**Novel Combination Therapy for Ductal Carcinoma In Situ**

Project Number: 1601

Principal Investigator: Prof. Yosef Yarden

Department: Biological Regulation

**Summary**

A potent combination therapy against non-invasive breast cancer

Breast cancer is the most common cancer in females. Among the different subtypes of breast cancer, ductal carcinoma in situ (DCIS) represents an intermediate step between normal breast tissue and invasive breast cancer. Currently, about 25% of breast cancers that are diagnosed in the US are DCIS. DCIS is commonly treated by surgical intervention followed by adjuvant radiation therapy. However, a significant fraction of the DCIS lesions, which display HER2 gene amplification, are associated with increased relapse rate following surgery. Therefore, in cases of HER2-overexpressing DCIS a molecularly targeted therapy might be necessary for complete eradication of microscopic remnants following surgical tumor removal. The current technology presents an potential DCIS therapeutic strategy that collectively targets the functionally linked HER2 and Notch pathways.

**Technology's Essence**

The HER2/Neu oncogene, a member of the HER/ErbB signaling network, encodes a receptor-like tyrosine kinase, whose overexpression in breast cancer predicts poor prognosis and resistance to conventional therapies. Pre-invasive lesions, such as DCIS, overexpress HER2 at higher frequency than invasive ones. Another signal transduction pathway critical for breast cancer progression comprises Notch family receptors and their membrane-bound ligands. In the current technology, a team of researchers from the Weizmann Institute of Science uncovered that overexpression of HER2 in a novel experimental model of DCIS leads to transcriptional upregulation of Notch pathway components, resulting in enhanced tumor cell survival and proliferation. Combined treatment with HER2 and Notch pathway inhibitors resulted in decreased proliferative and tumorigenic potential. The current technology offers specific and combined targeting of HER2 and Notch pathways for DCIS treatment. This approach may also be tailored for DCIS patients with enhanced co-expression of HER2 and Notch.

**Applications**

* Combination therapy for DCIS patients following surgical tumor removal.
* Classification of DCIS patients according to HER2 Notch activation patterns to identify patients with increased risk of relapse after surgery.
* Diagnostic antibodies to NRG4 to screen for cancer cell subtypes that express/over-express NRG4.
* NRG4 fusion conjugates, where NRG4 acts as a vehicle to direct the conjugate to cells specifically expressing the receptor ErbB4.

**Advantages**

* Targeted cancer therapies will give doctors a better way to tailor cancer treatment.
* Targeted cancer therapies hold the promise of being more selective, thus harming fewer normal cells, reducing side effects, and improving the quality of life.
* The proposed treatment strategy may prove beneficial in DCIS patients with poor prognosis.