which is limited to a maximum of 36 months funding by the SNSF.

Collaboration with research groups in other countries is highly appreciated, if the planned cooperation brings significant added value or substantially enriches Swiss research in respect to content or methodology. For this purpose, the German Research Foundation (DFG), the Austrian Science Fund (FWF) and the SNSF made an agreement offering two options for research partners from Germany or Austria: on the one hand, the “Money follows cooperation line” and, on the other, the “Lead Agency Process”. The choice of the suitable funding procedure for the foreign partner in a specific research project should be discussed in detail between the SNSF office and the researchers involved shortly after the invitation to submit a full proposal.

SNSF funds awarded are exempted from VAT (art. 33, par. 6). The SNSF does not issue contracts within the scope of its National Research Programmes, but instead awards grants for the promotion of scientific research in Switzerland.

7.2 Pre-proposals

Applicants will first submit a pre-proposal. The deadline for submission is 20 April 2009. The pre-proposal should give the following information:

To be submitted directly via *mySNF*:

- Basic data and abstract of the project

- National and international collaborations
- Estimation of financial support required for salaries and running costs (budget).

To be submitted additionally as a PDF file:

Research plan including

- Topic of the project and main goals
- Theoretical basis, concepts and research question(s)
- Approaches and methods to be used
- Time frame and milestones
- Possible applications of the results
- References

The project description must be submitted using the template document provided in the *mySNF* portal. The project description must be in English and the final PDF file should not exceed five pages in length.

Short curriculum vitae with five of the own, most important publications (max. 2 pages per applicant).

Pre-proposals will be subject to scientific peer review. Based on the reviewers' reports and its own evaluation, the steering committee will decide which pre-proposals should be developed into full proposals (see the criteria listed below).

For joint projects, an application package containing individual pre-proposals may be submitted. However, it is important that the individual pre-proposals in the application package are written in such a way that they can be reviewed and judged individually.

7.3 Full proposals

In the second stage of the submission procedure the Steering Committee will invite the authors of the selected pre-proposals to submit detailed full proposals online on the portal *mySNF* corresponding to standard SNSF rules and guidelines. Pre-proposals that do not progress to this stage will be rejected by the Steering Committee. All full proposals will be subject to peer review by a panel of international experts.

Applicants for the career development awards have to submit written proof of support from the host institution (either in Switzerland or abroad) with the full proposal. All applicants for fellowships, who submit a full proposal, will be invited to the panel meeting to present their projects. All other applicants should provide a telephone number, where they can easily be contacted by the panel on the day of the evaluation meeting.

Following the panel meeting, the steering committee will convene to select the projects to be recommended for approval or rejection by the Research Council of the SNSF (Division IV; Presidial Board).

7.4 Selection criteria

Pre- and full proposals will be reviewed on the basis of the following criteria:

- **Scientific quality and originality:** proposals should fulfil international criteria with respect to scientific quality, originality and methodology.
- **Feasibility and compliance with the objectives of the NRP 63:** proposals should reflect the programme's scientific objectives and comply with its overall framework.
- **Application and implementation:** proposals should describe the perspectives for therapeutic use.
- **Personnel and infrastructure:** Projects have to be carried out in a setting that provides adequate infrastructure and personnel.

The evaluation of the pre- and full proposals for the career development awards will be based on the same criteria as stated above; all proposals within a category of fellowship will be compared to others of the same type.

The Secretariat of Division IV checks for fulfilment of formal criteria before the proposal is passed on for content review (see SNSF grant regulations). Applications that do not satisfy formal criteria will not be processed further.

7.5 Research authorisation

Please note that research projects using human embryonic stem cells require authorisation. The necessary procedures are described on the web-page of the Federal Office of Public Health (FOPH):

<http://www.bag.admin.ch/themen/medizin/03301/03311/index.html?lang=en>

7.6 Schedule and budget

The following schedule has been set for NRP 63:

Call for pre-proposals	16 February 2009
Submission of pre-proposals	20 April 2009
Invitation to submit full proposals	July 2009
Submission of full proposals	September 2009
Final decision on full proposals	November 2009
Start of research	January 2010

The total funding for this NRP is CHF 10 Million. The provisional allocation of this funding to different types of activities is as follows and depends on the quality of the submitted projects.

4.1 Stem cells and organ development	CHF 1.5 mill.
4.2 Defining stemness, cell plasticity and stem cell niches	CHF 1.5 mill.
4.3 Role of stem cells in repair and regeneration	CHF 1.5 mill.
4.4 Comparison and functional analysis of normal and abnormal stem cells	CHF 1.5 mill.
4.5 Legal and ethical research on stem cells and regenerative medicine	CHF 0.3 mill.
Career development	CHF 2.1 mill.
Implementation and administration	CHF 1.6 mill.

8. Organisation and Management

Steering Committee

Prof. Bernard Thorens, Professor of Physiology, Center for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne, CH (President)

Prof. Olivier Guillod, Professor of Health Law, Director of the Health Law Institute, Faculty of Law, University of Neuchâtel, CH

Prof. Sheila MacNeil, Professor of Tissue Engineering, Head of the Biomaterials and Tissue Engineering Group, The Kroto Research Institute, University of Sheffield, UK

Prof. Elizabeth J. Robertson, Professor of Developmental Biology and Principal Research Fellow at the Wellcome Trust, Sir William Dunn School of Pathology, University of Oxford, UK

Prof. Michael R. Rosen, Pfeiffer Professor of Pharmacology and Pediatrics, Director of the Center for Molecular Therapeutics, Department of Pharmacology, Columbia University, New York, US

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

Delegate of Division IV of the National Research Council

Prof. Isabel Roditi, Institute of Cell Biology, University of Berne, CH

Programme Coordinator

Dr. Marjory Hunt, Swiss National Science Foundation (SNSF), Berne, CH

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Adrian Heuss, advocacy ag, Basel, CH

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