Letters to the Editor

The role of insulin-like growth factor-I receptor in the development of Herceptin resistance

To the Editor: We read with great interest the article by Tanner et al. regarding development of a novel cell line established from patient with Herceptin-resistant breast cancer (1). They showed that lack of growth inhibition was rationalized by the unaltered Akt phosphorylation in these resistant JIMT-1 cells. They discuss different Herceptin resistance mechanisms that may develop in these cells. We want to comment on another resistance mechanism. The insulin-like growth factor-I receptor (IGF-IR) initiates a strong proliferative and antiapoptotic signal (2). Binding of IGF-I to IGF-IR results in autophosphorylation of the receptor, leading to recruitment and phosphorylation of Src homology and collagen and IRS-1 adaptor protein. This action of IGF-IR results in activation of the Ras/Raf/mitogen-activated protein kinase pathway and/or the phosphatidylinositol 3-kinase pathway, which influence cell proliferation and survival (3, 4). Lu et al. (5, 6) showed that in breast cancer cell models that overexpress HER-2, an increased level of IGF-IR signaling seems to interfere with the action of trastuzumab by reducing p27 (Kip1) protein level by increased degradation. Therefore, strategies that target IGF-IR signaling may prevent or delay development of resistance to trastuzumab. Further clinical studies are warranted to support these preclinical results.

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In Response: The main goal of our report (1) was to characterize the newly established cell line JIMT-1, which could be a useful tool to study Herceptin resistance mechanism(s) *in vitro* and in xenograft-bearing immunodeficient mice. To keep the text short, we did not want to speculate on possible resistance mechanisms that we have not studied with JIMT-1 cells thus far. A detailed review on possible Herceptin resistance mechanisms was referred to in the article (2).

It is my pleasure to accept the authors' view that insulin-like growth factor-I receptor signaling could well be one of the mechanisms behind constitutively active phosphatidylinositol 3-kinase and Herceptin resistance. We have recently made the JIMT-1 cell line available for the research community via an international cell collection.[1] The role of insulin-like growth factor-I receptor signaling and many other possible resistance mechanisms can then be directly tested with JIMT-1 cells, which is the first patient-derived *in vitro* model of breast cancer derived from a clinically Herceptin-resistant patient.

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[1] www.dsmz.de

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