Small Molecule for Treating P-glycoprotein (Pgp)-Mediated Multi-Drug Resistance in Cancer

A potent, selective, and novel substituted quinoline, HG-829, has been identified as a non-competitive inhibitor of Pgp-mediated multi-drug resistance. Pgp is a transmembrane protein that exports amphipathic anti-cancer drugs, and overexpression of Pgp has been implicated in adverse clinical outcomes in leukemia and breast cancer. HG-829 significantly enhances the IC_{50}s of the chemotherapeutic drugs daunorubicin, doxorubicin, paclitaxel, vinblastine, vincristine, and etoposide in cell lines, and significantly potentiates the effect of daunorubicin in a murine xenograft leukemia model without added toxicity.

COMMERCIAL OPPORTUNITY

- Issued patents on the composition of matter of HG-829, a non-competitive Pgp inhibitor that is not a substrate itself for Pgp, with significant *in vitro* and *in vivo* data.
- Pgp expression studies have shown high levels of Pgp correlate with adverse clinical outcomes in leukemia and breast cancer, and in breast cancer Pgp expression is increased after chemotherapy and correlates with a worse response to treatment.
- Pgp inhibitors have failed in Phase 3 trials, including Valspodar (Novartis), Dofequidar (Schering AG), Tariquidar (QTL), and Zosuquidar (Lilly). However, Tariquidar like HG-829 is the only non-competitive inhibitor that is not a substrate itself for Pgp, and it failed in Phase 3 due to toxicity, not lack of efficacy, so a less toxic molecule with these characteristics may succeed.
- Of the four compounds above, Dofequidar showed a strong trend in a Phase 3 breast cancer clinical trial with a p-value of 0.077, suggesting that this class of therapeutic has a biological effect, just not a strong enough one with the molecules tested yet.
- The first generation Pgp inhibitor cyclosporine A showed a significant survival advantage in patients with high risk AML.

TECHNOLOGY

HG-829 significantly enhances antineoplastic cytotoxicity in cells that overexpress Pgp (also termed ABCB1) with a prolonged duration of action. Treatment with 500nM of HG-829 sensitizes K562-R daunorubicin-resistant human chronic myelogenous leukemia cells by 57-fold for daunorubicin, 144-fold for paclitaxel, 11,518-fold for vincristine, and 28-fold for etoposide; sensitizes H460-R vinblastine-resistant human lung carcinoma cells by 484-fold for vinblastine; and sensitizes MDR-19 human embryonic kidney cells engineered to overexpress Pgp by 114-fold for doxorubicin. Co-administration of HG-829 with daunorubicin in a K562-R xenograft tumor mouse model significantly reduces tumor volume compared to mice treated with daunorubicin alone ($p<0.01$).

PUBLICATION/PATENT

- Patents: US 6376514, Canadian 2421008, Japanese 4451060, and EP1326833.
- Cancer Res August 15, 2012 72(16); 1–10.

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