**ABSTRACT**

ConverGene has developed a first-in-class dual-active small molecule inhibitor that (i) inhibits BET family of bromodomain-containing proteins, and ii) antagonizes dopamine receptor D2 (DRD2). BET protein family includes BRD4, an epigenetic reader protein that mediates expression of MYC oncogene. Thus, BRD4 is considered as a cancer therapeutic target to indirectly suppress MYC expression. In addition to being a therapeutic target for psychiatric diseases, DRD2 is emerging as a potential therapeutic target in neuroendocrine tumors, subsets of pancreatic ductal adenocarcinoma and small cell lung cancer. Our lead compound showed high activity in a binding test against BRD4 (IC50 = 34 nM), exhibited high bioavailability upon oral administration, profoundly suppressed MYC expression both in vitro and in vivo, inhibited growth of AML and solid tumor cells in xenograft models; potently inhibited both isoforms of DRD2 (IC50 0.1 μM), and interfered with DRD2-ankyrin/Akt pathway in vitro. Therefore, our BRD4/DRD2 dual-active compounds may hold promises as a novel class of therapeutics that interferes with both cancer growth and solid tumor cell proliferation. Why Target BET proteins and Dopamine Receptor 2 (DRD2) in Oncology? BET Inhibitors DRD2 Inhibitors

- POC in Clinic
- Synergistic with immune checkpoint inhibitors
- DRD2 antagonists have been administered safely for > 45 years
- DRD2 knockdown down regulates Ras, AKT, MYC, FOSL1, and activates cAMP signaling pathways
- DRD2 antagonism is pro-apoptotic, anti-angiogenic, and depletes cancer stem cells
- BET/BDRD2 overexpressed in many cancers
- BET/BDRD2 antagonists have been administered safely for > 45 years
- BET/BDRD2 knockdown down regulates Ras, AKT, MYC, FOSL1, and activates cAMP signaling pathways
- BET/BDRD2 antagonism is pro-apoptotic, anti-angiogenic, and depletes cancer stem cells
- BET/BDRD2 antagonists have been administered safely for > 45 years

**Why Target BET proteins and Dopamine Receptor 2 (DRD2) in Oncology?**

- Antagonism of Go activation (alternative signaling pathway) verified by Go-BET
- Antagonism of endogenous cAMP verified by CAMYEL cAMP biosensor

**ConverGene’s BET/DRD2 Antagonist Potently Inhibit Targets Involved in Inflammation, Fibrosis, and Metastasis**

- Dynamic Immunomodulation
- Greater effect on Fibrotic pathways
- No elevation of EGFR in skin
- Potent ERk inhibition

**Inhibiting Both BET Proteins and DRD2 Halts Proliferative and Resistance Pathways**

**CG223 Potently Impacts Markers Pathogenic for Fibrosis**

- RVE (ng/mL) 5 1.58 10533 2.52 31118 97.6
- PO 23 0.67 34567 1.26 10526 65.0

**CG223 Exhibits Good Exposure Upon Oral Dosing and is Efficacious in Multiple Cancer Models Including AML Kasumi-1**

**CG250 is a Full Antagonist of B-arrestin Recruitment with High Selectivity for D2R vs D3R**

**CG223 Synergizes with Anti-PD-1 and Anti-PDL-1 Checkpoint Inhibitors and Prolongs Survival**

**CONCLUSIONS**

- The first dual inhibitor of BET proteins and Dopamine Receptor 2 has been developed
- Leads are efficacious in multiple preclinical models of hematologic cancer

- Well-tolerated in rat toxicity studies
- Further Preclinical characterization in solid tumors & Inflammation on-going