The Research Council of Norway

Evaluation of the Norwegian Center for Stem Cell Research

Report of the Evaluation Committee

The Research Council of Norway
P.O.Box 2700 St. Hanshaugen
N–0131 OSLO
Telephone: +47 22 03 70 00
Telefax: +47 22 03 70 01
bibliotek@rcn.no
www.rcn.no/english

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Evaluation Committee

Alan R Clarke (chair)	Cardiff University
Lukas Sommer	University of Zurich
Timo Otonkoski	University of Helsinki
Helen A Papadaki	University of Crete

Secretary: Dorne Edwards, Cardiff University

Executive Summary

The Norwegian Center for Stem Cell Research is funded through the *Stem Cell Research Programme,* administered by the Research Council of Norway (RCN). This evaluation has the remit of assessing the scientific quality of the stem cell research conducted in the center, and assessing the strategic role and development of the center in the context of being a targeted measure to strengthen stem cell research in Norway. An international committee has been tasked with the evaluation, and the members are listed on page 4 of this report.

The Evaluation Committee recognises that the Center is a relatively recent structure, and that as such it comprises a novel grouping of individuals. Within the Center, there is good developing evidence of synergies between these groupings, although the extent of such synergy varies across the Center. With respect to individual research activities, there are several clear areas of scientific excellence. The translational activity of the Center is one such highlight. Further, the Committee believes that the Center is beginning to make an impact on the stem cell community both within Norway and internationally. However, some weaker areas have been identified, and the Center Director should consider these when developing the strategic plan going forward.

The Committee also recognised that there have been key challenges facing the Center, notably:

- The funding framework
- The capacity to expand beyond their current size
- The absence of a PhD programme specific to the Center
- The differing levels of engagement of some of the groups with the Center.

Interaction with the funding partners is good, and the Committee encourages those links to be further developed to find effective ways of meeting the challenges above.

The Evaluation Committee feels that overall; the Center's scientific activity is very good. Whilst there are some areas that would benefit from being strengthened as the Center builds its strategy for the future, clear areas of excellence are evident and these will stand the Center in good stead in the future.

Terms of Reference

Framework for the evaluation

1.1 Introduction

Research on stem cells is a priority area in Norway, and the Stem Cell Research Programme launched in 2008 is an important instrument in this context. With the objective of *developing and enhancing expertise within basic and clinical research on stem cells in order to find treatment for seriously and chronically ill patients*, open calls for research proposals as well as establishment of the Norwegian Center for Stem Cell Research have been the primary instruments of the Research Programme.

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 of Norway with the task of establishing a national center for stem cell research under the auspices of the South-Eastern Norway Regional Health Authority. The center is hosted by Oslo University Hospital, and is physically located at the Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo. The center establishment built on an existing national network for stem cell research, funded by the Programme's predecessor *Strategic effort on stem cell research* (2002-2007). The center has been allocated a lump sum of NOK 5 600 000 per year for five years, from 1.7.2008. The center was officially opened 27.11.2009.

The center's principal objectives are to increase the pace of existing stem cell research in Norway, establish a platform for human pluripotent stem cell research, and build translational bridges that facilitate the clinical use of stem cells to treat patients. The center has a national role in organizing meetings, seminars and courses, stimulating national and international collaboration, as well as for dissemination of knowledge.

In the contract between the RCN and the South-Eastern Norway Regional Health Authority it is specified that funding for the last two years of the five-year period is based on a satisfactory mid-way evaluation of the center. In 2011 the Programme Board of the Stem Cell Research Programme resolved to postpone the evaluation. The evaluation is carried out in 2012.

1.2 Purpose of the evaluation

The purpose of the evaluation is to assess the scientific quality of the stem cell research conducted in the center, and to assess the strategic role and development of the center in the context of being a targeted measure to strengthen stem cell research in Norway. Furthermore, the evaluation should provide recommendations for further development of the center.

At the completion of the evaluation, less than one year will remain of the allocation to the center. The Stem Cell Research Programme is intended to be extended for a new five-year period from 2013. Thus, the evaluation of the Norwegian Center for Stem Cell Research will provide data to underpin the decision as to whether an extension of the center allocation is recommended.

1.3 Organization

The evaluation will be carried out by an international Evaluation Committee. The Evaluation Committee should base its evaluation on the written material provided, as well as a hearing and a site visit to the center. The Evaluation Committee will present its findings and recommendations in a written report.

1.4 Background material for the evaluation

- Contract between the RCN and the South-Eastern Norway Regional Health Authority, and information regarding the process preceding the center establishment.
- Project summary and project description of the Norwegian Center for Stem Cell Research.
- Self-evaluation and Fact sheet from the center, as well as Self-evaluations and CVs from the individual groups, according to a standardized outline.
- Report from the International Advisory Board of the center from 2011.
- Assessment from Oslo University Hospital, and from the University of Oslo.
- The center's annual reports from 2009, 2010 and 2011

Mandate for the Evaluation Committee

The evaluation of the center is to emphasize the following elements:

Scientific quality of the stem cell research
The evaluation is expected to assess to what extent:

- The center groups conduct stem cell research at a high international level, as judged by the significance of contributions to their field, prominence, and scientific impact of their research
- The scientific production of the center groups, like number of scientific publications and PhD degrees, is reasonable
- The center groups are actively and successfully taking part in national and international research collaborations

Strategic role and development of the center
The evaluation is expected to assess to what extent:

- The center has reached its main strategic goals:
    - increase the pace of existing stem cell research in Norway
    - establish a platform for human pluripotent stem cell research
    - build translational bridges that facilitate the clinical use of stem cells to treat patients
- The center has fulfilled its national strategic roles in
    - organizing courses and meetings
    - dissemination activities
    - stimulating collaboration nationally and internationally
- The center has developed successfully in terms of inclusion and recruitment of groups and associated members, as well as collaboration with relevant centers, clinicians, industry and patient organizations
- The center establishment has resulted in increased collaboration and synergy between participating groups
- The center has been successful in developing infrastructure and facilities
- The center has been satisfactorily organized and led
- The center has been satisfactorily integrated into Oslo University Hospital and the University of Oslo
- The center has satisfactory strategic and practical plans for future development

Strategic role and development of the Center

Firstly, it is important to note that the Evaluation Committee has no doubt that the Center has advanced stem cell research in Norway, having increased the pace of such research and started to build a platform for human pluripotent stem cell research. It is a relatively young center with limited funding and despite this its output is impressive, making an impact on the stem cell community both within Norway and internationally. There are several clear areas of scientific excellence, and the translational activity of the Center is one such highlight. On saying this, the Center should consider how its strategy furthers the emphasis on stem cell research in the future, as few of the PIs have a purely stem cell background. That should not be an issue if the planned model includes a number of dedicated stem cell researchers supported by strategic collaborations with researchers who have a strong interest in stem cell research.

It is clear that there are some very good international collaborations currently, but the Center should look at how it identifies further opportunities and links, and engages more with potential international partners. Internally, the Committee feels that further collaborations could be fostered between the basic scientists and the clinicians so as to further strengthen the translational outputs of the Center.

The Center has extremely good facilities – GMP, imaging, technical expertise etc. However, the management might want to consider whether certain roles should be reviewed to assess exactly what their integration with the Center's strategy should be.

A number of PIs affiliated to the Center are at an age where succession planning is something that should be a priority when developing the strategic plan. To ensure the longevity of those groups' work it is crucial to make sure that early career researchers are fostered and are collaborating in the important areas of research. The Committee is reassured to learn that this issue has been considered by management and the group leads and that provision for the work will be carefully planned.

It is noted that at times the Center management feels that it is in a situation where it has to be reactive rather than proactive, and that more dialogue with funders could address this. They question whether their mandate might be more ambitious than the funding can allow and consider that to expand productivity and integration would require a review of the funding envelope.

The key stakeholders have clearly demonstrated a willingness to recognise the need for their engagement and support, and that they are committed to working towards shared solutions to any areas in need of development. The Committee acknowledges that starting from scratch is difficult and that without the current structure and the clear integration with the University of Oslo and Oslo University Hospital, the Center would not have the strengths it has clearly demonstrated. This being the case, it is important to look at what is needed from funders and stakeholders to move the Center forward.

To summarise, certain issues stand out that will facilitate the Center's progress if addressed:

1. The nature of the Center and the way it is funded

   The core funding is quite small, which means that in effect it's working as seed corn funding and giving critical mass to stem cell research. The question for the Center going forward is: how can that be elevated with a view to developing the Center as a whole and overcoming the challenges noted?

2. The development of a training programme within the Center profile.

   A session with students and post docs during the site visit was extremely positive, demonstrating enthusiasm for and understanding of the Center amongst the students and post docs, who felt a strong sense of being part of the Center and collectively expressed a view that the Center is tangible. Regular seminars and discussions are available via the University and the Center, and students are able to propose speakers. The students felt that the Center is increasing collaborations, which is a strong advantage to them. Some of the post docs are cross-group, which further enhances the potential for future collaboration. There were plenty of suggestions for activities that could be incorporated in the training programme, for example Center away days and exchange programmes. The students were confident that there is support for meetings from the Center, but at the same time sufficient resourcing is key to this.

3. Building on the initial mandate set out by the Research Council, namely to focus on Research, Training and Dissemination.

   The first two areas are progressing well and will be reinforced by a strong strategic plan, but it is noted that dissemination is an area in which the Center feels itself to be weaker, so this will need work moving forward.

The Committee notes the importance of allowing for how new stem cell research is in Norway, and of bearing in mind that the Center's profile has raised since it began. It is recommended that in the short term the Center works on raising its profile, which is something the University can help with, and in the longer term to consider the structure as a whole.

The Committee also notes that the issues raised are relevant for all Centers, and are not unique to the Stem Cell Center, and to fulfil the mandate would need an appropriate level of funding.

Scientific quality of the stem cell research

The 11 core groups

Group 1

Short Description of the Group

Prof Joel Glover is the head of a relatively large research group, comprising 1 senior scientist, 6 post docs, 3 PhD students and 2 technical/administrative staff. The group leader is also the Director of the Norwegian Center for Stem Cell Research.

The group's research is focussed on the developmental programs governing the specification and functional differentiation of brainstem and spinal cord neurons, the utilization of these programs to direct the differentiation of human pluripotent and multipotent stem cells to specific neuronal types, the study of the formation and regeneration of brainstem-spinal cord motor circuitry, and the use of human stem cells to treat spinal cord injury and other spinal cord-related diseases through neuron replacement.

The group's main projects are:

1. Anatomical and functional mapping of brainstem-spinal cord circuits
2. Establishing a SCID mouse spinal cord injury (SCI) model for high throughput functional imaging of human stem cell-derived neurons
3. Generation of human serotonergic neurons from hES cells
4. Generation of Purkinje neurons from iPS cells derived from SCA-14 patients
5. Transdifferentiation of human adipose stem cells to neurons
6. In vivo tracking of human stem cells
7. Glioblastoma in embryonic niche

Scientific Quality

The PI has published seminal papers in the field of neuronal circuit formation, having established innovative optical recording techniques for neuron tracing. Apart from continuing these activities (which are rather indirectly related to stem cell research), the group is engaged in several collaborations on human stem cells. These include the generation of specific neuronal subtypes from human embryonic stem cells (hES) and human induced pluripotent stem cells (hiPS), the derivation of neurons from adipose stem cells, in vivo tracking of differentiating stem cells using MRI, and the analysis of tumorigenic cells in an embryonic environment. The group has been working with human stem cells since 2003, when it initiated a study of the differentiation of human hematopoietic stem cells implanted into chicken embryos. This study, published in PNAS with the group leader as senior author, was the first to demonstrate that human somatic stem cells of any type could differentiate into bona fide functional neurons in an in vivo model.

Based on published track record the group has not yet published many papers in the stem cell field, these studies may be judged to be rather preliminary, and it may be that the question of

research fit needs to be carefully considered. Irrespective of this, the quality of the studies is high and they are relevant to stem cell research.

Conclusion and Recommendations

Overall the group's focus is good and moving in the right direction. A solid part of the Center, the group has a clear plan and the focus is clear. The duties linked to organizational and administrative work associated with the directorship of the PI seem to be manifold, and the question arises as to whether some organizational restructuring of the Center would not be beneficial for all parties involved, including giving consideration to hiring more administrative staff, and the establishment of more centralized structures, etc.

Group 2

Short description of the group

The activities within the group headed up by Prof Philippe Collas, which according to the self-evaluation comprises 13 individuals, cover a broad range of studies of the regulation of chromatin states, primarily focused around adult mesenchymal stem cells (MSCs). The group's objectives are to:

1. examine the epigenetic profile of adipose stem cells in relation to their capacity to drive differentiation (eg chondrogenesis or hepatogenesis)
2. to manipulate the chromatin state to address the inherent predisposition to adipogenesis;
3. to investigate the specific role played by the histone variant H3.3
4. to investigate the capacity of cell extracts to mediate reprogramming
5. to investigate 3D chromatin structure using a variety of cutting edge techniques including Micro-ChIP, Hi-C, methylation studies and mathematical modeling
6. to investigate the role of AKAP proteins in the regulation of chromatin
7. To determine the role of nuclear lamins on the 3D organization of the genome

Finally, the group is asking a fundamental question about the role of chromatin remodeling in the initiation of transcription in very early embryonic development.

Scientific Quality

Overall the programmes of work appear very strong, although there is slight concern about the very wide breadth of studies being undertaken, and it will be useful to explore the research priorities within the group. Another minor concern is that it is a little difficult to understand the balance between observational and mechanistic studies, which may be a reflection of the nature of the scientific descriptions in the papers provided.

Both these criticisms are largely mitigated by the very good and apparently improving publication record (see below). One notable feature is the very heavy investment in technological development, which gives a high level of confidence that the objectives will be delivered. Evidence of both national and international collaborations is given and appears strong.

The group's publication track record is very strong, with a series of papers in leading specialist journals, such as Molecular and Cellular Biology and Stem Cells. There is also a small number of very high impact publications, for example in Nature Methods and Developmental Cell. The recent Developmental Cell publication and a paper in review at Nature is suggestive of a recent increase in impact for the group and strong upward progression.

Conclusions and recommendations

The work of this group is interesting and productive, and is being applied to a range of stem cell topics. The group's publishing is on an upward trajectory, but the science is very broad. In light of this it would be worth exploration the precise areas of focus in terms of their direct relevance and impact upon stem cell biology.

The Committee acknowledges a very impressive programme of work, and that the group is engaged well with the Center. The science is somewhat disparate but can clearly relate to the core, and this reflects in the publication record and ability to get funding. It is the belief of the Committee that this group is a fundamental member of the Center.

Group 3

Short description of the group

Dr Gareth Sullivan was recruited to the Center as a group leader through a competitive international call in 2011. He has previously worked as a senior research fellow at the MRC Center of Regenerative Medicine in Edinburgh, UK, and he obtained his PhD from the University of Dundee in 2007. He has only very recently established his laboratory at the Center and the group currently consists of two PhD students. In addition to his own line or research, an important task for the PI is to act as the Core Manager for the human pluripotent stem cell (hPSC) facility of the Center.

Scientific Quality

The group aims to develop new non-integrating methods for the derivation of iPS cells, to conduct genome-scale analysis of endodermal differentiation, to improve current established methodologies in terms of efficiency and maturity for the differentiation of hepatic cells from hPSCs, and to establish 3D culture systems for the development of physiologically relevant tissue (particularly hepatic) models. All of these aims are interesting and valuable. However, during the site visit, the Committee was not provided with concrete data or details of the approaches used, to justify the projects. It appears that the group is heavily dependent on both local and international collaborations in these projects. The Committee felt that it was quite difficult to evaluate the science from the information presented. The current research plans are quite broad and ambitious, taking into account the resources.

Conclusions and recommendations

The group's emerging research may lead to important possibilities for the development of ambitious collaborative projects within the Center (for example, with the Collas group to study the epigenetics of pluripotent reprogramming and with the Brinchmann group to develop 3D culture systems). However, at this early point, the Committee felt that the PI should focus the group's work in one well-planned area – a single solid, realistically achievable project in order to establish the group, and that this will need to be supported by the Center.

Furthermore, since the pluripotent stem cell core facility is still at an early phase of development, it seems that the PI will need to give a considerable amount of time to this. The split presented to the Committee of 80% of time as a PI and 20% taken up with facilities was not felt to be ideal; whilst it seems at first to be a good target it might be difficult to achieve if the PI is to devote sufficient time to build his own independent research programme.

The Committee feels that the Center should consider what it needs from this group in strategic terms, and what resources it needs to make available to achieve the redefined objectives.

Group 4

Short description of the group

The group leader Prof Arne Klungland has a long high-quality research line in the area of DNA repair. An important area of focus has been the AlkB proteins which play important roles in DNA repair and beyond. More recently, the group has published important studies in the identification and functional characterization of a specific form of DNA methylation involving 5-hydroxymethylcytocine. To summarise current projects:

1. Role of DNA base lesion repair by direct reversal in ageing, cancer and neurological disease.
2. Characterization of the novel Alkbh family of hydroxylases.
3. 5-hydroxymethylCytosine (5hmC); methods for identification and biological relevance.

A subgroup within the group, headed by Elisabeth Larsen, is using iPS cells for disease modelling including Huntington's disease and genetic imprinting disorders. The group collaborates closely with the Bjørås group within the Center.

Scientific Quality

It is obvious that the group is performing at a high international level within its specific areas of focus, which is highly relevant to the aims of the Center. However, the Evaluation Committee felt unclear as to the level of integration with the Center.

The Evaluation Committee was left with a strong impression that the group is not functionally integrated in the Center. For example, it appears that iPS cells are reportedly already derived and studied in the Klungland laboratory, and this does not seem to be connected in any way with the pluripotent stem cell core facility. On saying this, the Committee acknowledges that the group joined the Center relatively recently – in 2011 – and so recognises that there is potential for clearer integration in the future.

Conclusions and recommendations

There is no doubt that the group conducts international top quality research. However, it is not currently evident that the group is, or is aiming to become, an integrated part of the Norwegian Center for Stem Cell Research. For the next term, a strategic plan needs to be developed where integration of this group is either decisively strengthened, or alternatively, it may be decided that the group is best placed as an Associate Member.

Group 5

Short description of the group

Prof Magnar Bjørås is Professor at the Department of Microbiology and head of a research group composed of 1 senior scientist, 5 postdocs, 2 PhD students, 2 Master students, and 4 TA/administrative staff.

The group investigates basic biological processes associated with cellular responses to DNA damage including DNA repair pathways and mechanism for tolerance and adaptation. The main projects in the group are:

1. Role of oxidative DNA base lesion repair in ageing, viral infections, cancer and neurological disease.
2. Structural biochemistry of DNA base lesion repair and establishment of core facility in structural biology.
3. DNA repair and biological responses to DNA damage in microbial cells.

Scientific Quality

The group is involved in many national and international collaborations, mostly in its core research field of DNA repair mechanisms. The PI has been and still is very successful in this field, being author on an impressive list of high quality papers on molecular mechanisms underlying DNA damage repair and on DNA repair responses in various biological systems. Together with his senior researcher, he has started in recent years to apply his expertise to stem cell research and has already published several nice studies, in particular in the field of neural stem cells and neurogenesis.

Conclusions and recommendations

Given the growing evidence for stem cell-specific DNA repair and DNA damage response mechanisms, it makes perfect sense that the group became a member of the Norwegian Center for Stem Cell Research in 2011. However, as with the Klungland group the Committee has not seen evidence that this group is an integrated part of the Norwegian Center for Stem Cell Research, and therefore the strategic plan should decisively set out whether the group is to be seen as an Associate Member or become fully integrated, in which case plans for strengthening the integration should be clear within that strategy.

Group 6

Short description of the group

The group leader Jan Brinchmann is one of the founding members of the Center. Dr Brinchmann's background is in T-cell immunology but for the last 10 years the group has mainly focused on stem and progenitor cells in the context of tissue engineering for cartilage, bone and cardiovascular tissues. The PI is the director of the Ex Vivo cell production facility at the Institute of Immunology, Oslo University Hospital. Current projects are:

1. Tissue engineering of hyaline cartilage
2. Tissue engineering of bone
3. Tissue engineering of cardiovascular tissues

Scientific Quality

The group has systematically developed approaches in the use of mesenchymal stem cells for tissue engineering, particularly for regeneration and repair of hyaline cartilage defects of the knee joint. This has already enabled Phase 1-2 clinical trials. Another active area of research is in the angiogenic properties of mesenchymal and endothelial progenitor cells. The group has successfully established itself as an internationally important player in the field of mesenchymal stem cell biology and orthopaedic tissue engineering, as evidenced by the continuous production of solid scientific papers in good international journals. Importantly, the group collaborates with several other Center members, particularly the Collas group.

Conclusions and recommendations:

This group is clearly an integral part of the Center. Its research profile fits very well with the aims of the Center and the GMP (good manufacturing practice) level cell production facility is an important asset for clinical translation. Very appropriately, it aims to utilize this possibility by actively developing clinical trials, both for cartilage repair and for angiogenic purposes. It appears that the cartilage area is the most developed and, in order to make the best possible international impact, perhaps should be the major area of focus, in conjunction with basic research of mesenchymal stem cell biology together with collaborators. The Committee believes there is strong evidence of a move into translational research, and it is a very good example of the positive outcomes from creating the Center.

Group 7

Short description of the group

Prof Jan Moskaug is part of the Laboratory of Stem Cell Epigenetics at the Institute of Medical Basic Sciences, Faculty of Medicine, University of Oslo and represents a core lab in the Center. The group, consisting of group leader and 1 PhD student (as of December 2011), is focused on *in vitro* and *in vivo* studies of functional properties of adipose tissue derived mesenchymal stem cells (MSCs) aiming to improve prospects for using these cells for clinical purposes. The group's main activities are focused on non-invasive *in vivo* imaging of genetically labelled mammalian cells.

Briefly, the group's ongoing/planned projects are:

1. Immunomodulatory effects of MSCs,
2. Epigenetic modification of MSCs as consequences of *in vitro* culture and differentiation relative to *in vivo* differentiation after transplantation into various animal tissues,
3. Redox regulation of stem cell epigenetics, and
4. Cysteine and adipose stem cell (ASC) differentiation.

Scientific Quality

Previous publications in the field of *in vivo* imaging (Moskaug J et al, *Mol Imaging* 2008; Moskaug J et al, *Mech Ageing Dev* 2004) represent evidence for the group's contribution in this field of research. Furthermore, the group has a number of active collaborations with other researchers from the University.

The group has not published recently; however, according to their report, the project on the characterization of immunomodulatory effects of MSCs from human and murine adipose tissue is well under way.

The Moskaug lab displays activities focused on immunosuppressive effects of adipose tissue MSCs using state-of-the-art technology by means of *in vivo* imaging transgenic reporter mice. A number of local collaborations have been established and results are expected for publication(s).

Conclusions and recommendations

Overall, the group is a rather small group focusing mainly on the immunosuppressive effects of adipose tissue MSCs. The *in vivo* imaging technology is an important tool for the group's research that might favour the interaction and collaboration with other groups in the Center.

There are some weaknesses in the overall group's contribution:

- The group has only two previous publications (2004 and 2008) using *in vivo* imaging, a technology which is presented as the main expertise of the group.
- The PI describes a number of local collaborations; however no data have been published since 2010.
- The absence of funding sources other than that from the Norwegian Stem Cell Center is a concern.

The group has a clear stem cell remit and is collaborating. However both the group and the Center are aware of the weakness in terms of publications etc., and that as the work is totally

dependent on the Center, care needs to be taken in managing the way forward. The group has developed a good technological platform and the Center should concentrate on finding ways of disseminating its expertise. There is a considerable diversity of projects, and thought should be given to establishing a clearer focus. Also, the Evaluation Committee would have liked to have seen a clearer indication of the PI's own interests. In moving forward, it will be critical for the Center management to carefully consider the best way to use their limited funds in supporting the activities of this group.

Group 8

Short description of the group

In Prof Ola Myklebost's group 1 senior scientist, three post docs, 1 PhD student and 2 support staff work with stem cell related projects.

The primary focus of the group's activity lies in mesenchymal tumorigenesis. Briefly, the key aims are:

1. To analyse the potential role of a truncated HMGA2 protein in cancer, possibly through deregulation of the sarcoma associated protein SSX1, a project being attempted in telomerase immortalized MSCs. The importance of this protein in regulating/maintaining EMT is also being pursued in a breast epithelial model.
2. To determine if a HMGA2 is methylated, a change which may alter subsequent sumoylation.
3. To look at histone modifications in osteogenesis,
4. To examine the effect of Wnt repression upon the differentiation of osteosarcoma cells.
5. To look at reprogramming events in cancer, although this is currently unfunded.

These objectives are largely mirrored in the Center's annual reports, with the addition of aims to better characterize stem-like subpopulations in sarcomas and to look at TGF-beta driven mechanisms in the generation of stem/stem-like cells.

Scientific Quality

According to the self-evaluation, several of the stem cell-related projects appear to have encountered significant problems, are to terminate or are as yet unfunded, making the ongoing aims rather difficult to assess. The Center support for the group is considerably outstripped by external grant income (although it is understood that this is not unusual). It appears that the Center has funded a PhD studentship on the regulation of mesenchymal differentiation by micro-RNAs; although this project appears to be terminating with the studentship.

Publication record is very solid, with 37 publications in the last five year period. These tend to be in specialist journals, including some which are leaders in their respective fields (eg Blood, Cancer Research). However, the majority of papers are in slightly lower impact journals.

Conclusions and recommendations

The Committee believes there should be a clearer set of objectives, and would like to have seen that the group has resolved the problems identified in its self-evaluation. However, the group is publishing at a good level and the group's work is extremely relevant for the Center. A strategic vision of where the group wants to be is not currently evident, which may reflect some uncertainty at the level of Center management, but it is clear that it is producing good quality science and is undertaking interesting and relevant projects.

Group 9

Short description of the group

Prof Langmoen is Professor of Neurosurgery and supervises a research group of 1 senior scientist, 2 post docs, 6 PhD students, and 4 TA/administrative staff.

The group's research focus is on human adult brain stem cells and the potential use of these cells for therapeutic applications (generation of DA neurons; potential application in Parkinson's disease). Another important research topic is the characterization of tumor-initiating cells in glioblastoma. Here, a clinical trial is ongoing which assesses the efficacy of potential vaccination against glioblastoma stem cells.

To summarise, the main areas of research are:

1. Stem cells from the adult human brain
2. Stem cells and brain cancer
3. Glioblastoma behavior in embryonic niches

Scientific Quality

Being apparently more clinically oriented, the group is maybe somewhat less productive in terms of first or last author publications than other groups of the Center. However, the group continues to publish solid studies, many of which are directly related to their work on human stem and progenitor cells.

The group is involved in several collaborations with other members of the Norwegian Center for Stem Cell Research as well as with a number of well-known international researchers and clinicians. However, the group's research topic is scientifically very competitive and the Center might want to consider how the group faces this challenge and in particular where the group sees its standing and association with other leaders in the field in the future.

The Committee felt that the role of the Senior Scientist in the group was unclear. The Committee questioned whether he is directly involved in the research carried out in the Langmoen lab (maybe supervises the actual experiments), or performs more independent research (although there are no last author papers yet with original data to point to this).

Conclusions and recommendations

The Committee has the impression that the neural cell project might be something that is slowly coming to an end and that the group is beginning to focus more on the tumour vaccination projects, which were presented very enthusiastically and showed clear relevance to the Center. This clinical group is an excellent addition to the Center and the Committee's overall impression is very positive.

Group 10

Short description of the group

The Moe lab is located at the Center for Eye Research (CER) which is headed by Prof Bjørn Nicolaissen and is co-located with Norwegian Eye Bank at the Department of Ophthalmology, Oslo University Hospital (OUH). The department, which is one of the largest of its kind in Scandinavia, employs about 50 MDs. The personnel working mainly on stem cell research at CER (2011) comprises a Senior Researcher, a PhD student, a medical student, a Research technician, and four PhD students working to different extents on stem cell related projects.

CER has a wide experience in cell culture procedures, tissue/organ culture for transplantation, characterization of cells/tissue by immunohistochemistry, electron microscopy and RT-PCR. Overall, the close association of CER with both clinics and operation theatres confers the ideal environment for translational research and clinical trials. The following projects are currently ongoing or planned:

1. Characterization of epigenetic regulation of genes known to regulate stemness and cell viability in adult human limbal epithelial stem cells (LESCs).
2. Development of protocol for cultivation of corneal endothelial cells for clinical transplantation to patients with endothelial cell dysfunction.
3. Characterization of stem-like cells in human uveal melanomas.
4. Characterization of retinal stem/progenitor cells in human eyes with proliferative diseases of the retina.
5. Prospective study enrolling patients for clinical transplantation of expanded autologous corneal epithelial cells to patients with limbal stem cell deficiency using a culture medium with human serum as single growth supplement.

Scientific Quality

The contribution of the group in the advancement of translational eye research and promotion of stem cell based therapies seems to be of great significance. Specifically, the group has recently described a method of expansion of autologous corneal epithelial cells using a culture medium with human serum as single growth supplement and transplanted to patients with limbal stem cell deficiency, and is the first describing that the adult human eye may harbour two different populations of neuroepithelial stem/progenitor cells. In addition, the group has provided evidence showing that the adult human iris pigment epithelium is unlikely to be a source of retinal stem/progenitor cells and has characterized the autophagic cell death in ARPE-19 cells by professional and non-professional phagocytes in vitro. Importantly, from the clinical point of view, CER/Department of Ophthalmology is currently offering transplantation of autologous *ex vivo* expanded human corneal epithelial cells to patients with limbal stem cell deficiency.

The most important international research collaborations of the group are those with: (a) the University of Debrecen, Hungary (Goran Petrovski, MD, PhD) for the characterization of corneal and retinal stem cells with special emphasis on cell death/viability, (b) Ofthalmologica del Mediterraneo, Valencia, Spain (Prof. Francisco J. Romero) for the identification of oxidative stress parameters in undifferentiated/differentiated corneal and retinal stem cells, and (c) the Institute for Klinik Medicin, Aarhus, Denmark (Prof. Jesper Hjortdal) for the preclinical and clinical isolation, propagation and characterization of corneal limbal stem cells.

The effectiveness of the collaborations of the group is evident from the number (12 in PubMed) and quality of recent publications related to stem cell research. In four of these publications, the PI signs as senior author or senior co-author. The PI has been also invited to give a number of lectures in national and international meetings, a fact that indicates the recognition of the group's contribution in the field of stem cell eye research.

Conclusions and recommendations

This group appears to be of paramount importance for the realization of one of the main objectives of the Center, namely the promotion of translational research and the application of stem cell-based therapies in the clinic. Notably, cornea diseases represent a major cause of blindness worldwide. The group displays active and effective collaborations at national and international level. The fruitful collaboration between Prof Moe and eye surgeons has already led to the successful transplantation of autologous limbar stem cells into patients, and the current and planned projects of the group are expected to strengthen further the position of OUH/UiO in the field of stem cell based therapies for ocular diseases at both national and international level. Overall, the Committee is very impressed by both the outputs and integration of this group.

Group 11

Short description of the group

The Kvalheim Group joined the Center relatively recently, in 2011. The group is located at the Department of Cellular Therapy, Radiumhospitalet. The staff at the Department of Cellular Therapy consists of two senior fellows, three post docs (two MDs), one senior researcher, and 14 technical scientists with special knowledge on GMP -production of cell products.

The group occupies one of the largest and best equipped GMP facilities for cellular therapy in Europe, prepares/delivers hematopoietic stem cells for allogeneic/autologous usage at OUH, and produces cell-based cancer vaccines for phase I/II studies with different types of cancer. The following projects are in progress:

1. Training and quality assessment of the clinical use of a cell separator system (Celution800/CRS system) in association with the development of methods for enumeration, phenotypic characterization and in vitro function of ADRCs.
2. A clinical phase I/II study in breast cancer patients using ADRCs isolated by the Celution800/CRS system. The Group will perform the quality assessment of the ADRCs and compare the results with the engraftment properties of the injected adipose tissue.
3. A clinical phase I/II study in chronic wounds using ADRCs from the Celution800/CRS system. The Group will perform the quality assessment of the cells used and study if there is a dose response effect of the cells used for treating the chronic wounds.
4. Preclinical and clinical studies on osteoradionecrosis. The group will initially use animal models to study if ADRCs or *ex vivo* expanded adipose stem cells can be used to treat radionecrosis and will proceed further to phase I/II studies in women with severe radionecrosis following local radiotherapy in the pelvic area, if the preclinical results are successful.
5. Study of the influence of hypoxia on expansion and differentiation of adipose tissue derived mesenchymal cells.

The strengths of the group are (a) the GMP facility which is reported to be one of the largest in Europe and (b) the existing experience on basic and translational research and cell-based (immuno)therapies. The group has national function on hematopoietic stem cell transplantation procedures and also prepares hematopoietic stem cells for export in collaboration with the National Bone Marrow Registry; therefore, it is evident that the group has tremendous experience in collecting, processing and delivering cells for clinical purposes. The group has established a number of research collaborations at the national level, namely with the Langmoen group for the brain tumors' immunotherapy program and with Dr Gullestad (Department of Surgery, Radiumhospitalet) for the tissue engineering program using adipose derived stem cells for breast reconstruction and chronic wounds.

Scientific Quality

At the international level, the group collaborates with Professor Schendel (Helmholtz Zentrum, Munich) for the immunotherapy program for prostate cancer as well as with other groups from Scandinavia and North America. The recent (2011-2012) collaborations of the group have resulted in a number of publications (12 in PubMed, including two papers in *Bone Marrow Transplant*, one in *Leukemia*, two in *PLoS One*, one in *Br J Haematol*, one in *Cancer Immunol Immunother* among others) whereas in two publications the PI is the senior author (*Eur J Haematol*, *Adv Pharmacol Sci*). Eleven of these publications are relevant to stem cell therapies.

The group is highly productive in the field of cell-based therapies with publications in highly respected international journals.

Conclusions and recommendations

The recruitment of the Kvalheim group to the Center is strategically and scientifically important in view of the Center's interest in developing translational projects and stem cell based clinical trials. The major strengths of the group, namely (a) the outstanding GMP facility (as was also evident from the site visit) and (b) the longstanding experience in isolation, expansion, delivery of stem cells and in cell-based therapies are of great importance for the development, expansion and promotion of translational and clinical projects. The longstanding existence of the Lab in the health care system seems to facilitate current collaborations and future plans for translational/clinical studies at the national level. Overall the Committee is again impressed by the level of output and integration into the Center. The Committee believes that coordination of stem-cell based clinical trials could be a future goal of this group. This appears feasible given the combination of the outstanding facility and PI's experience in the field.

Conclusions

The vast majority of the Center's original objectives have been/are being met, and given the short period since it was set up, the Center has done a good job of engaging with key individuals to stimulate stem cell research, particularly in the context of a limited budget. The Center should be considered to be a success in terms of scientific output and is moving towards expanding its portfolio of clinical trials, and again the level of funding should be taken into account.

Looking specifically at the relatively low level of funding and how it has affected the Center's development, it is evident that there are some issues about the capacity to establish a true international profile as a Center rather than as a network of individual PIs; and following on from that, the dissemination with which it was tasked. In light of the goal of creating an international profile, the Center should explore funding mechanisms with a view to (1) enhance capacity, (2) enhance the number of groups by supporting them with appropriate resource and (3) create a training programme.

In terms of internal management of the budget, the Center does have a financial model which is used to support its activities; but the model is fairly rigid and in some cases supports weaker groups. That being the case the Evaluation Committee considers that the Center management may wish to reconsider the funding model, and perhaps introduce an element of competition if possible.

The Committee strongly recommends the development of a postgraduate programme, as a training programme would generally be seen as integral to a center. This could bring the groups and early career scientists closer together, and would serve as a link to medical students. It is clear that the post docs and PhD students feel strongly engaged with the Center, and this commitment could be capitalised upon. As mentioned above, such a programme would help in raising the Center's profile.

A clear strategy for taking the Center forward in the future should be a priority, perhaps even a prerequisite for funding renewal – it may be that the use of a formal application format would help shape the focus of such a strategic plan. It should have clear plans for expansion and collaboration, productivity and profile as well as for engaging more with key stakeholders and funders.

Grading:

Overall, the activity in the Center was considered to be **very good,** especially in the light of the funding envelope and the relatively short period of existence of the Center. However, amongst the overall activity, small areas were considered to be weak and the Center is encouraged to consider how these areas might be strengthened if they are to remain part of the Center. It was also observed that there are clear areas of excellence, and these will stand the Center in good stead moving forward.

Committee member signatures

Alan R Clarke		Date: 22.10.2012
Lukas Sommer		Date: 22.10.2012
Timo Otonkoski		Date: 22.10.2012
Helen A Papadaki		Date: 22.10.2012

Appendix 1

Overview of evaluation meeting

The evaluation was held over two days at the Research Council and at relevant scientific and clinical venues in Oslo. The Evaluation Committee was able to see the research at the Radiumhospital and to visit the Center at Domus Medica in a site visit. During the second day the Committee was given a series of presentations and the opportunity to question group leaders and funding partners to assess the quality of the scientific output and to look at how the Center is meeting its objectives.

Day 1, 19 June 2012

Morning: Introduction and Committee discussion
Afternoon: Site visit

12:30-12:50	Welcome, run-through of the day's program, short presentation of Center
12:50-13:20	Tour of Center layout at Domus Medica and of the Core Facility
13:20-13:35	Discussion of plans for expansion of Core Facility activities
13:35-14:20	Discussion with group leaders at Domus Medica about ongoing/future activities Virtual presentation of whole animal imaging
14:20-14:50	Round table meeting with selected PhD students and postdocs
14:50-15:10	Walk to National Hospital, with short look at Ex vivo GMP facility, with mention of ongoing clinical trials
15:15-15:50	Tour of GMP facility at Dept of Cell Therapy, with mention of ongoing clinical trials
15.50-16:10	Discussion with PI at Radiumhospitalet about ongoing/future activities
16.30-17.30	Committee discussion – conclusion day 1 and preparations day

Day 2, 20 June 2012

09.30-10.00	Center presentation and hearing	Center management
10.15-11.15	Center groups I – presentations and hearing	Glover group, Collas group, Sullivan group, Klungland group, Bjørås group
11.30-12.10	Center groups II – presentations and hearing	Brinchmann group, Moskaug group, Myklebost group
13.10-13.45	Center groups III – presentations and hearing	Langmoen group, Moe group, Kvalheim group
14.00-14.45	Center and relevant institutions	Center management, South-Eastern Norway Regional Health Authority, Oslo University Hospital, University of Oslo
14.45-16.00	Committee discussion conclusions	

Appendix 2

Core group leaders of the Center

Group 1	Joel Glover
Group 2	Philippe Collas
Group 3	Gareth Sullivan
Group 4	Arne Klungland
Group 5	Magnar Bjørås
Group 6	Jan Brinchmann
Group 7	Jan Øivind Moskaug
Group 8	Ola Myklebost
Group 9	Iver Langmoen
Group 10	Morten Moe
Group 11	Gunnar Kvalheim