The Research Council of Norway

Work Programme 2013-2017

The Stem Cell Research Programme - STAMCELLER

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1. Summary

Research on stem cells has been a priority area at the Research Council of Norway since 2002. The primary objective of the Stem Cell Research Programme (STAMCELLER) 2013–2017 is to develop and enhance expertise within basic and clinical research on stem cells with the aim of finding treatments for seriously and chronically ill patients.

Investment in stem cell research in most industrialised countries has increased steadily in recent years. The award of the 2012 Nobel Prize in Physiology or Medicine for groundbreaking discoveries in the field of stem cell research illustrates what a timely and important field it is. The knowledge generated from stem cell research offers tremendous potential for expanding our understanding of, and improving treatments for, disease and injuries. The use of stem cells for clinical applications opens up a myriad of opportunities, as well as many challenges.

The STAMCELLER programme will employ research and innovation activities with the long term aim of providing patients in Norway with a future range of stem cell-based treatments equivalent to those found abroad. Norway will seek to contribute to research in this area in a manner that protects the integrity of the individual, safeguards the value of human life and maintains a high ethical standard. Priority will be given to increasing translational research by encouraging cooperation between scientists engaged in basic research and clinicians.

The STAMCELLER programme has four thematic priority areas: research to gain a deeper understanding of basic processes related to the growth and differentiation of stem cells; characterisation and validation of stem cells for use in clinical settings; development and implementation of procedures and protocols to repair damaged tissue or organs; and use and further development of induced pluripotent stem cells (iPS cells). In addition, the programme will work to boost international research cooperation within relevant priority areas under the programme, and will attach special importance to promoting international researcher exchange.

2. Background

2.1 Strategic perspectives

Stem cell research has become a priority field worldwide. The knowledge generated from stem cell research offers tremendous potential for expanding our understanding of, and improving treatments for, disease and injuries. Research on stem cells has been a priority area at the Research Council of Norway since 2002. The objective is to develop and enhance expertise within basic and clinical research on stem cells with the aim of finding treatments for seriously and chronically ill patients. Stem cell research activities at the Research Council were first organised under a *strategic initiative on stem cell research* (2002–2007), with a budget of approximately NOK 50 million for the entire period. The funding announcements issued under the initiative were open to all types of applicants, but those funded were required to participate in the national stem cell research network.

An amendment to the Biotechnology Act has permitted research on supernumerary fertilised eggs, including research on embryonic stem cells, as from 1 January 2008. The Government was seeking to increase investment in the stem cell research effort, on somatic and embryonic stem cells alike. The Stem Cell Research Programme (STAMCELLER) was launched in

2008, with a five-year programme period. Activities under the programme have encompassed calls for proposals with project funding awarded in an open competitive arena, the establishment of a national centre for stem cell research and annual networking meetings. On the basis of Recommendation No. 62 (2006–2007) to the Odelsting and Proposition No. 1 (2007–2008) to the Storting, the Ministry of Health and Care Services charged the Research Council with the task of establishing a national centre for stem cell research under the auspices of the South-Eastern Norway Regional Health Authority. The centre was to be located at Rikshospitalet University Hospital (now part of Oslo University Hospital) and to incorporate the existing national network for stem cell research. *The Norwegian Center for Stem Cell Research* was officially opened in 2009, and has received an annual grant of NOK 5.6 million under the STAMCELLER programme. The programme had a total budget of just over NOK 115 million for the 2008–2012 period, and is being extended for a new five-year period from 2013.

Stem cell research encompasses a wide range of research questions and potential application areas, and advances on the research front vary from research area to research area. In this context the STAMCELLER programme has a strength in its targeted thematic focus combined with flexibility to fund basic research and clinical research alike. This makes it possible to adapt research activities to developments and fluctuations in the field, while still maintaining the ultimate aim of helping patients. Cooperation, between basic research groups and between scientists engaged in basic research and clinicians, is essential. Promoting more translational research is vital to ensuring that knowledge generated by the basic research community is implemented by the clinical research community, and vice-versa. As a small country, it is difficult for Norway to cover all aspects of stem cell research on its own. Thus, a national initiative in this area must build on areas where Norway has well-entrenched research and clinical environments. Wide-ranging international cooperation will also be of major importance.

Better health and health services is one of the Government's five strategic goals set out in the white papers on research, Report No. 30 (2008–2009) to the Storting: *Climate for Research* and Report No.18 (2012-2013) to the Storting: Long-term perspectives – knowledge provides opportunity. In addition to the five strategic goals, four overarching goals are articulated for research policy: a well-functioning research system; high-quality research; internationalisation of research; and efficient use of results and funding. The Government gives priority to the integration of women's and gender perspectives into research activities. The STAMCELLER programme will therefore promote awareness of gender differences in health where this is appropriate.

The Strategy for the Research Council of Norway, *In the Vanguard of Research*, sets out the objectives of enhancing the quality and capacity of Norwegian research; strengthening research in areas of particular importance for research, trade and industry; promoting constructive cooperation, distribution of responsibility and structures in the research system; and helping to translate research results into action. *The Research Council of Norway's Policy for Medical and Health Science Research 2007–2012* names stem cell research and translational research as priority areas.

The Government has drawn up a *National Strategy for Biotechnology* for the 2011–2020 period. Health, health services and health-related industries comprise one of four thematic focus areas in which biotechnology can play a role in addressing social challenges and where

Norway has national competitive advantages. The STAMCELLER programme will be an integral component of the efforts in this focus area.

2.2 Scientific perspectives

Stem cells – a background

Stem cells are immature cells with unique characteristics, and they play essential roles in our bodies. They have the capacity to self-renew, i.e. to make more stem cells, but alsoto mature (differentiate) into specialised cell types, such as neurons, muscle cells and insulin-producing cells. Stem cells are found not only in the embryo and foetus, but also in the body's adult tissues and organs. Research is increasing our knowledge about the function of stem cells, and we are beginning to understand the mechanisms that drive a stem cell from an undifferentiated state to mature into a specialised cell. This knowledge is an important key to successfully engineering in the laboratory the different cell types needed for cell therapy. The aim of regenerative medicine is to treat diseases involving damaged, lost or diseased cells and tissue with the help of stem cell transplantation. For example, all blood cells originate from stem cells in the bone marrow (the haematopoietic system), and we now understand in considerable detail how a stem cell differentiates into a white blood cell rather than a red blood cell. Based on this knowledge, scientists can reconstitute a complete haematopoietic system by transplanting only a small number of haematopoietic stem cells from bone marrow. This has important implications for bone marrow transplantation, and new research will lead to further improvements of this type of treatment. Understanding the molecular factors that steer a stem cell towards a specialised function also has major clinical potential, e.g. where treatment may be based on activating the body's own stem cells. One example of this is the discovery of the hormone erythropoietin, which increases red blood cell production, and is now being used to expand the population of red blood cells from a patient's own stem cells to treat anaemia and other illnesses. More knowledge about the machinery that makes a cell select a certain lineage pathway, and about the mechanisms that transfer signals from a cell's surroundings to genetic regulatory signals inside the cell, is essential to be able to control the differentiation of stem cells into desired cell types. This represents an intensive field of research worldwide.

Facts about stem cells
Stem cells: Cells that can form new copies of themselves as well as give rise to other types of cells.
The body's stem cells have a varying capacity to give rise to mature cell types. They may be:
Pluripotent - have the developmental potential to give rise to all cell types in the body;
Multipotent - can give rise to all cell types in the tissue/organ in which they are found;
Unipotent - can give rise to only a certain type of mature cell.

Somatic stem cells
Somatic stem cells, as opposed to embryonic stem cells (see below), are found in various organs throughout a human's life. It is becoming increasingly clear that most organs contain somatic stem cells and progenitor cells, and such stem cells have already been put into clinical use in certain cases. Transplantation of haematopoietic stem cells is an established form of treatment for certain diseases of the blood, and technological improvements are enabling more and more patients to receive the correct type of transplant. Likewise, the lives of patients with severe burns are being saved through skin transplants, in which new skin is grown in the laboratory from stem cells harvested from the patient's own skin. Stem cell therapy has also

been developed for replacing damaged corneas. There is now widespread interest in stem cells in the brain and spinal cord, as well as the pancreas, with the long-term aim of developing treatments for Parkinson's disease and diabetes. Recent research has resulted in breakthroughs in the use of stem cells for growing tendons and various endodermal derivatives, such as the intestine. These new lines of research have not yet become clinical realities, and more research is needed to steer the differentiation of stem cells into the various cell types found in the brain and pancreas. It is also essential to ensure that the transplanted cells will respond normally to the body's control signals and will not develop into malignant tumours, for instance.

Embryonic stem cells

Some of the most exciting discoveries in the field of stem cell research in recent years are the result of research on embryonic stem cells (ES cells). ES cells are immature cells that resemble the cells of a four-to-five-day-old embryo. ES cells can be cultured indefinitely in the laboratory and are pluripotent, i.e. they have the capacity to differentiate into any cell type of the body. These characteristics have triggered considerable interest in ES cells as a potential source for stem cell transplantation in regenerative medicine. The cells' broad-spectrum differentiation potential was first demonstrated in experiments with mice, and constitutes the basis for gene targeting technology (gene knockout). Human ES cells are grown from supernumerary fertilised eggs (eggs fertilised in vitro) and were first cultivated by Sir Martin Evans in 1998. Sir Evans was awarded the Nobel Prize for Physiology or Medicine in 2007 for his discovery, together with Mario Capecchi and Oliver Smithies for developing gene targeting technology. Intensive research activity in recent years has led to the development of robust protocols for controlling stem cell differentiation into specific cell types. These include dopamine-producing neurons, pancreatic beta cells and motoric neurons, which may be used in future treatment of Parkinson's disease, diabetes and amyotrophic lateral sclerosis (ALS), respectively. Recent successes in the field include ES cell transplants to treat glaucoma and primate models for transplantation of ES cell-derived dopaminergic neurons.

There are, however, important questions that must be answered before ES cells may be used for patient treatment on a large scale. These questions touch not only on ethical concerns relating to the cells' origin in human embryos, but also on the risk of tumour development following transplantation. There are also issues around immunological rejection reactions after cell transplantation when patient-matched ES cell lines are unavailable. One means of solving this problem would be to generate a larger panel of high-quality ES cell lines that cover a wider scope of human leukocyte antigen (HLA) compatibility. In this manner, pre-testing of cells could be implemented to select the cells that are best adapted to the individual patient, as is already the case for bone marrow and organ transplants. This has not been pursued systematically for ES cell-based transplantation.

iPS cells

Another tremendous stride was made in 2006 when Shinya Yamanaka and his colleagues showed that differentiated cells could be reversed or reprogrammed back to a pluripotent state that closely resembles that of embryonic stem cells. This state is called an induced pluripotent state (iPS). Since then iPS cells have been generated from various types of cells derived both from embryos and from adults, with the use of relatively simple genetic technology. We are beginning to understand the principles of how a developmental programme can be run in reverse in order to generate a very broad differentiation potential. iPS technology is developing rapidly, and there is hope that iPS cells can be implemented in future cell therapy,

as the cells are derived from the patient's own cells which will avoid problems with immunological rejection. As an alternative to using ES-cells, stored cells for example from umbilical cord blood, may be used as the basis for iPS-based reprogramming and provide a bank of patient-specific (autologous) cells for transplantation. However, a number of technical and safety-related issues must be solved before the use of iPS cells in patient treatment can become a reality. It is particularly important to give consideration to the potential risk of developing tumors in the wake of transplantation; this is true for both ES and iPS cell transplantation. There are also indications that there may be more mutations in iPS cells than in ES cells, and that iPS cells retain some degree of epigenetic memory of the cell type from which they were derived. A potential disadvantage with the use of iPS cells in regenerative medicine is that the cells may already contain the mutations that originally caused the disease. Thus more research is needed in this field.

In addition to their potential for application in cell therapy, iPS cells are also a very valuable research tool for understanding disease processes. Because iPS cells can be generated from patients suffering from complex diseases, the cells can be used to examine the mechanisms behind these diseases. Disease-specific iPS cells have now been generated for a range of disorders, such as the heart condition long QT syndrome (LQTS), ALS, Progeria (also known as Hutchinson-Gilford Progeria Syndrome), Parkinson's disease and Alzheimer's disease. These cells have been shown to reflect relevant aspects of their respective diseases.

Alternative strategies

Alternative strategies for generating cells for use in cell therapy are to partially dedifferentiate the original somatic cell type, or to directly steer a somatic cell into another type of somatic cell, a process called transdifferentiation. Transdifferentiation has proven possible for cardiac muscle cells, in haematopoietic systems, in the pancreas and through the development of neurons from fibroblasts. This type of transdifferentiation is opening up entirely new vistas in regenerative medicine.

Facts about stem cells

Blastocyst: Early embryonic stage between fertilised egg and foetus.
Embryonic stem cells (ES cells): Prepared from the pluripotent stem cells in the blastocyst and cultured in vitro under defined conditions that preserve its immature state.
Induced pluripotent stem cells (iPS cells): Generated in the laboratory by inducing dedifferentiation of somatic cells (e.g. fibroblasts or skin cells) to a state that highly resembles that of ES cells.
Progenitor cells: Partially mature cells with limited differentiation potential that can gradually differentiate along defined lineage pathways towards a specific type or types of cells.
Somatic cells: Mature, often specialised cells in the body's various organs which perform a range of functions; e.g. neurons, cardiac muscle cells and intestinal epithelial cells.
Reprogramming: A process in which a mature cell is returned to an immature state (dedifferentiated), before being differentiated into another type of mature cell.
Transdifferentiation: A mature cell is directly steered into another type of mature cell.
Autologous: Tissue and cells derived from an individual's body which can be cultured/modified/stored and used in treatments/transplants in the same individual, without causing immunological rejection reactions.

The future of the field of stem cell research

Investment in stem cell research in most industrialised countries has increased steadily in recent years. This is rooted in the conviction that stem cell research holds great promise for developing new forms of cell-based treatments in the field of regenerative medicine. The use of stem cells for clinical applications opens up a myriad of opportunities, as well as many challenges. There is the potential, for example, to produce patient-specific pluripotent cells by reprogramming the body's cells using stem cell-specific factors and to further develop these protocols to make it possible to reprogram the cells without genomic insertions. However, there are still many challenges that must be solved before we can induce the differentiation of pluripotent cells into all cell types. Not enough is known about the molecular mechanisms and external factors that are necessary for steering differentiation into many common cell types. More knowledge in this area will pave the way for the (further) development of methods using somatic cells or cells from umbilical cord blood and applying external factors for direct transdifferentiation into another type of mature cell. Such methods will in all likelihood have reduced risk of tumor development, because the cells are not forced into an undifferentiated pluripotent state.

The potential of stem cell research is tremendous, and the long term aim of research activities is to increase the use of stem cells in clinical treatment. Given the many knowledge-related and technological challenges that still exist, it is important to have realistic expectations regarding how rapidly new findings can be of direct benefit to patients. Ongoing stem cell studies worldwide show that the field is moving towards increased clinical use of stem cells, but there are obstacles to overcome before such treatment can be offered to patients without risk, such as the risk of developing tumors. This is particularly true with regard to iPS cells and ES cells. A great deal of effort is still needed to develop and implement procedures and protocols to repair damaged tissue or organs. In many cases, there are unresolved issues relating to culturing stem cells, the purity of animal components and stem cell characterisation. This applies to all types of stem cells.

There is also considerable activity in the field of cancer stem cell research. While there is controversy surrounding the term "cancer stem cell" itself, there is general agreement that cancer stem cells share certain characteristics found in the body's normal stem cells. Valuable knowledge about cancer diseases and cancer cells and their stem-cell-like characteristics may be obtained through stem cell research. Conversely, much can be learned about the functions controlling cell growth and differentiation in normal stem cells by studying cancer stem cells. For example, more knowledge is needed about the significance of intact genomes for normal stem cell development. Moreover, it is important to learn more about the normal adaptive capacity of stem cells in tissue that contains differentiated cells. This type of knowledge is vital to preventing transplanted cells from developing into cancer cells.

Stem cell research in Norway

Norwegian stem cell research ranges from basic research on the characteristics of stem cells in relation to signal pathways and their adaptation to the microenvironment (niches) of organs and basic research on epigenetics, to clinical research on the use of stem cells in treating human disease. Subsequent to the amendment of the Biotechnology Act in 2008, research is now being carried out in Norway on somatic stem cells, ES cells, iPS cells and stem cells from umbilical cord blood.

Norway has made advances in the following fields in particular: studies on 1) haematopoietic and bone marrow stem cells; 2) mesenchymal stem cells; 3) neural stem cells; 4) cancer stem

cells; and 5) imaging of stem cells. Research on embryonic stem cells and iPS technology are under development. Norway is home to internationally leading research groups in the areas of epigenetics and plurpotency, neural stem cells and cancer stem cells. There are also strong research groups addressing clinical applications of stem cells.

Norway has a relatively large research community investigating regulation and differentiation in mesenchymal stem cells, and the characteristics of neural stem cells and stem cells of the eye. There are clinical trials using mesenchymal stem cells to repair cartilage and bone tissue, and clinical trials using stem cells of the eye are underway. Research is also being conducted on the transdifferentiation of haematopoietic and mesenchymal stem cells. ES cells are not used in clinical trials in Norway; research activities focus on the experimental development of specific cell types from human ES cells. During the 2008–2012 period, the STAMCELLER programme invested in increasing the expertise in the iPS field, and there are now several research groups working in this field. In the years to come, iPS cells will probably be used primarily as a tool for studying disease mechanisms and epigenetic reprogramming. A substantial part of the stem cell research in Norway is carried out at the Norwegian Center for Stem Cell Research in Oslo. In addition to traditional stem cell research, research on cancer stem cells is an active field in Norway. The Cancer Stem Cell Innovation Center (SFI-CAST), a Norwegian Centre for Research-based Innovation (SFI), is an important contributor in this field.

International stem cell research spans a wide scope, and it is highly unlikely that Norwegian stem cell researchers can make their mark in every field. For Norway, it will be most expedient to expand existing expertise, while at the same time making room for the emergence of new, future-oriented research areas. International research cooperation will be vital in this context. Norwegian stem cell research is expected to have an advantage in areas where leading research groups already exist (see the list of fields above), for example in basic research on signalling mechanisms and epigenetic regulation of stem cells, defective regulation of stem cells in individuals with cancer, and derivation of various stem cells from somatic stem cells for clinical applications. Research on iPS and ES cells are also strategically important fields under development.

A key challenge for Norwegian stem cell research in the years ahead will be to intensify efforts to strengthen basic and translational research, with increased focus on international cooperation. It is crucial for Norway to participate in the extremely rapid development taking place internationally. For example, the field of iPS research is showing dramatic development in relation to the potential use of modified somatic stem cells as a basis for generating specific mature cell types which can be safely transplanted into patients. Making the results of basic stem cell research available via translational research is also an important long-term goal that will be given considerable attention. Stepping up the level of activity in translational research will require the investment of substantial economic resources. It may be challenging to find sufficient funding and decide which focus areas to give priority.

Another challenge will be to find a way to provide all of Norway (with settlement dispersed over a large geographic area) with access to the results of these developments. Here the first step will be to establish national researcher constellations and networks. Concurrently, increasing the level of clinical research activity, preferably through international cooperation, will make experimental treatment, for example in connection with cell transplants or stimulation of the body’s own stem cells, more widely available to Norwegian patients.

Legal regulations and ethical perspectives

Research using supernumerary fertilised eggs and ES cells is permitted in Norway for the purpose of generating new knowledge to apply in future treatment of serious human illnesses. Research may be conducted using supernumerary fertilised eggs up to 14 days after fertilisation, at which point they must be destroyed. Cell lines established from supernumerary fertilised eggs, however, may be cultivated for a longer period. Fertilising eggs solely for research purposes is prohibited in Norway.

In the late 1990s and early 2000s, the use of human ES cells in research triggered an ethical debate both in Norway and abroad with particular focus on the moral status of the embryo and the use of "a germ of human life" in medical research. A legislative amendment in 2008 made it possible to use supernumerary fertilised eggs in research in Norway, and the ethical debate concerning ES cell research and the use of supernumerary fertilised eggs has died down to a certain extent. Research has been carried out on cell lines imported from the US and Sweden; thus far, no research has been conducted using ES cells from Norwegian supernumerary fertilised eggs.

The question can be raised as to whether there is a risk of ignoring other equally relevant and pressing ethical aspects of stem cell research if we assume that we have already had the "principal" ethical debate. One ethical question that has been posed involves the use of next-generation sequencing techniques on stem cell lines.[1] Sequencing genomes or exomes in these cells will reveal information – in certain cases important information – about the donor and his or her relatives. This gives rise to ethical questions pertaining to genome and exome sequencing in general: Who owns the information, who has the right to know, and do researchers have an ethical obligation to disclose important findings?

Given that the issue of whether to permit or prohibit the use of ES cells in research has been resolved in Norwegian society, future ethical challenges will not revolve around *whether* stem cell research should be permitted but rather *how* stem cell research can be conducted in an ethically justifiable manner. Many of the ethical questions surrounding stem cell research are not specific to stem cell research; these include: consent-related problems, use of research findings and patenting, establishment of research biobanks, unforeseen negative effects of new treatments, and unrealistic expectations among the general public and in political circles in relation to research findings, as well as the above-mentioned issue of information about the donor being revealed through genome sequencing in stem cells. However, several of these general issues may take on special characteristics in the context of stem cell research. A discussion of the ethical aspects of stem cell research must be an integral component of all stem cell research projects and may facilitate rather than hinder research activities in this field.

Norway has a regulatory framework and structures in place to deal with ethical questions relating to stem cell research.

[1] Isasi, R et al. (2012). Disclosure and management of research findings in stem cell research and banking: policy statement. *Regenerative Medicine* 7 (3); 439-448.

3. Objectives of the programme

a. Primary objective

The primary objective of the STAMCELLER programme is to develop and enhance expertise within basic and clinical research on stem cells with the aim of finding treatments for seriously and chronically ill patients. The programme will employ research and innovation activities aimed at providing patients in Norway with a future range of stem cell-based treatments equivalent to those found abroad. Norway will seek to contribute to research in this area in a manner that protects the integrity of the individual, safeguards the value of human life and maintains a high ethical standard.

b. Secondary objectives

- To provide funding for researcher-driven projects within the thematic priority areas of the programme.
- To clarify the future role of the Norwegian Center for Stem Cell Research as a tool for achieving the objectives of the programme, on the basis of an evaluation of the centre and an application process in the RCN.
- The programme will seek to advance basic stem cell research in the direction of translational and clinical research as quickly as possible in a scientifically and ethically justifiable manner. In the course of the programme period, to establish well-functioning research activities on induced pluripotent stem cells (iPS cells) in Norway that satisfy the need for expertise in this technology area and are focused on clinical realities.
- To promote internationalisation of Norwegian research by providing support for research stays abroad for younger researchers, among other measures.
- To take an active role in disseminating knowledge throughout the country and to initiate and maintain communication with relevant clinical environments.
- To encourage Norwegian stem cell researchers to seek funding from external sources, including international sources.

4. Priority research tasks

a. Overall priorities

Collaboration within the basic research community as well as cooperation between researchers engaged in basic research and clinical research is crucial to ensure that the results of stem cell research will benefit patients. To this end, the programme will promote increased cooperation at both the national and international level.

The programme will seek to advance basic stem cell research in the direction of translational and clinical research as quickly as possible in a scientifically and ethically justifiable manner. The programme will also cultivate contact with user groups and reach out to relevant clinical environments. Preparing these environments to take advantage of the potential inherent in stem cell research must be a dynamic process and one in which the programme must play an active part.

Advances in the field are taking place at a very rapid pace internationally, with increasing use of ES cells, iPS cells and various somatic cells to generate new knowledge about how stem

cells can be differentiated into selected cell types for use in regenerative medicine. Priority will be given to boosting international researcher exchange in these areas in order to quickly incorporate international findings into Norwegian stem cell research. Activities originating in the programme should be extended and coordinated nationally to ensure that the entire country can take part in the knowledge development and benefit from the same treatment opportunities in the future.

The programme will promote the recruitment of younger talented researchers and support the development of their careers. The programme will also seek to improve the gender balance in the field of stem cell research. Following up both of these priorities may lead to greater activity and renewal in Norwegian stem cell research.

The stem cell research community in Norway can be said to be somewhat fragmented, and it will therefore be important to develop strong national constellations for cooperation. It takes time to build up critical mass and collaborative relationships that manifest themselves in research findings. It will therefore be vital to utilise and further develop existing methods and infrastructure, and gradually direct focus towards the use of individualised stem cells in clinical medicine.

b. Thematic priority areas

1. Research to gain a deeper understanding of basic processes related to the growth and differentiation of multipotent and pluripotent stem cells from various sources. This will also involve studying the adaptive capacities of normal and diseased stem cells.

2. Improving the characterisation and validation of stem cells for use in clinical settings, with particular focus on genetic/epigenetic characteristics, the risk of disease transmission and the risk of cancer development.

3. Development and implementation of procedures and protocols to repair damaged tissue or organs, including clinical studies, incorporating research ethics-based risk-benefit assessments with a focus on patient perspectives.
4. Use and further development of induced pluripotent stem cells (iPS cells) for application in relevant cellular and pre-clinical disease models, and for enhancing understanding of how iPS cells can be used in clinical regenerative medicine.

Research projects on cancer stem cells and their characteristics may also be funded under the programme, with the aim of determining these cells' significance for tumour development and progression, and development of therapy resistance. This type of research will also provide insight into the growth of cancer cells and their capacity to adapt to new microenvironments.

Given the rapid advances in the field internationally, it is important to leave room for activities addressing new research areas. One challenge will be to incorporate these into research programmes under development, and to ensure that these areas are closely linked to the international research front via collaborative efforts.

c. Instruments

Funding under the programme will primarily be channelled via researcher-driven projects within the thematic priority areas of the programme, but the programme board may also decide to initiate projects in specific areas where a need for research has been identified.

Projects will be assessed on the basis of their scientific merit and relevance relative to the programme's thematic areas and objectives. Grant proposals are expected to describe how the proposed project will help to fulfil the objectives of the programme and to specify which of the work programme's thematic areas the project addresses. When assessing grant proposals, importance will be attached to the incorporation into the projects of ethical aspects of stem cell research, and potential perspectives and needs of user groups in the short and long term.

The programme board may stipulate more specific priorities within the thematic priority areas described in the work programme. These and other more detailed guidelines will be specified in the funding announcements issued by the programme.

The Norwegian Center for Stem Cell Research is another key instrument employed by the programme, and has received annual allocations under the programme since 2008. A process will be initiated at the start of the programme period to determine whether allocations to the centre should be continued.

The programme seeks to promote international researcher exchange and will give priority to this by providing support for research stays abroad for Norwegian researchers. Special attention will be focused on encouraging younger researchers to conduct research abroad and plans for such stays should be included in grant proposals for Personal Post-doctoral Research Fellowships and Researcher Projects.

5. International cooperation

Many of the key challenges in Norwegian research are the focus of research activity in other countries as well. International research collaboration and the flow of knowledge across national borders are essential, especially if we are to find viable solutions to global challenges. International cooperation is vital for improving quality and enhancing capacity in Norwegian research, and Norwegian researchers should both benefit from and contribute to international knowledge sharing. The Norwegian research community must also seek to attract the very best researchers and position itself at the international forefront in selected research areas.

The measures to be implemented by the programme board to promote international research cooperation within the programme's sphere of responsibility are firmly rooted in fundamental documents: the Government white papers on research, *Climate for Research*, 2009–2012 and *Long-term perspectives – knowledge provides opportunity* 2012-2013, and the Research Council of Norway's Strategy on International Cooperation 2010–2020. The programme board is responsible for implementing strategic activities to boost international research cooperation within relevant priority areas under the programme. International researcher exchange is an important task under the programme, and will be given special weight. It will be particularly important to provide younger researchers with opportunities to conduct research stays abroad and to better enable them to combine this with their family lives, for example by allocating additional overseas research grants. Creating attractive career opportunities that will bring younger researchers with international experience and expertise back to Norway is crucial as well. International network-building and active participation in international meetings and conferences are also vital to the internationalisation of Norwegian research.

The following measures can be used:

- allocate funding for research stays abroad for Norwegian researchers and stays at Norwegian institutions for guest researchers;
- encourage Norwegian researchers to establish contacts with researchers and researcher networks, and to initiate project collaboration and grant proposals to relevant Nordic and European programmes or schemes, such as NordForsk, the EU Framework Programme, the European Research Council (ERC), Joint Programming Initiatives and European Cooperation in Science and Technology (COST);
- based on the letter of intent between the Research Council and the National Institutes of Health (NIH), encourage Norwegian researchers to collaborate with US research groups and take advantage of the opportunities offered by the NIH system;
- promote international research cooperation that makes use of joint European infrastructure;
- ensure that information about the programme and projects under the programme is available in English;
- assess relevant forms of international cooperation at the programme level.

Under the EU Seventh Framework Programme (FP7), Health Research is the second largest of the ten thematic programmes. The EU's Health Research programme is divided into four main areas, and there is a special initiative on regenerative medicine. Funding has been awarded to a number of studies on stem cells under both FP6 and FP7. So far it is unknown how the field of stem cell research will be addressed in the successor to FP7, *Horizon 2020*, which will be implemented from 2014. Participation in EU research programmes and other international activities is only possible if there are dynamic Norwegian research groups that can take part in such cooperation. While efforts to facilitate participation by relevant research groups in such cooperation should be encouraged, it is also important to build competence in other research environments to make them attractive to partners from abroad.

When it comes to medical research, Nordic cooperation will in many cases be particularly useful due to the similarities between the Nordic countries. The strong stem cell research groups in other Nordic countries represent a resource for Norway. The Joint Committee of the Nordic Medical Research Councils (NOS-M) has drawn up a Nordic White Paper on Medical Research, which provides an analysis of Nordic medical research and the opportunities for enhancing it, both in the individual countries and through cooperation at the Nordic level. (http://www.nordforsk.org/files/present-status-and-future-potential-for-medical-research-in-the-nordic-countries)

6. Communication and dissemination activities

Project results are expected to be presented in recognised scientific fora and published in international scientific journals. The programme board will give priority to dissemination of research findings, and considers it essential to make researchers aware of the importance of communicating their results to others. In addition to the research community, the target groups for communication activities are politicians, the public administration and the public at large.

The programme will assist in creating meeting-places and facilitate relevant dissemination activities such as seminars, conferences, etc. These will be targeted towards existing stem cell research groups, relevant clinical environments, user groups and Norwegian society in

general. The programme will assess relevant communication, information and dissemination measures on an annual basis.

The programme's webpages http://www.forskningsradet.no/stamceller are a key tool in the programme's communication and dissemination activities, and will be updated on a regular basis with news, information about the programme's objectives and sphere of responsibility, contacts, projects and funding announcements.

Aspects pertaining to information and dissemination activities must be taken into account when research projects are planned.

Researchers receiving funding from the programme are encouraged to participate actively in debates, seminars and conferences in Norway and abroad. Researchers are also encouraged to promote transparent communication with the community and to be open to discussing and sharing knowledge about stem cell research with society at large.

7. Budget

The programme spans a five-year period from 2013 to 2017, and is funded by the Ministry of Health and Care Services. The programme's budget for 2013 is NOK 20 million. The proposed budget for 2014 is NOK 25 million, and budget increases will be required if the programme is to be able to deal with the research challenges and achieve its objectives. Efforts will be made to ensure that the projects awarded funding receive realistic allocations and have satisfactory working conditions. At the same time, this must be balanced against the need to ensure adequate scientific breadth within the programme.

8. Coordination with other related programmes and instruments at the Research Council

The programme shares an interface with other research programmes and activities at the Research Council, and seeks to ensure further coordination with these. The most important are:

The open competitive arenas:

- *Independent Projects in Medicine, Health Sciences and Biology (FRIMEDBIO)*
- *Centres of Excellence (SFF) and Centres for Research-based Innovation (SFI), especially the Cancer Stem Cell Innovation Center (SFI-CAST)*
- *National Financing Initiative for Research Infrastructure (INFRASTRUKTUR)*
- *The programmes for Commercialising R&D Results (FORNY2020) and User-driven Research-based Innovation (BIA)*

Relevant thematic programmes:

- *Biotechnology for Innovation (BIOTEK2021)*
- *Research Programme on Clinical Research (KLINISKFORSKNING)*
- *NevroNor – A National Initiative on Neuroscience Research*
- *Programme for Publicly-initiated Clinical Cancer Studies (KREFT)*
- *Research Programme on Environmental Exposures and Health Outcomes (MILPAAHEL)*

- *Ethical, Legal and Social Aspects of biotechnology, nanotechnology and neurotechnology (ELSA)*

Stem cell research is also carried out at the *Centre for Molecular Medicine Norway (NCMM)*, which is the Norwegian node of the Nordic EMBL Partnership for Molecular Medicine with the European Molecular Biology Laboratory (EMBL).

The Research Council administration ensures close contact and cooperation regarding initiatives/programmes that share thematic similarities, particularly in the planning phase and during the programme period, for example with regard to funding announcements and seminars/conferences.

9. Organisation

The programme is administered under the auspices of the Division for Science, which is responsible for appointing the programme board. The programme board acts on behalf of the Research Council, and reports to the division research board via the Director of the Department for Medicine, Natural Sciences and Technology and the Executive Director of the division. The tasks of the programme board are primarily strategic in nature. It is responsible for ensuring that the programme achieves its stipulated objectives and is implemented as efficiently as possible in relation to this work programme and other plans that have been drawn up, within the framework approved by the division research board. The Research Council administration is responsible for the day-to-day operation of the programme, and for conducting any evaluations.