# ABSTRACT

Breast cancer (BCa) is the leading cause of women death worldwide. The members of ErbB family of transmembrane receptor tyrosine kinases (RTKs) have been implicated in progression of several human carcinomas. Overexpression of ErbB2 has been reported in 20-30% breast cancer patients and is associated with poor clinical outcome. Herceptin (Trastuzumab), a monoclonal antibody, is used for the treatment of ErbB2-positive BCa. However, approximately 60% of patients do not respond to this therapy and most of the initial responders develop resistance within one year. There are high expectations with Pertuzumab recently introduced for adjuvant therapy. *In vivo* and *in vitro* studies indicated a synergistic effect of Herceptin and Pertuzumab antibodies and more effective ErbB2 dimerization blockade than with monotherapy. The mechanism underlying resistance to anti-ErbB treatment is not fully understood. Increasing evidence suggested that CD151, one of the best characterized members of the tetraspanin family, is involved in progression of human cancers. Recent studies showed that CD151 plays a crucial role in ErbB2-dependent signaling and sensitizes cells to Herceptin. Therefore, we further investigated a role of tetraspanin CD151 in regulation of ErbB2 function, ErbB2-dependent signal transduction in breast cancer cells and its impact on cell response to Herceptin and Petuzumab treatment.

Two human breast cancer cell lines overexpressing ErbB2 (SKBR3 and BT474) were used in this study. Firstly, we showed that CD151 has a different effect on cell proliferation depending on environmental conditions. Then, we investigated a functional link between CD151 and ErbBs for cell growth in three-dimensional environment in the presence of heregulin (HRG, triggers ErbB2/ErbB3 heterodimerization) and/or Herceptin (HER, targets mainly ErbB2). An impact of CD151 on ErbB2/ErbB3 heterodimerization was next evaluated and verified by co-immunoprecipitation and co-localization studies.

Herein, we found that CD151: i) impairs heregulin-dependent cell growth, ii) inhibits heregulin-triggered signalling pathways, iii) attenuates heterodimerization of ErbB2/ErbB3 and cell response to Herceptin and Pertuzumab. These results have supported previous findings and showed that CD151 is involved in ErbB2/ErbB3 mediated signaling pathways which has implication for breast cancer progression and resistance to therapy.

In summary, our study demonstrated that not only the ErbB2/ErbB3 receptor status, but also other factors, such as the presence of dimerization regulators e.g. CD151 and the availability of the ligand determine the response of the ErbB2-overexpressing breast cancer cells to Herceptin and Pertuzumab.