Newsletter

CREATE Health - a Strategic Centre for Clinical Cancer Research at Lund University December-2009

CREATE Health

CREATE Health is a Strategic Centre for Clinical Cancer research located at the Biomedical Centre in Lund. The vision of CREATE Health is to use an integrative approach to develop novel diagnostics and therapeutics, based on identified markers and molecular signatures and to create a substantial social impact for the patient, through direct application of research for selection of an optimal, individually-based, cancer treatment. "After four years of successful research we have come very close and in some cases even fulfilled this vision. Also, as is quite evident from the present Newsletter we are in a unique position to further contribute to our translational goals for 2010", says professor Carl Borrebaeck, Program Director of CREATE Health.

Prediciton of local recurrence

Some patients with breast cancer develop local recurrence after breast-conservation surgery despite postoperative radiotherapy, whereas others remain free of local recurrence even in the absence of radiotherapy. Clinical parameters are insufficient for identifying these two groups of patients but researchers at CREATE Health have now identified a highly distinct gene expression profile for patients developing local recurrence after breast-conservation surgery despite radiotherapy. The profile is now being verified in further studies, and promising results suggests that this profile will be a most important tool in the decision making for surgery and adjuvant therapy. Read more in Niméus-Malmström et al. Breast Cancer Res. 2008;10(2) at http://dx.doi.org/10.1186/bcr1997

Breast Cell Protein Index

Cancer starts as the results of non-eliminated errors in the cell. There is a fine line between introducing enough errors to become a cancer cell and introducing too many and being eliminated - a system controlled by multiple DNA repair pathways in the cell that try to maintain the integrity of the genome. We have recently completed a large-scale combined genomics, transcriptomics, and proteomics study on 475 hereditary and sporadic breast tumours. We are currently performing an in-depth analysis of protein expression, post translational modification and intracellular localisation in the different tumours subgroups to create a Breast Cell Index. This will allow us to carry out focussed studies on changes in the expression of DNA repair pathways at diagnosis to predict the effectiveness of possible adjuvant radio- or systemic chemotherapy or to indicate a more focussed treatment, using a new generation of cancer drugs that act on DNA repair systems.

HIF2a - a target for therapy?

We previously showed that high hypoxia-inducable factor-2α (HIF-2α) protein levels associate with distant metastasis and predict poor outcome in neuroblastoma and breast cancer. Furthermore, hypoxia dedifferentiates cultured neuroblastoma and breast cancer cells toward stem cell-like phenotypes and in neuroblastoma, cells with high HIF-2α expression are immature, grow adjacent to blood vessels and express VEGF and we postulated that these cells are the tumor initiating/stem cells of neuroblastoma. Now Pietras et al. have shown that HIF-2α is high also in normoxic neural crest-like neuroblastoma tumor-initiating/stem cells (TICs) isolated from patient bone marrows and that these cells express VEGF, the primary pro-angiogenic factor in solid tumors. Knockdown of HIF-2α reduced VEGF expression and induced partial sympathetic neuronal differentiation when these TICs were grown *in vitro* under stem cell-promoting conditions. Xenograft tumors of HIF-2α-silenced cells were widely necrotic, poorly vascularized, and most importantly, resembled the bulk of tumor cells in clinical neuroblastomas by expressing additional sympathetic neuronal markers, whereas control tumors were immature, well-vascularized, and stroma-rich. Thus, HIF-2α maintains an undifferentiated state of neuroblastoma TICs. Because low differentiation is associated with poor outcome and angiogenesis is crucial for tumor growth, HIF-2αis an attractive target for neuroblastoma therapy. Read more in Pietras et al. Proc Natl Acad Sci USA 106 (2009) 16805-16810 at http://dx.doi.org/10.1073/pnas.0904606106

Why CREATE Health?

Bo Ahrén, Dean of Medical Faculty. I believe CREATE Health to be a cutting edge research environment. It has a proven and clear translational focus, which facilitate basic results to be rapidly brought into clinical use. Its high quality ensures the development of tools for future improved diagnostics and treatment of cancer.

Carsten Rose, Head of Oncology, SOK. Currently Skane is reorganizing its cancer health system, to reinforce treatment , education and research. In this process CREATE Health is playing not only a crucial role but also will be a prerequisite for the overall success of the up coming Comprehensive Cancer Center in Skane.

Anders Axelsson, Dean of LTH. CREATE Health is a positive role model, showing how strong research combining medicine and technology create synergies and significantly added value. 1 + 1 becomes 3! It sounds easy, but it is of course an advantage that the researchers within the centre are among the most award-winning at LTH.

Risk assessment of breast cancer patients using a blood sample

Serum contains thousands of different proteins and is consequently one of the richest sources of information. Furthermore, since the immune system is one of the earliest responders to disease, researches at CREATE Health have tried to decipher this information, using changes in expression patterns of immunoregulatory factors. This approach is based on so called antibody microarrays, where hundreds or thousand of antibodies are spotted on a small plastic chip, which is then subjected to a serum sample. The different protein expression patterns, formed by molecules derived from the tumor secretome, as well as from the systemic response against the tumor, are interpreted by the bioinformatic experts at the center. In a recent publication (Eur. J. Cancer) it was shown that serum from metastatic breast cancer patients displayed a different biomarker signature, as compared to healthy individuals. In a most recent and extended study, the risk of relapse after primary resection could be predicted in breast cancer patients, using a simple blood sample. In this case the analyte velocity, i.e. the rate several serum proteins changed over time, was used as the basis for prediction. In brief, this development promises to pave the way for a novel way of analyzing cancer patients.

Tumor Cell Search in blood

The Veridex Cell Search technique is being establish within CREATE Health for detection and molecular analysis of Circulating Tumor Cells (CTCs) in blood from patients with breast cancer, as well as in colorectal cancer and other malignancies. The number of CTCs in peripheral blood is correlated to disease progression in metastatic breast cancer and response to preoperative (neoadjuvant) treatment and can easily be followed during systemic treatment. The role of CTCs in primary breast cancer is not yet fully elucidated but can now be prospectively evaluated and related to clinical outcome. Characterization of captured CTCs will enrich research on the metastatic process, origin of disseminated cells, cancer cell clonality and the cancer stem cell concept. Dr Lisa Rydén working together with Carsten Rose and Åke Borg at CREATE Health, will be responsible for this project.

Acoustophoresis – a new tool for rapid antibody development in cancer research

Antibodies are key proteins used in research including cancer research. These proteins can specifically target molecules e.g. on cells and they may be used e.g. to treat or diagnose cancer. Such antibodies are often developed by genetic engineering technology. To further facilitate the development of such antibodies in the laboratory we have now exploited an acoustic phenomenon, acoustophoresis. This technology now greatly facilitates the process through which such antibodies can be isolated. It holds the potential to be used in high through-put generation of antibodies, a process of vital importance to meet the challenges of modern biomedicine. It thus promises to improve the generation of antibodies that will translate into improved clinical research and clinical practice. For more information, please review http://dx.doi.org/10.1111/j.1742-4658.2008.06691.x.

Treatment response and prognosis

The CREATE Health researcher Anna-Maria Larsson has recently published that the expression of the Erthropoietin receptor (EPOR) correlates to tamoxifen response and prognosis in breast cancer. EPOR is abundantly expressed in breast cancer specimens. The high expression of EPOR is related to an impaired tamoxifen response in ER+/PR+ tumors and to improved survival in untreated patients. This suggests that EPOR expression in breast cancer do affect tumor behavior. Read more in Larsson et al. Clin Cancer Res 15 (2009) 5552-5559 at http://dx.doi.org/10.1158/1078-0432.CCR-08-3014

New Research

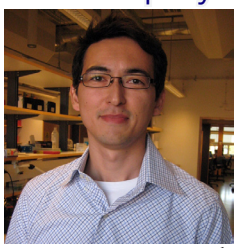
Sven Påhlman has received 1.5 Msek/year over 3 years from Cancerfonden for the HIF2α and EPOR-projects.

The International Cancer Genome Consortium (ICGC) coordinated from the Welcome Trust Sanger Center in Cambridge, was recently granted by the EC 7th FP for a project (BASIS) that will conduct a complete mapping of the cancer cell genome in 500 estrogen-receptor positive breast tumors. The project will utilize state-of-the-art microarray and next-generation sequencing technology for analysis of gene expression, genomic and epigenetic alterations. The project will partly be carried out at CREATE Health (Åke Borg), using the service and platforms available at the SCIBLU Genomics facility.

Thesis on micro- and noncoding RNA

MicroRNAs have recently emerged as important players in tumor development. These ~22 nucleotide small RNAs can act as oncogenes or tumour suppressors by post-transcriptional regulation of the expression of protein-coding genes. Helena Persson, Dept Oncology in Lund, studies the functional impact of microRNAs in breast cancer and used next-generation sequencing to chart the small RNA transcriptome of normal and tumour breast tissue. Several hundred new microRNAs were identified, genes that could have potentially interesting roles in tumourigenesis. The research has also shown the existence of a new class of small RNAs that regulate gene expression using mechanisms similar to miRNAs (Nature Cell Biology, 2009). Helena Persson is working together with Carlos Rovira (thesis supervisor), Anders Kvist and Åke Borg at CREATE Health.

New employees



Lao Saal, MD, PhD has joined the CREATE Health team after 9 years at Columbia University, New York. He is now building up a research group around translational breast cancer research with a focus on the development of personalized therapeutic strategies to attack the particular constellation of cancer mutations and pathways that are active in a patient's tumor. This work involves a comprehensive analysis of patterns of gene expression, gene mutations, gene amplifications, and gene deletions in human breast tumors combined with functional and pharmacogenetic studies in model systems.

Mattias Ohlsson, PhD and ***Patrik Eden***, PhD, Department of Theoretical Physics, have recently re-joined CREATE Health. Mattias is working on prediction models in general but with a special focus on protein profiling in breast cancer. Patrik is working on mathematical models in the stemcell-paradigm of glioma and with the project concerning profiling of transcriptional factors in lymphoma.