Overcoming trastuzumab resistance with nordihydroguaiaretic acid?

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We congratulate Youngren and his colleagues for their fascinating study showing that nordihydroguaiaretic acid (NDGA) inhibits the IGF-1 and c-erbB2/HER2/neu receptors and suppresses growth in breast cancer cells [1]. Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody, which targets an epitope in the extracellular domain of the HER2 protein. Preclinical models demonstrated that this antibody has significant anti-tumor activity as a single agent and has synergy with certain chemotherapeutic drugs. Phase II and III clinical trials performed in women with metastatic breast cancer that overexpress HER2 have shown that trastuzumab has clinical activity when used as first-, second- or third-line monotherapy, and improves survival when used as first-line therapy in combination with chemotherapy [2]. Unfortunately 30–40% of HER2-overexpressing cancer cells respond to treatment with trastuzumab, and the clinical benefit of the drug is limited by the fact that most cancers become resistant to trastuzumab therapy in less than 12 months [3]. Mechanism of resistance to trastuzumab therapy includes overexpression of the insulin-like growth factor receptor (IGF-1R), downregulation of p27kip1 and loss of PTEN [4]. Moreover, Lu et al. [3,5] showed that in breast cancer cell models that overexpress HER-2, an increased level of IGF-1R signaling seems to interfere with the action of trastuzumab by reducing p27 (Kip1) protein level by increased degradation. Therefore, use of NDGA alone or combination with trastuzumab may

prevent or delay development of resistance to trastuzumab in breast cancer cells. Further *in vitro* and *in vivo* studies are warranted to support this proposal.

References

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