INTRODUCTION
Granulocyte colony-stimulating factor (G-CSF) regulates neutrophil production by binding to a specific receptor expressed on cells of the granulocytic lineage, the granulocyte colony-stimulating factor receptor (G-CSFR). Recombinant forms of G-CSF are used clinically to treat neutropenias. Previously we reported on the discovery of a series of novel, non-peptidyl, small molecules that selectively activate the human G-CSFR in a manner distinct from G-CSF and similar to the mechanism of small molecule human thrombopoietin receptor (hTPOR) agonists. A small molecule, oral G-CSFR agonist may offer a convenient alternative to injectable GCSF therapy with potential advantages, including anti-tumor activity, that have not been observed with recombinant GCSF.

RESULTS
Induction of Granulocyte Differentiation: LG7455 induces the expression of the granulocyte-specific marker CD15 in CD34-positive, human bone marrow cells. LG7455 was additive to the effect of 0.1 ng/mL G-CSF, comparable to a normal serum concentration of G-CSF.

Increase in Peripheral Blood Neutrophils with TID Dosing: LG7455 significantly increases peripheral blood neutrophils, 500 ng/mL once a day for 5 days via IV injection. Blood samples evaluated 6 hrs post-dose on day 5 revealed no significant increase in neutrophil counts with once daily LG7455.

IV Pharmacokinetics of LG7455 in Cynomolgus Monkeys:LG7455 was additive to the effect of 0.1 ng/mL G-CSF.

Zinc Enhances Activity of LG7455 on hG-CSFR Function: LG7455 Reduces Free Intracellular Iron and Increases Apoptosis in HL-60 Cells: The addition of Fe(III) to HL-60 cells was able to overcome the anti-proliferative effect of LG7455 (15 µM) and SIH (32 µM), indicating that a reduction in intracellular iron plays a role in the effect. The transition metals Zn(II) and Cu(II) also blocked the effect, but not the non-transition metals Ca(II) and Mg(II).

SUMMARY
- LG7455 is a novel small-molecule, selective hG-CSFR agonist that activates the receptor in a manner distinct from G-CSF but similar to the mechanism of small molecule nTPO agonists.
- LG7455 significantly increases peripheral blood neutrophils, demonstrating the first reported proof-of-concept in a primate model.
- LG7455 inhibits tumor cell growth mediated in part by a reduction in intracellular iron and an increase in ROS formation.
- Further optimization of the LG7455 series may provide a novel, orally-available adjuvant anticancer therapy that is also a supportive care agent to treat neutropenia in patients receiving bone-marrow suppressive treatments.

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Abstract 3462

Keith B. Marschke, Eric G. Vajda, and Lin Zhi
Ligand Pharmaceuticals Incorporated, 1119 North Torrey Pines Road, Suite 200, La Jolla, CA 92037

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