

Norwegian expertise in stem cell research

Opportunities for translational collaborative work...

The Norwegian Center for Stem Cell Research is a national organisation dedicated to basic and translational stem cell research, technical training, and public education. It was established in 2008 through a directive from the Norwegian Ministry of Health and is funded by the Norwegian Research Council's stem cell research programme. The centre is part of Oslo University Hospital, and is located at Domus Medica, Institute of Basic Medical Sciences, immediately adjacent to the hospital. The centre collaborates closely with another Norwegian stem cell consortium located in Oslo, the Cancer Stem Cell Innovation Center (CAST, csc.rr-research.no), whose main aim is the development of new therapeutic approaches to human cancer that target tumour stem cells.

The Norwegian Center for Stem Cell Research comprises eight core research groups, four located at Domus Medica and four located at Oslo University Hospital branches and the nearby Research Park. The centre's facilities at Domus Medica and Oslo University Hospital include a National Core Facility for the production, characterisation and storage of human pluripotent stem cells, a GMP-approved facility for the production of human cells for clinical applications, and a teaching lab for theoretical and practical courses in stem cell biology.

Basic and preclinical research

Mesenchymal stem cells

Research on human mesenchymal stem cells at the centre includes molecular and cellular studies of chondrogenesis and osteogenesis, the design of 3D scaffolds for cartilage implants, and epigenetic aspects of

mesenchymal stem cell differentiation, reprogramming and diseases.

Jan Brinchmann's group is developing therapies for focal lesions of hyaline cartilage and for ischemic heart disease. Earlier clinical trials have shown that treatment of focal cartilage lesions with autologous chondrocytes in suspension gives unsatisfactory results. The group is now developing 3D scaffolds of biomatrices and mesenchymal stem cells to develop a superior implant. To better understand the molecular biology of chondrocyte redifferentiation, the group is characterising profiles of RNA, microRNA, and cell surface and intracellular proteins in chondrocytes from articular cartilage, and developing alginate-based 3D scaffolds that promote chondrogenesis. The group is also studying 3D cocultures of endothelial and myogenic stem cells as a possible replacement therapy for ischemic heart disease.

Ola Myklebost's group at Oslo University Hospital-Radiumhospital studies the development and progression of human mesenchymal cancers (sarcomas) and has identified a number of proteins and pathways that may contribute to mesenchymal oncogenesis. His group is performing functional analyses of several of the candidate proteins, using a model system based on immortalised (telomerase-transduced) human bone marrow-derived stroma cells (iMSC). The iMSCs are non-tumorigenic, can differentiate to adipocytes and early osteocytes, and support B cell maturation.

Philippe Collas' group studies epigenetic mechanisms that control mesenchymal stem cell differentiation. The work is prompted by evidence that somatic stem cells may not be as

multipotent as previously thought. Since differentiation plasticity is dictated in large part by epigenetic status, that is, the nature and combinations of DNA methylation and histone modifications, the group is characterising epigenetic modifications, assessing epigenetic commitment to specific lineages *in vivo*, and exploring epigenetic plasticity using nuclear reprogramming strategies. Collas' group is also studying chromatin rearrangements and epigenetic states of mesenchymal stem cells in the context of nuclear envelope-linked diseases and of oncogenic transformations.

Jan Øivind Moskaug's group is comparing epigenetic modifications in mesenchymal stem cells induced to differentiate *in vitro* versus *in vivo* following transplantation into various animal tissues. Projects include the redox regulation of stem cell epigenetics and the role of cysteine metabolism in the regulation of adipose stem cell proliferation, maintenance and differentiation.

Ocular stem cells

Morten Moe's group at Oslo University Hospital-Ullevål is focusing on a variety of ocular-derived stem and progenitor cells. These include limbal stem cells that can be used to regenerate the cornea, retinal progenitor cells from the pigmented iris epithelium that may open a future scenario for autotransplantation to treat retinal diseases, and conjunctival stem cells.

Neural stem cells

Research on human neural stem cells at the centre focuses on the mechanisms that regulate normal neurogenesis as well as the use of neural stem cells to treat brain and spinal cord injuries and neurological diseases.

Iver Langmoen's group at Oslo University Hospital-National Hospital studies stem cells from the adult human brain. The group has isolated neural stem cells from adult human patients undergoing neurosurgery for epilepsy and shown that these have the capacity to differentiate into glia and functional neurons *in vitro*. They have injected the stem cells into immune-deficient rats and shown that they can survive, migrate into an ischemic lesion and differentiate into neurons. The group is now focusing on ways to genetically manipulate adult human neural stem cells to differentiate into specific neuronal phenotypes to facilitate cell replacement strategies for neurodegenerative diseases.

Joel Glover's group studies the regulation of neurogenesis during normal brain development and within regenerative niches in the embryo. The group has characterised the expression of progenitor- and neuron-specific transcription factors and growth factors during regulative regeneration of the spinal neural tube and showed that the normal patterning of spinal cord neuron types can be recapitulated. The group uses this regenerative scenario as a model system for xenotypic transplantation of human stem cells from various sources. These integrate into the spinal neural tissue where they can be subjected to functional characterisation as components of *in vivo* neural networks. The group also carries out *in vivo* stem cell tracking studies using fluorescent and MRI approaches.

Tumour stem cells

In addition to the work of Ola Mylebost's group on sarcomas, two other groups at the centre are studying tumour stem cells.

The main focus of Stefan Krauss' group, located at the Research Park, is the role of stem cell signalling pathways in development and cancer. His group has identified subpopulations of slow cycling cells (SCC) in specific adenocarcinomas and carcinomas. The SCC exhibit increased invasive

potential and morphological changes resembling the epithelial to mesenchymal transition (EMT) and exhibit selective up-regulation of specific components of the Hedgehog (Hh)/TGF beta and Wnt pathways. His group is interested in exploiting these findings to develop novel diagnostic and therapeutic approaches that target SSC.

The treatment of glioma is currently surgical, but because of excessive infiltration into healthy tissue, most gliomas are essentially non-resectable. Adjuvant radio- and chemotherapy may prolong life, but eventually most patients relapse. Iver Langmoen's group has cultured glioma stem cells and compared them to adult neural stem cells *in vitro*. Both exhibit the characteristic hallmarks of self-renewal and proliferation, but the glioma stem cells differentiate into tumour cells with abnormal morphology and nuclear atypia. The group is characterising gene and protein expression and cell signalling pathways in the glioma stem cells, as well as attempting prospective isolation using tumour-specific antigens.

Translational projects

The physical link between preclinical and clinical environments embodied by the centre provides exceptional opportunities for the promotion of translational research designed to bring stem cell-based treatments into the clinic. Several clinical trials are already in progress and others are in planning.

Stem cells for replacement of hyaline cartilage

Collaboration between Jan Brinchmann and orthopaedic surgeon Lars Engebretsen at Oslo University Hospital-Ullevål: the trial involves an effect-comparison between autologous chondrocytes and autologous mesenchymal stem cells directed to chondrogenesis in adult patients with knee cartilage damage.

Stem cells for corneal replacement

Collaboration between Morten Moe and eye surgeons Liv Drolsum and

Bjørn Nicolaisen at Oslo University Hospital-Ullevål: autologous limbal stem cells are being used to regenerate corneal tissue in patients with unilateral limbal stem cell deficiency.

Immunogenetic therapy targeting glioblastoma stem cells

Collaboration between Iver Langmoen and Jan Brinchmann and CAST member Gustav Gaudernack at Oslo University Hospital-Radiumhospital: glioblastoma cells from patient biopsies are being used as a source of mRNA with which the patient's dendritic cells are transfected to facilitate MHC-based presentation of glioblastoma antigens to the immune system.

Technological platforms

The centre maintains or collaborates with several advanced technological platforms, including the Norwegian Microarray Consortium in Oslo (high-throughput genomics, epigenomics, and deep sequencing), the FUGE MIC platform in Trondheim (MRI-based *in vivo* stem cell tracking), and a variety of in house functional imaging capabilities, including calcium and voltage sensitive dye-based functional neuronal imaging and photostimulation and non-invasive whole animal bioluminescence imaging.



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