Title of the project

Risk stratification in drug resistant breast cancer using clinical systems biology approach: A pilot study

Category (translational/bioengineering/biodesign): Translational

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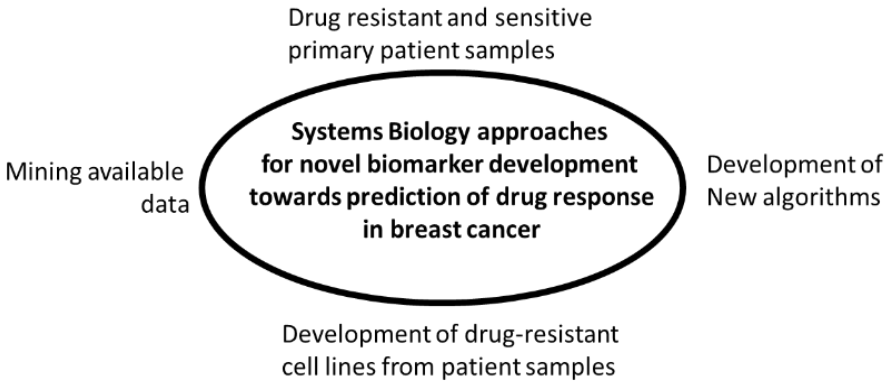
Statement of research

Resistance to chemotherapy is a serious problem in the management of breast cancer. Resistance can be intrinsic or may develop over the course of the treatment. It is a complex phenomenon involving participation of different mechanisms and is further complicated by genetic/physiological differences across patients resulting in differences in response to the same therapy. Therefore, certain drugs are seen to work better in a particular class of breast cancers than others. Prior knowledge of a patient's predisposition towards developing resistance can hence be of immense help in ultimately deciding a suitable chemotherapy regimen. The probability of positive or negative response to therapy can be predicted from the extent of similarity between the gene expression profiles of therapy-sensitive and therapy-resistant individuals. Differences in gene expression profiles can result in different metabolic and signalling activities in different patients which can be systematically analyzed using systems biology approaches. To this end, using genome scale interaction networks and gene expression data of sensitive and resistant breast cancers, we seek to identify a gene signature from that can predict which samples are likely to respond to chemotherapy. For this, we will obtain patients' tumour resection samples prior to chemotherapy, test sensitivity to chemotherapy in the laboratory, attempt to evolve them as well as breast cancer derived cell lines into resistant varieties and study the transcriptomic patterns between sensitive and resistant samples. Using network approaches, we will study genome-wide protein-protein interaction networks in both categories and identify the set of perturbations between the two in an unbiased manner. Using further network analyses, we will compute a shortlist of most influential genes among them and derive hypotheses about putative mechanisms that may provide insights into effectiveness of therapy. We will verify some of the selected mechanisms experimentally by studying their effect on metabolism and signaling. We will evaluate the identified markers for their ability to stratify risk in an independent patient cohort. In this phase, we plan to carry out a pilot study involving a few patients in the discovery cohort and a few more in the pilot validation cohort.



Systems biology based novel biomarker discovery to aid breast cancer treatment