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

**A Novel Method for Treating Ductal Carcinoma in situ by Targeting the HER2 and Notch Pathways**

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| **Project Number:** | 1601 |
| **Principal Investigator:** | Prof. Yosef Yarden |
| **Patent Status:** | Pending |

**Overview**

**A novel method for treating ductal carcinoma in situ (DCIS) by targeting the HER2 and Notch pathways using anti-HER2 antibodies and kinase inhibitors.**

**Background and Unmet Need**

Invasive ductal carcinoma (IDC), is the most common type of breast cancer. About 80% of all breast cancers are invasive ductal carcinomas. One aggressive subtype, comprising 20–25% of all invasive ductal carcinomas, is characterized by over-expression of the HER2 oncoprotein. Commonly, ductal carcinoma in situ (DCIS) is recognized as a precursor of IDC, the key difference being that in DCIS the malignant cells have not invaded through basement membranes.

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, there is a need for a molecularly targeted therapy in cases of HER2-overexpressing DCIS for complete eradication following surgical tumor removal**. The current technology presents an potential DCIS therapeutic strategy that collectively targets the functionally linked HER2 and Notch pathways.

**The Technology**

HER2 is a member of the human epidermal growth factor receptor family. Over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. Once activated, HER2 can instigate a number of potent signaling pathways, leading to unregulated cell proliferation.

Another signal transduction pathway critical for breast cancer progression, comprises Notch

family receptors and their membrane-bound ligands which play fundamental roles

in self-renewal and proliferation of cells in the mammary gland.

Prof. Yarden and his team have discovered an association between the notchinduced pathway and overexpression of HER2. Specifically, overexpressed HER2 transcriptionally up-regulates several components of the Notch pathway. The team’s findings imply that HER2-Notch3

collaboration is required during early steps of mammary tumorigenesis and therefore a combined treatment targeting both pathways could have a better therapeutic outcome for HER2-overexpressing DCIS.

***Advantages and Applications***

* A novel treatment strategy that combine anti-HER2 antibodies with Notch antagonists
* Classification of DCIS patients according to HER2 Notch activation patterns to identify patients with increased risk of relapse after surgery.

**Development Status**

The team of Prof. Yarden have generated an *in-vitro* model of DCIS using a three-dimensional culture system comprised of immortalized human mammary cells. Using this model the team have made several key findings: 1. HER2 over-expressing cells also up-regulate Notch pathway components. 2. These cells do not go through programed cell death when becoming detached from the extracellular matrix. 3. HER2 over-expressing cells form lumen-filled spheroids whereas normal cells do not. These phenotypes were reversed when the cells were treated with either anti-HER2 antibodies or kinase inhibitors that target HER2 downstream proteins. Additionally, Notch3 knockdown-cells also did not exhibit these phenotypes even when HER2 is over expressed, indicating that Notch mediates the effects of HER2 on luminal filling.

To further support the claim that Notch is important for the HER2 phenotype the team have shown in transgenic mice carrying an activated form of the HER2 oncogene also over-express Notch3.

To confirm the relevance of the Notch3-HER2 connection to human breast cancer the team has also analyzed two clinical datasets of approximately 200 breast cancer patients. In line with the in vitro expression data Notch3 presented highly significant correlations with HER2 expression, both at the RNA level and the protein levels.

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