Molecular mechanisms involved in organ-specific metastatic growth processes in breast cancer

Keywords
Breast cancer, metastasis, gene profiling, organ-specific metastasis

Summary
Breast cancer is often accompanied by the development of metastases, particularly in bone, liver, lung, brain or lymph node tissues. The metastases cause a range of symptoms ultimately leading to increased morbidity and mortality. Metastasis is a complex multi-step process and little is known about the molecular mechanisms that direct metastases to form in certain organs in different patients. MetaBre will analyse differential gene and protein expression in primary breast cancers and metastases in order to identify the molecules involved in organ-specificity. These will be investigated as potential novel therapeutic targets and biomarkers for prognosis of organ-specific metastasis in breast cancer patients. MetaBre has research activities aimed at:

• gene profiling and proteomic analysis to identify new molecular targets
• functional analysis of new targets in in vitro and in vivo models
• mechanisms of angiogenesis and invasion
• organ-cancer cell interactions
• development of new pharmacological therapies and diagnostic techniques
• preliminary clinical trials.

MetaBre is using state of the art AffymetrixTM technology for gene profiling and will develop in vivo models for validation of molecular targets and screening of therapeutic molecules. Metastases will be detected in vivo with optical imaging of cancer cells transfected with optical reporter genes, and magnetic resonance techniques.

Problem
Metastasis in breast cancer is a complex multi-step process. Genetic changes in tumour cells give rise to aggressive metastatic cells, and their subsequent development in specific sites depends on a web of cellular and matrix interactions within each organ microenvironment. Understanding the key molecular mechanisms of these metastatic processes can lead to improvements in the prognosis and treatment of breast cancer patients.

Aim
MetaBre aims to discover new gene and protein markers, which can be used for diagnosis as a signature of metastasis to specific organs, and also be targeted for therapy. To achieve this, the partners will analyse samples of breast primary tumours and metastases, with due care of the ethical aspects, as well as established breast cancer cell lines. MetaBre will also study genes and molecules that are already suspected of involvement in metastasis. This builds on previous work of the partners and will enhance understanding of the role of these molecules in metastasis, as well as identifying new opportunities for development of therapies and diagnostic methods.
MetaBre aims to generate the following results:
• Identification and characterisation of molecular signatures including serum biomarkers for diagnosis of organ-specific metastatic potential in breast cancer
• Identification of new molecular targets for inhibition of angiogenesis, invasion of metastatic cells, and growth of metastases in specific organs
• Development of a catalogued collection of primary tumours, metastases and related samples
• Development of new clinically relevant in vitro and in vivo models for study of metastatic disease in breast cancer
• Development of diagnostic techniques and identification of at least one novel pharmacological therapy.

Potential applications
The project will identify novel molecular mechanisms that may be targeted for therapy of metastatic disease in breast cancer. The genes related to organ-specific metastasis may be used as biomarkers for stratification of breast cancer patients according to the risk of developing metastases, either through gene expression microarray analysis of primary tumours, or through measurement of those markers present in serum.

Project website: www.metabre.org