財團法人生物技術開發中心
Development Center for Biotechnology

Development of an Orally Active Hedgehog Inhibitor

Development Center for Biotechnology

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Hedgehog-pathway Status in Several Cancers

State	Hedgehog expression	PTCH expression	SMO expression	Frequency (%)	Ref.
Normal	*Off*	*On*	*Off*	-	-
Basal-cell carcinoma	*Off*	Mutant-off *On*	On Mutant-on	95	[53,55,54]
Medulloblastoma	*Off*	Mutant-off	On	30–40	[26,57,64]
Pancreatic cancer	On	Off	On	100	[74,75]
Prostate cancer	On	Off	On	100	[76,77]
Small-cell lung cancer	On	Off	On	50	[83]
Hepatocellular cancer	On	Off	On	N/A	[78]
Breast cancer	On	Off	On	100	[81]
Ovarian cancer	On	Off	On	58	[111]

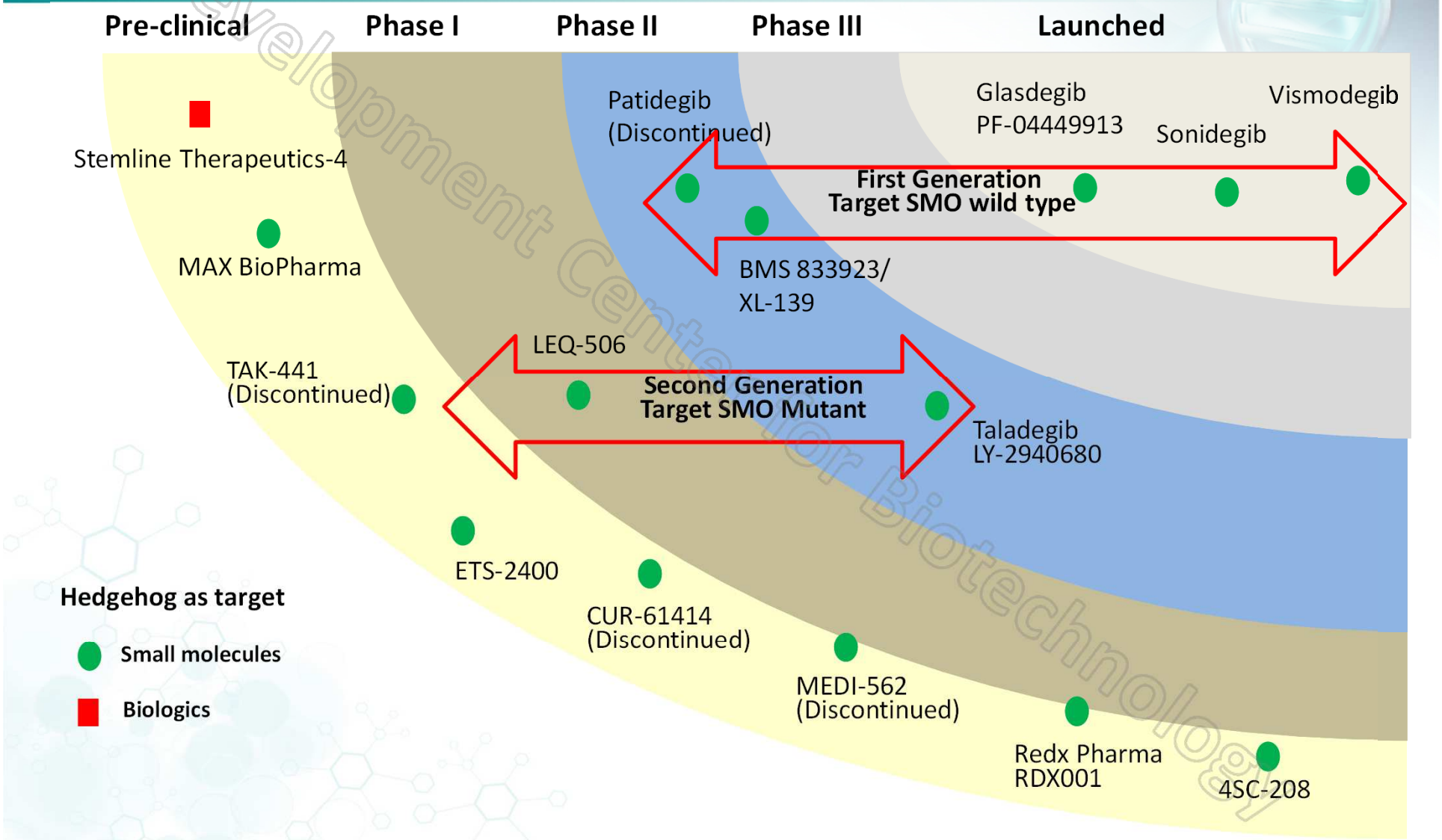
Pathway activating events are non-italic and pathway inhibitory events are italicized.
N/A: Not available.

Clin. Invest. (2012) 2(4)

Executive Summary

Project Goal	To develop novel Smo inhibitor for overcoming vismodegib resistance of Hh pathway with anti-cancer activity
Molecular Hypothesis	Increased Hedgehog ligands produced by cancer cells activate the Hedgehog pathway which enhances tumor survival and proliferation
Therapeutic Rationale	Inhibition of the Hedgehog signaling pathway using the small molecule which targets the Smoothened protein (Smo) led to reduced tumor cell proliferation
Portfolio Fit	Small Molecule, Best-in-class
Molecule	Chemical, Synthetic
R2D	Preclinical stage
Clinical Plans	Basal cell carcinoma, solid tumors (Cholangiocarcinoma…)

Competitive Landscape of SMOi



(Data was updated via Pharmaprojects on Jan. 18, 2019)

Highly Potent Hedgehog Inhibitor Identified with Anti-acquired Resistance Mutant Smo-D473H Activity

compounds	Inhibition of Gli-Luc expression [IC_{50}, nM]	Growth Inhibition [@ 1uM]	Inhibition of SV40-Luc expression [@ 1uM]	Inhibition of C3H10T1/2-Gli-Luc-Smo-WT [IC_{50}, nM]	Inhibition of C3H10T1/2-Gli-Luc-Smo-D473H [IC_{50}, nM]	Smo binding assay BODIPY-cyclopamine Competition Assays [IC_{50}, nM]
Vismodegib (GDC-0449)	11 [a] (16.8)	20%	-3%	167.6	>1000	7 [a] (34.6)
Erismodegib (NVP-LDE225)	20 [a]				>1000	8 [a]
NVP-LEQ506	4 (3.8)	0.3 %	18.4 %	2.4	96 (107.5)	2 (9.4)
DCBCO1303	3.5	0.4%	1.8%	5.1	43.7	15.7

- DCB bioassay results

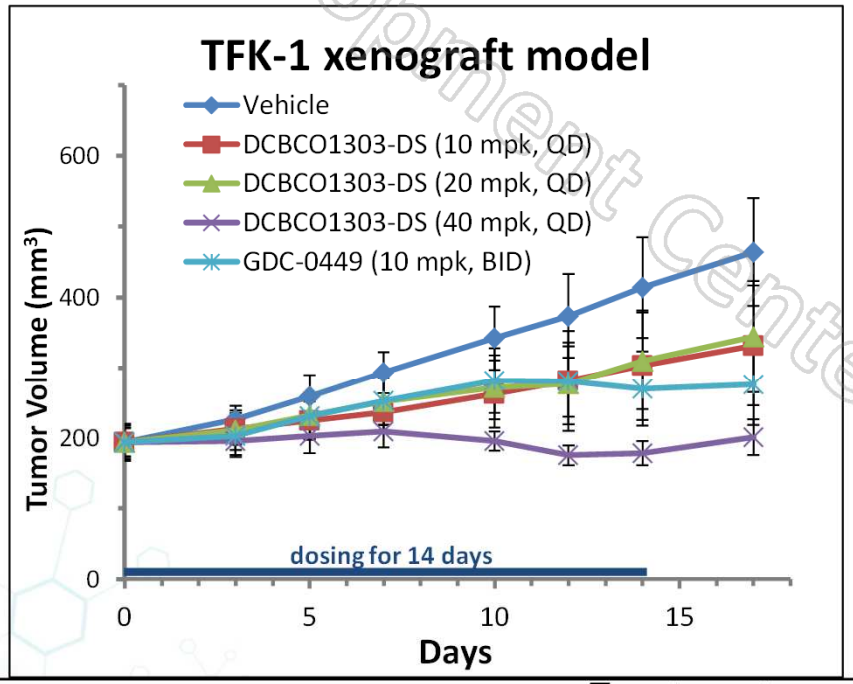
a. FASEB J. 29, 1817–1829 (2015)

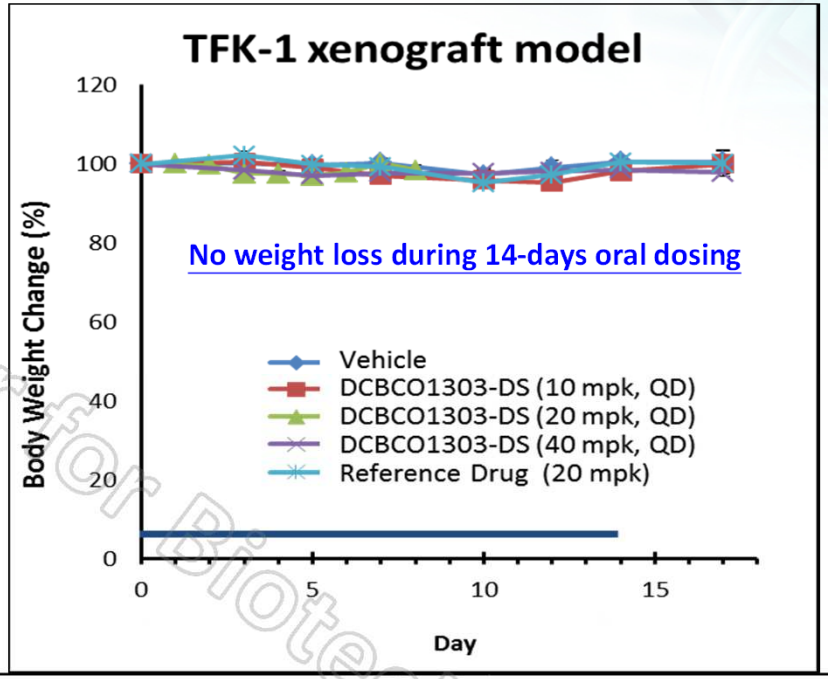
b. 11combination with low-dose cytarabine (LDAC), for newly-diagnosed acute myeloid leukemia (AML) in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy

2017.11 Patent application(Republic of China) (No. 106140517)
PCT Patent application (No. PCT/US2017/062974)

DCBCO1303 inhibited the Growth of Cholangiocarcinoma Xenograft

Highly effective in in Cholangiocarcinoma xenograft model





Treatment	*Treatment* [1- (Tt-T0)/(Ct-C0)]*100						
	Day 3	Day 5	Day 7	Day 10	Day 12	Day 14	Day 17
Vehicle	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DCBCO1303-DS (10 mpk, QD)	39.7	52.4	56.6	53.4	51.1	50.1	48.8
DCBCO1303-DS (20 mpk, QD)	46.4	42.2	41.6	47.2	53.5	47.2	44.3
DCBCO1303-DS (40 mpk, QD)	96.0	86.2	84.5	98.8	**110.3**	**107.0**	97.5
Reference Drug (20 mpk)	72.1	43.7	40.9	41.0	51.9	65.3	69.5

DCBCO1303 Has Superior in Vivo Pharmacological Properties over GDC-0449

Highly effective in animal tumor model with hedgehog pathway mutation