Orally Bioavailable Small Molecule that Binds VEGF or PDGF for the Treatment of Cancer

Our technology is an orally bioavailable novel synthetic small molecule that inhibits angiogenesis by binding either VEGF or PDGF and blocking those ligands from binding to their receptors. This pharmacological agent also potently inhibited endothelial cell migration and capillary network formation in vitro as well as in vivo blood vessel formation and human tumor growth in nude mouse xenografts, including brain, lung, breast, prostate, pancreas and renal models. Tigris Pharmaceuticals had completed several IND-enabling toxicology studies for GFB-204.

COMMERCIAL OPPORTUNITY

- Anti-angiogenic cancer therapy is based on the idea that growth of any tumor beyond $2cm^3$ is contingent on its ability to build and sustain new blood vessels (angiogenesis), and suppression of angiogenesis may cause tumor growth to stop due to "starving" the tumor. VEGF is thought to be involved in blood vessel formation, while PDGF may be involved in blood vessel maintenance.
- The currently FDA-approved marketed anti-angiogenic therapeutics include anti-VEGF therapeutics that bind VEGF and block its ability to bind the VEGF receptor, or small molecule multi-targeted tyrosine kinase inhibitors that target the VEGF and PDGF receptors, in addition to other tyrosine kinases. These therapies have been approved for either cancer or age-related macular degeneration.
- The cancer therapeutics include Avastin (bevacizumab), a monoclonal antibody, approved to treat colorectal, lung, glioblastoma, and kidney cancers. Also several small molecule multi-targeted tyrosine kinase inhibitors have been approved, including sarafenib, sunitinib and pazopanib for liver, kidney, and neuroendocrine cancers. Avastin annualized US sales for 2013 were about $2.6B.
- In the age-related macular degeneration (ARMD) market, there are three drugs that are all bind VEGF, including Lucentis (anti-VEGF antibody fragment), Eylea (VEGF-Trap that combines the VEGF receptor and the Fc portion of IgG), and Macugen (anti-VEGF aptamer). In June 2012, a Phase 2b trial of the combination of Fovista (anti-PDGF aptamer) and Lucentis was superior to Lucentis alone, suggesting that the combination of anti-PDGF and anti-VEGF mechanisms works well in ARMD.
- Tigris completed several IND-enabling toxicology studies for GFB-204, including rat and dog dose escalation and sub-chronic repeated dose studies, and a 28-day chronic rat study. Tigris also showed GFB-204 has activity against ARMD and has identified topical and injectable ocular formulations.

TECHNOLOGY

GFB-204 (and parent compounds GFB-202 through GFB-213) binds VEGF and PDGF causing potent inhibition of tumor growth *in vivo*. In nude mice implanted with human lung cancer A-549 cells subcutaneously, GFB-204 treatment resulted in statistically significant ($p<0.05$) tumor growth inhibition of 73%. GFB-204 was effective at inhibiting the growth of brain, lung, breast, prostate, pancreas and renal tumors when given to mice orally at 150mg/Kg/day. Toxicity studies in mice revealed no significant side effects at the 5-10 times the effective dose of the drug. Studies by Tigris identified a MTD for single and repeat doses in rats and dogs, and in a 28-day chronic rat study, no new toxicities were identified.

PUBLICATION/PATENT

- Sun et al. *Oncogene* (2005) **24,** 4701–4709
- US and international patents granted for Drs. Sebti, Hamilton and Jain.

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LICENSING OPPORTUNITY

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