CREATE Health

A Strategic Centre for Translational Cancer Research
Lund University

EVERY
TEN MINUTES
SOMEONE GETS
CANCER

Our recent achievements

During the recent five years CREATE Health has focused on biomarkers mainly for cancer diagnosis and prognosis. We are now entering into a new era when the mission is to transfer our knowledge to benefit the patients and also to explore the full potential of advanced translational science.

Identified serum biomarker signatures that allow risk classification of breast cancer patients regarding tumor recurrence.

Developed a high-through-put and sensitive protein affinity extraction platform, which directly interfaces with MALDI. This offers new means for rapid screening of biomarkers in complex biofluids.

Discovered serum biomarker signatures that identify pancreatic cancer, forming the basis for an early diagnostic test.

Identified an association between the expression of EPO receptor and Tamoxifen response in breast cancer patients.

Identified protein signatures that define five main types of breast cancer.

Discovered new genomic breast tumor subtypes on whole-genome patterns of DNA aberrations.

Identified gene expression subtypes with correlation to prognosis in stage IV malignant melanoma.

Discovered SOX11 to be a novel histological marker for mantle cell lymphoma forming the basis for an improved clinical diagnosis.

Developed a method to monitor the state of DNA repair pathways, which opens up for defining targets for therapeutic interventions.

Discovered specific DNA methylation patterns in different subtypes of breast cancer.

Discovered a prognostic gene expression signature from sub-classification of HER2 amplified/expressing breast cancers.

Designed a novel serum-based clinical test for ovarian cancer, which makes it possible to distinguish between benign, malignant and 'borderline' cases.

Identified HIF-2α as a therapeutic target for tumor stem cells of neurally derived tumors.

Identified SOX11 as a potential tumor suppressor gene inmantle cell lymphoma and ovarian cancer.

CREATE Health is a Strategic Centre for Translational Cancer Research, funded mainly by the Swedish Foundation for Strategic Research, VINNOVA, Knut and Alice Wallenberg Foundation and Lund University. The centre is unique in its kind, integrating researchers from the Faculties of Medicine, Science and Engineering (LTH) with researchers and clinicians from Skåne University Hospital in facilities with advanced "omics" platforms, superbly equipped for translational cancer research.

CREATE Health is the acronym for Cancer Research using Emerging Advanced Technologies for Health.

Lund University and Biomedical Center
Lund University was founded in 1666. Today it is the strongest research university in Sweden and harbors approximately 46 000 students. Internationally renowned research is carried out in several strategic research fields, including cancer, nanotechnology, diabetes and stem cell biology. The Biomedical Center (BMC), located adjacent to Skåne University Hospital, is the single largest unit for research and teaching. Over one hundred research groups work together in this inspiring environment, encompassing a total of 1250 investigators and students.

The CREATE Health team

CREATE Health is formed by 7 research groups together focussing on 5 main research areas.

Carl Borrebaeck
Program Director
Cancer Immunology

Dr Ulrika Ringdahl
Research Coordinator

Carsten Peterson
Bioinformatics

Peter James
Proteomics

Translational Research

To improve human health, scientific discoveries must be translated into practical applications. In translational research the aim is to identify clinical relevant problems, solve them, and translate the result into practical applications, for the benefit of the patients. The translation of basic discoveries to the clinic is in general slow, expensive, and time demanding as it requires multi-disciplinary collaborations, involving basic researchers, clinicians, pathologists, patients, and regulatory bodies. Cancer mortality has stayed up, despite recent advances in understanding the molecular pathogenesis of these diseases. The focus within CREATE Health is to address these problems by integrating cutting-edge technologies with clinical needs, and to translate laboratory findings into improved outcome for the patients.

Åke Borg
Oncogenomics

Sven Påhlman
Tumor biology

Carsten Rose
Deputy Program Director
Clinical Research Unit Oncology

Thomas Laurell
Nanobiotechnology

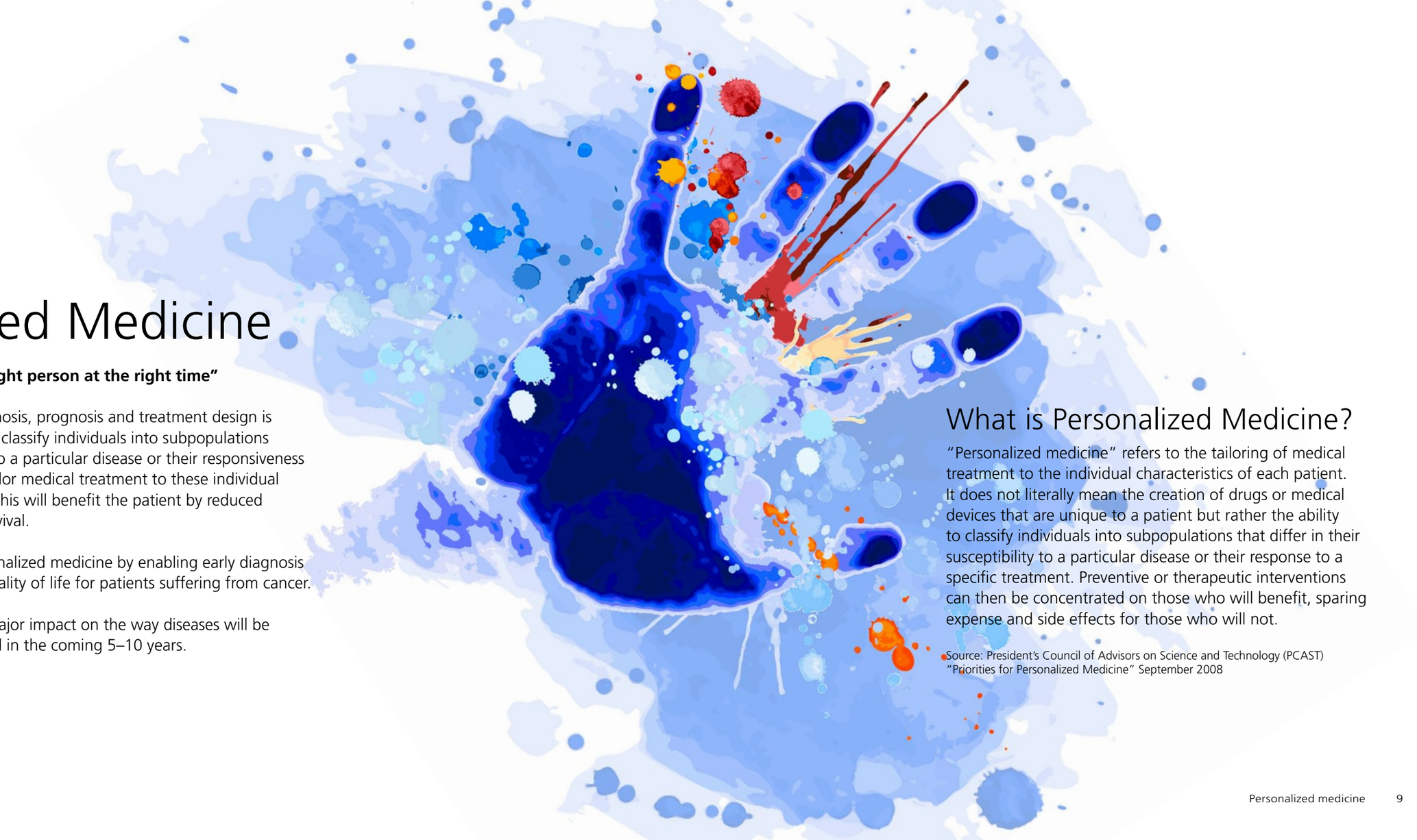
Personalized Medicine

“The right treatment to the right person at the right time”

The need for individualized diagnosis, prognosis and treatment design is imperative. To have the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their responsiveness to a specific treatment and to tailor medical treatment to these individual characteristics is highly desired. This will benefit the patient by reduced overtreatment and increased survival.

CREATE Health focuses on personalized medicine by enabling early diagnosis and prognosis to improve the quality of life for patients suffering from cancer.

CREATE Health aims to have a major impact on the way diseases will be diagnosed, treated and managed in the coming 5–10 years.



What is Personalized Medicine?

“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Source: President’s Council of Advisors on Science and Technology (PCAST) “Priorities for Personalized Medicine” September 2008

The fingerprint of Breast Cancer

Individualized therapy requires a fingerprint of each tumor. This was pointed out already by Hippocrates who said: **"It's far more important to know what person the disease has than what disease the person has."**

Disease characterization
Breast Cancer is one of the most common diseases among women. In Sweden alone, more than 4 women die every day from breast cancer. Even though the five-year survival in breast cancer today is more than 80 %, the prognosis for patients with recurring disease (1 out of five) is still very poor. Thus, one of the main focuses within CREATE Health is **"The Breast Cancer Initiative"** where the aim is to solve clinically relevant problems regarding diagnosis, prognosis and treatment decisions. This is done by characterizing the genome, transcriptome and proteome of each breast tumor.

Using genomic and transcriptome analysis we are:

- developing a faster and more comprehensive method for germ line mutation screening in familial breast cancer, including both high- and moderate-risk susceptibility genes. This may provide an explanation of a large fraction of familial cases that today are negative in BRCA1 and BRCA2 analysis, and improve possibilities for screening and early diagnosis, or disease prevention.
- studying the genetic heterogeneity of HER2+ tumors. Tumors expressing this marker are associated with poor prognosis, although some respond to HER2-targeted treatment. If we could select those that benefit from these targeted drugs, it would optimize the use of expensive therapy and allow a choice of more effective drugs.
- identifying tumor markers to monitor treatment efficacy and detect disease recurrence before symptoms occur. Using genome-wide sequencing we will identify and precisely map inter- and intra-chromosomal rearrangements. This will enable design of highly specific PCR-based assays for sensitive detection of the individual rearrangements in circulating tumor-DNA.

The fingerprint of Breast Cancer

Using proteomic analysis we are:

- developing a serum-based assay aiming at predicting the risk for distant recurrences, monitor therapy efficacy and aiding in treatment selection for breast cancer patients. By analyzing the molecular serum portraits it seems for the first time possible to assess the risk in each patient for a future tumor relapse, i.e. metastatic disease. This would be an evidence-based tool, which allows the clinicians to fine tune therapy.
- developing the **Breast Cancer Index** (BCI) of all proteins and their modifications that occur in breast tissue, both normal and diseased. This will enable us to rapidly develop assays for any new marker protein that is identified. These assays can be implemented in a clinical test than can identify and quantitate 300 proteins within 30 minutes.
- developing the **Breast Cancer Atlas** (BCA) that shows where a protein is normally found in a cell and how this changes with disease. Many mutations result in a change in cellular location and hence function of the protein which subsequently may lead to cancer. The BCA will enable us to detect changes that cannot be seen by normal protein analysis methods.
- developing mass **spectrometric assays** (MRM) using the BCI to cover all DNA repair pathways including approximately 250 proteins and possibly 500 phosphorylation sites. This will enable a new approach to define appropriate treatments.

Improve early diagnosis

During the last 10 years, technologies based on multiplexed serum analysis have been developed within CREATE Health. Instead of measuring only one or two serum proteins the goal has been to measure hundreds at the same time. The rationale behind this is to decipher more of the information harbored in a serum sample.

Pancreatic cancer
Pancreatic cancer is the 14th most common, but the 4th most deadly, form of cancer, with a median survival time of only 3–4 months. The short survival time can be explained by the fact that the disease often is diagnosed at a very late stage, when only 15 % are operable. We have, using antibody microarrays, identified a biomarker signature that can distinguish between pancreatic cancer patients and healthy individuals. Even more important, it has the ability to distinguish cancer from differential diagnoses, e.g. inflammation in the pancreas. Based on these findings, we aim to develop and implement screening procedures for high-risk patients e.g. patients with a known family history of pancreatic cancer or individuals (50+ years) with new-onset diabetes. Our aim is to identify individuals with pancreatic cancer at an early stage, when the tumor is still operable.

Prostate cancer
Today, one of the biomarkers used to diagnose prostate cancer is PSA (prostate specific antigen). However, subsequent invasive examination shows that only 25–30 % of patients with elevated levels of PSA suffer from prostate cancer. Our most recent project aims to identify, using a simple blood test, patients with elevated PSA that do not suffer from cancer, to optimize the need for more expensive and often painful examinations.

Autoimmune disease
The antibody microarray platform developed within CREATE Health has been shown to be applicable also in other diseases. We have shown that flares in the autoimmune disease SLE (systemic lupus erythematosus) is associated with specific biomarker signatures, which could aid in deciding treatment strategies.

The Cancer Diagnostic Clinic

Recent technological advances have made it possible to carry out advanced genomic and proteomic analyses within a very short period of time. This provides not only an opportunity to fast, at-time-of surgery, treatment decision-making, cutting investigations from days, weeks to hours but also the opportunity to run advanced analyses not possible to perform on frozen/ preserved tissues. CREATE Health, together with the Regional Cancer Center South (RCC Syd), is therefore establishing a Cancer Diagnostic Clinic at the site of the operating theater.

When a blood sample is drawn, a tumor removed, or a needle biopsy performed, the cells will immediately be preserved in an instrument that rapidly kills all enzyme activity, while retaining histological structure. Thus, intact nucleic acids and proteins can be isolated and analyzed using advanced microarray, sequencing or mass spectrometry methods. Within hours the Cancer Diagnostic Clinic will deliver an advanced cancer profile including:

- advanced cancer diagnosis and subtype classification
- sentinel node status, extent of lymphogenic spread and confirmation of margins
- readout of degree of malignancy and tumor aggressiveness
- a measure of residual disease

All these data will be available while the patient is still at the clinic allowing for better stratification and treatment decisions.

Main functions

The Cancer Diagnostic Clinic will be the first on-site omics laboratory. The two main functions are to:

- provide an advanced, rapid and flexible readout of samples at the time of surgery, to aid the surgeon in state of invasion of the tumor thus minimizing the need for additional surgery.
- facilitate the work of the multi professional team of physicians at the clinicopathological meetings in further treatment decisions.

Identifying New Cell bound Markers for Therapy

The identification of **Cancer Stem Cells** (CSCs) or Tumor Initiating Cells has been a breakthrough in understanding tumor responsiveness, or lack thereof, to therapy. These cells are poorly defined in most tumor types, but based on findings in hematopoietic and brain tumors they are phenotypically distinct from non-malignant stem cells and bulk tumor cells. Importantly, tumor stem cells appear to be more resistant than the tumor bulk to conventional treatment strategies such as chemotherapy or radiation. Understanding the molecular biology of cancer stem cells will be crucial for developing more effective cancer treatments.

Phenotyping CSCs for specific treatment

CREATE Health researchers are well on the way to define CSC populations and their markers focusing on subsequent, small molecules and antibody-based therapy. This involves advanced in vitro cultures, orthotropic xenograft tumor models, proteomics and antibody engineering technologies, to reach novel therapy modality for CSCs. In addition, we have shown that CSCs have stem cell-like properties with an immature phenotype, capacity for self-renewal and pluripotency. Furthermore, the CSCs pool might be phenotypically heterogeneous also within a given tumor case. Our aim is to develop routine methodologies to isolate and propagate CSCs from surgical biopsies of primary tumor, bone marrow metastases, pleura and ascites fluids in case of breast cancer, hematopoietic, kidney and neural tumors. The isolates will form the basis for identification of treatment targets including surface bound protein markers suitable for antibody-based therapy.

Defining hypoxic biomarker

Cell surface proteins translated from hypoxia-driven genes are highly attractive as targets for cancer treatment. Membrane bound and integral proteins have previously been difficult to analyze, but recently a methodological breakthrough was made within CREATE Health. For the first time, we are able to profile plasma membrane proteins isolated from normoxic and hypoxic regions of tumors as well as isolated CSCs.

Technology and Bioinformatics Initiatives

Development of new technology and tools has been a crucial part of CREATE Health under the parole **"technology for the benefit of the patient"**, and is one of our success factors. If the health care systems can be provided with tools to diagnose or predict disease early, there would be a tremendous opportunity to reduce cancer prevalence in the future.

Compound Tissue Imaging

Precise readouts defining the cellular distributions of administered drugs is a much desired, but difficult task. Compound Tissue Imaging (CTI) is a technology development program initiated in collaboration with Professor Marko-Varga. This program aims at localizing unlabeled drugs and drug metabolites in tissues, by matrix-assisted laser desorption/ionisation i.e. mass spectrometric imaging. For the first time, drug levels can now be quantified directly in tumor tissue sections with high sensitivity. Tissue imaging at surgery will give an accurate picture to be made of how deep the chemotherapy drug(s) penetrated the tumor and hence how the most effective treatment should be selected.

Global Proteome Survey

The limitations with affinity proteomics today is the number of antibodies capturing serum proteins in the assay. To circumvent this we are developing a new technique, GPS (Global Proteome Survey), using so called, Context Independent Motif Specific (CIMS) antibodies. The principle is to define peptide motifs (four to six amino acids), commonly found in proteins of the human serum proteome. Using a bioinformatics approach, each motif could be selected in such a way that it defines anything from 10 to 100 different proteins. In this way, close to 50 % of the human non-redundant proteome could be analyzed by 100 recombinant antibodies. Furthermore, it would be applicable to any proteome and protein classes, including membrane-bound proteins, and not biased to abundant proteins. The final antigen identification will be performed by tandem MS/MS.

Gene-expression-based outcome

CREATE Health has also developed a new web-based and user-friendly gene-expression-based outcome (GOBO) tool. GOBO allows a range of different analyses to be performed including: 1) rapid assessment of gene expression levels in subgroups of breast tumors and cell lines, 2) identification of co-expressed genes, 3) association with outcome for gene expression levels of single genes, sets of genes, or gene signatures in multiple subgroups of the merged breast cancer data set. GOBO will be ideal for clinical and preclinical scientists for hypothesis-generation and fast evaluation of new biomarkers in breast cancer and, after further development, also other malignant diseases.

CREATE Health´s vision is to create an integrative approach to develop novel diagnostics, prognostics and therapeutics based on identified markers, which will create a substantial social impact for the patient, through selection of Individually-based, cancer treatment.

The innovations created within CREATE Health are diagnostic and therapeutic products, focusing on clinical solutions, for the benefit of the patients and society. Our approach is translational in the sense that it starts from a specific need, identified by our clinical partners. We use novel technological approaches to find relevant solutions, which consequently can be implemented into the clinic with much shorter lead times. We aim to provide individualized and improved therapeutic efficacy, based on the ability to select which patient benefits from a particular treatment. This will reduce costs for health care providers and society, and create innovations leading to novel business opportunities.

From left to right: Carsten Peterson, Carl Borrebaeck, Åke Borg, Carsten Rose, Peter James, Ulrika Ringdahl, Marianne Olsson, Thomas Laurell and Sven Påhlman.

Photo: Goranmedia Production

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CREATE Health is a collaborative endeavor between LTH – Faculty of Engineering, Faculty of Medicine, Faculty of Science

www.createhealth.lth.se