Development of a First in Class Inhibitor of BET Bromodomains and Dopamine Receptor 2

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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 (Ki = 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/ß-arrestin/Akt pathway in vitro. Therefore, our BRD4/DRD2 dual-active compounds may hold promise as a novel class of therapeutics that interferes with both cancer growth and maintenance by simultaneously interfering with MYC and DRD2 pathways. We currently are investigating these dual-active compounds in multiple in vitro and in vivo models and expect to report the outcomes at the AACR Annual Meeting in 2017.

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

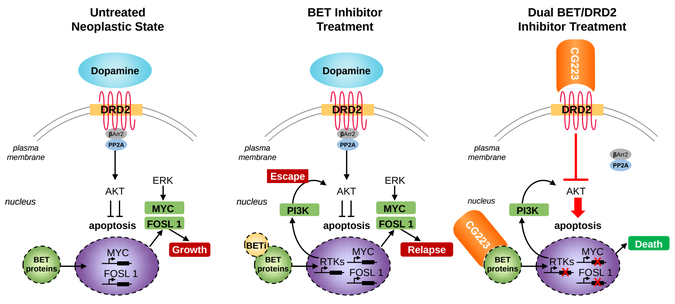
BET Inhibitors

- POC in Clinic
- Synergistic with immune checkpoint inhibitors
- Efficacious in "resistant" cancers (Nut midline Carcinoma)
- Promising activity in models of inflammation and fibrosis

DRD2 Inhibitors

- DRD2 overexpressed in multiple cancers
- DRD2 antagonists have been administered safely for > 45 years
- DRD2 knockdown down regulates Ras, Erk, and β-catenin signaling pathways
- DRD2 antagonism is pro-apoptotic, anti-angiogenic, and depletes cancer stem cells

Inhibiting Both BET Proteins and DRD2 Halts Proliferative and Resistance Pathways



The CVG101 Program Contains Product Candidates with Unique Target Selectivity Profiles

CVG 101 Lead Compounds	Target Engagement		
	BET Potency		DRD2 Potency
	BromoscanKd (nM)	Alpha Screen IC50 (nM)	IC50 (μM)
CG250 (panBET/DRD2)	44	50	0.10
*CG223 (panBET/DRD2)	34	100	0.66
CG202 (panBET/Weak DRD2)	34	54	3.04
CG214 (panBET)	54	81	13.97
CG209 (DRD2 antagonist)	>10000	nd	1.00

** Nominated for IND-enabling studies*

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

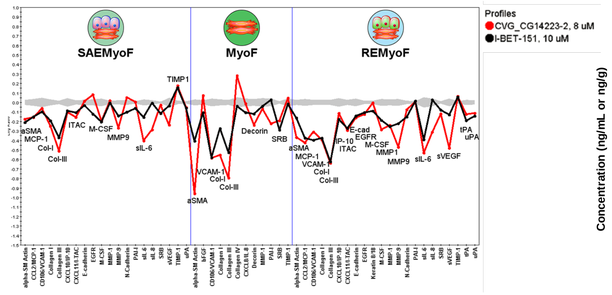
CG250 D2R Ki (nM) 103

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

ConverGene's BET/DR2 Antagonist Potently Inhibit Targets Involved in Inflammation, Fibrosis, and Metastasis

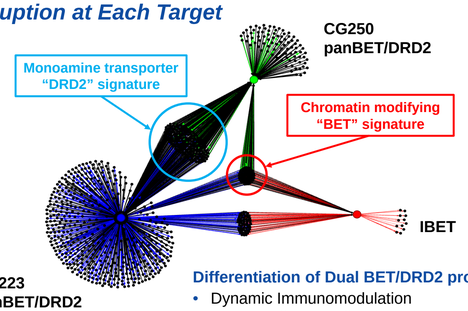
CVG_CG250	Database Match	BioMAP Z-Standard	Pearson's Score	# of Common Readouts	Database Match (Mechanism Class)
8 μM	Valproic Acid, 9000 μM	14.880	0.844	148	GABA Transaminase / HDAC Inhibitor
	Olmutinib, 3.3 μM	13.044	0.794	148	EGFR Inhibitor
	JQ1, 370 nM	12.934	0.791	148	BET Inhibitor
1.6 μM`	JQ1, 370 nM	14.407	0.833	148	BET Inhibitor
	BI-2536, 1.1 μM	13.586	0.810	148	PLK1/BET Inhibitor
	SGC-CBP30, 10 μM	13.586	0.810	148	CBP/p300 Bromodomain Inhibitor
320 nM	JQ1, 41 nM	10.578	0.706	148	BET Inhibitor
	OTX015, 41 nM	9.628	0.664	148	BET Inhibitor
	I-BET-151, 120 nM	9.569	0.661	148	BET Inhibitor

CG223 Potently Impacts Markers Pathognomonic for Fibrosis



- Overlay of **CG223-2 (8 μM)** and **I-BET-151 (10 μM)**
  - There are 31 common activities that are annotated within the following systems: SAEMyoF (Collagen I, Collagen III, I-TAC, M-CSF, MCP-1, MMP-9, TIMP-1, α-SMA, sIL-6), MyoF (Collagen I, Collagen III, Decorin, SRB, VCAM-1, α-SMA), REMyoF (Collagen I, Collagen III, E-Cadherin, EGFR, I-TAC, IP-10, M-CSF, MCP-1, MMP-1, MMP-9, VCAM-1, α-SMA, sIL-6, sVEGF, tPA, uPA).
  - **I-BET-151** is a imidazolonoquinoline-based inhibitor of the BET (bromodomain and extra terminal domain protein) family of acetyl-lysine recognizing, chromatin adaptor proteins.

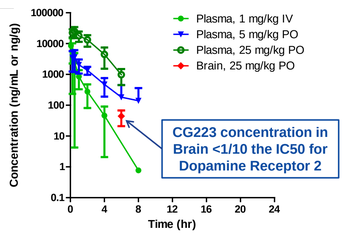
Gene Expression Signatures in AML Tumor Bearing Animals Treated with ConverGene's panBET/DRD2 Antagonist Indicate Potent Disruption at Each Target

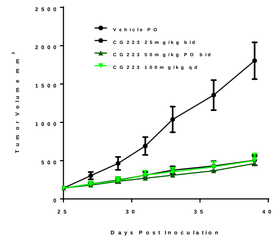


Differentiation of Dual BET/DRD2 products

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

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

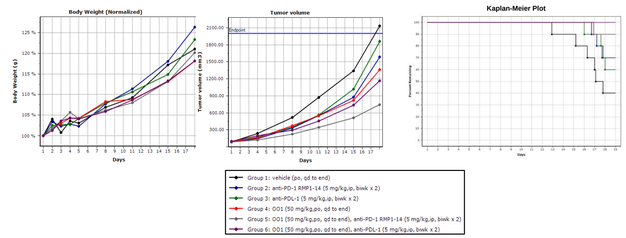




Route	Dosage (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	F (%)
IV	1	0.083	7620	0.98	6374	
PO	5	1.58	10533	2.52	31118	97.6
PO	25	0.67	34567	1.26	103625	65.0

Extended release Clinical Formulation developed (data not shown)

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



Dual BETi & DRD2 Preclinical Program Summary

Unmet Need	• Orphan Indications in Hematologic Oncology
Market Opportunity	• Multi $B Global Market Potential
Patent	• ConverGene Owns CVG101 • Patent Life to 2034 +
Preclinical Package	• Superior Pharmacological Profile • Excellent Safety & Tolerability • Extended Release Formulation
Differentiation from Competition	• Novel MOA • Broad Spectrum of Activity • First-in-Class • Expected to Delay Resistance

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**