

## **A comprehensive analysis of Trastuzumab-induced signaling suggests the role of HER2 in several cell processes and highlights alternative targets for HER2-positive breast cancer therapy**

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20-30% of breast cancers display a ErbB2 (HER2) gene amplification or protein over-expression. HER2 is constitutively activated receptor belonging to the ErbB RTK family, which comprises also ErbB1 (EGFR or HER1), ErbB3 (HER3), and ErbB4 (HER4). HER2 triggers the activation of ERK1/2 MAPK and AKT signaling pathways. Although most of our knowledge on HER2 is mutated from EGFR (1-3), due to the absence of an HER2 ligand, the use of drugs targeting HER2 (4) has shed light in its specific role in endocytosis and trafficking. Trastuzumab (TZ, a humanized inhibitory antibody to HER2) is a front line drug for the therapy of HER2-positive breast cancers, and has improved clinical course and overall prognosis; however it faces frequent primary or acquired resistance involving the AKT pathway. Our goal is to dissect the molecular events downstream TZ treatment and identify key hits for an alternative target therapy bypassing the resistance. TZ treatment induces the activation of the ERK1/2 signaling pathway and the downregulation of AKT phosphorylation. Our results demonstrate for the first time that ERK1/2 phosphorylation drives the signaling leading to the AKT de-phosphorylation. We have excluded a role for the kinase pathway controlling AKT phosphorylation identifying a role for Ser/Thr phosphatases. This pathway is uniquely activated by the TZ-HER2 interaction. Therefore we are now pursuing the identification of a key regulator of this pathway to screen a library of orphan drugs in search of a putative hit candidate. Beside the potential interest in the identification of alternative therapeutic strategies to HER2 positive breast cancer, the use of TZ in our studies has highlighted the role of HER2 in controlling new and relevant physiological cell processes, such as endocytosis and invasion

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### **References**

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