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

Highly Selective FLT3 Kinase Inhibitor as anti-AML Drug

Institute of Pharmaceutics
Development Center for Biotechnology

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Development Center for Biotechnology, DCB

400+

RD/BD professionals serving as the innovation hub for early drug development.

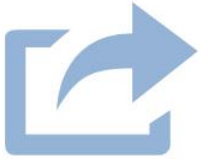
36

Founded in 1984, non-profit RD institution subsidized by the Ministry of Economic Affairs of Taiwan.

1200+

The premium drug development entity and connected with **1200+ biotech** of TW.

25

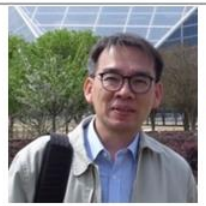


20+ out licensed assets and 5 Spin offs under **out-licensing** and **co-development** model.

Project Team

T **Project leader (pharmacologist)**
Chu-Bin Liao, Ph.D.

E **Chemistry leader**
Shao-Zheng Peng, Ph.D.

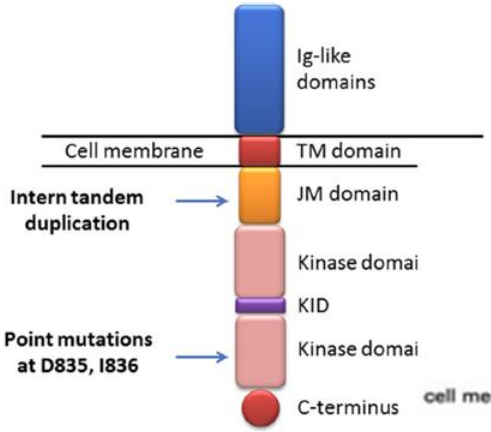


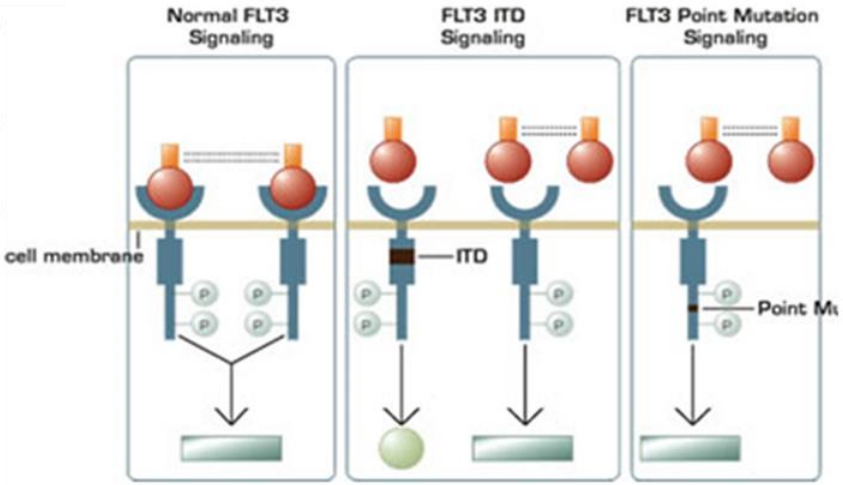
A **DMPK leader**
Yih-Chiao Tsai, Ph.D.

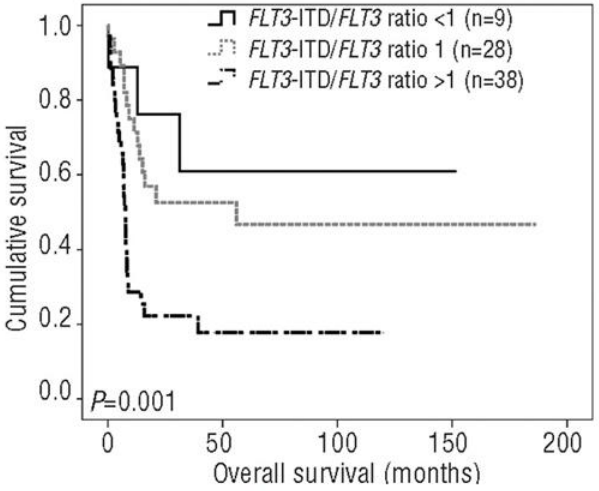
M ***In vivo* pharmacology leader**
Pei-Yi Tsai, Ph.D

Targeting FLT3 Mutation for AML Treatment

- FMS-like tyrosine kinase 3 (FLT3) is a common driver mutation occurred in approximately 30% of all AML case
  - The internal tandem duplication (ITD) insertion representing the most common type (~25%)
  - The tyrosine kinase domain mutation (FLT3 TKD) has a relative lower incidence (7–10%)
- FLT3-ITD or FLT3 TKD mutations trigger ligand-independent FLT3 signaling activation
- FLT3-ITD mutation is associated with poor prognosis in patients with AML
- FLT3 had been well characterized as "actionable" mutations in AML







The Hematologist, 2007
Stem Cell Investig 2017;4:48.

FLT3 Inhibitors in AML Clinical Trials

- First-generation FLT3 inhibitors are broad-spectrum, multi-kinase inhibitors. Off-target activities cause toxicities and monotherapy generally demonstrated limited anti-leukemic activity.
- Next-generation FLT3 inhibitors are more specific, more potent, and have fewer toxicities-associated off-target effects. Monotherapy exhibits clinical benefit.

◎First-generation FLT3 inhibitors

Drug name	Targets	Phase in AML		Drug name	Targets	Phase in AML
KW-2449	Aurora, ABL, FLT3	Withdrawn		Lestaurtinib (CEP-701)	JAK2, Trk & RTKs	Phase II
Tandutinib (MLN-518)	PDGFR, c-KIT & FLT3	Withdrawn		Sorafenib (Nexavar®)	RAF, VEGFR, c-KIT & FLT3	Phase III
Sunitinib (Sutent®)	KIT, KDR PDGFR & FLT3	Phase II		Midostaurin (Rydapt®)	PKC, Syk, Src & RTKs	Approval (Combine Chemo)

◎Next-generation FLT3 inhibitors

Drug name	Targets	Phase in AML		Drug name	Targets	Phase in AML
Quizartinib (AC220)	Class III RTKs	Phase III		Crenolanib	PDGFR, FLT3-ITD & -TKD	Phase III
Gilteritinib (Xospata®)	FLT3/AXL	Approval (monotherapy)		PLX3397	Kit, CSF-1R, FLT3	Phase I/II

CR/CRh~21%, Hematological & Liver toxicity

Highly Selective FLT3 Kinase Inhibitor DCBCO1901

Compound	Biochemical activity (Mean IC_{50}, nM)								
	FLT3	FLT3-ITD	FLT3* (D835Y)	KIT	CSF-1R	PDGFRβ	AXL	Met	VEGFR2
Quizartinib	3	15	47	132	26	142	>10 μM	>10 μM	235
Gilteritinib	2	3	1	805	258	>3 μM	28	1008	606
DCBCO1901	0.3	1	0.5	>10 μM	>10 μM	>3 μM	>10 μM	>10 μM	>3 μM

*FLT3 (D835 mutation): quizartinib-resistant activation loop mutation

- DCBCO1901 exhibits highly selective and potent inhibition activity against FLT3 and its mutants
- The kinase selectivity of DCBCO1901 is better than current benchmark Quizartinib and Gilteritinib

DCBCO1901 Exhibits FLT3-specific Cytotoxicity

Cancer cell line	Cancer Type	Stimulating growth factor	Target	Cytotoxicity (Mean IC_{50}, nM)	
				Gilteritinib	DCBCO1901
MV4-11	Leukemia		FLT3-ITD	2	12
Molm-13	Leukemia		FLT3-ITD	24	38
Molm-14	Leukemia		FLT3-ITD	15	49
OCI-AML5	Leukemia	FL (10 ng/mL)	FLT3 Signal	16	78
OCI-AML5	Leukemia	M-CSF (10 ng/mL)	CSF-1R Signal	56	>10,000
OCI-AML5	Leukemia	GM-CSF (10 ng/mL)	GM-CSF Signal	340	>10,000
M-07e	Leukemia	SCF (10 ng/mL)	KIT Signal	425	>10,000
M-07e	Leukemia	IL-3 (10 ng/mL)	IL-3 Signal	1,084	>10,000
HCC827	NSCLC		EGFR (Exon19 del)	345	>10,000

Normal cell line	Tissue	Cell type	Cytotoxicity (Mean IC_{50}, nM)	
			Gilteritinib	DCBCO1901
HUVEC	Vein	Endothelial cell	1,797	>10,000
HAoSMC	Heart	Smooth muscle cell	3,168	>10,000

The selective cytotoxicity of DCBCO1901 is superior to Gilteritinib

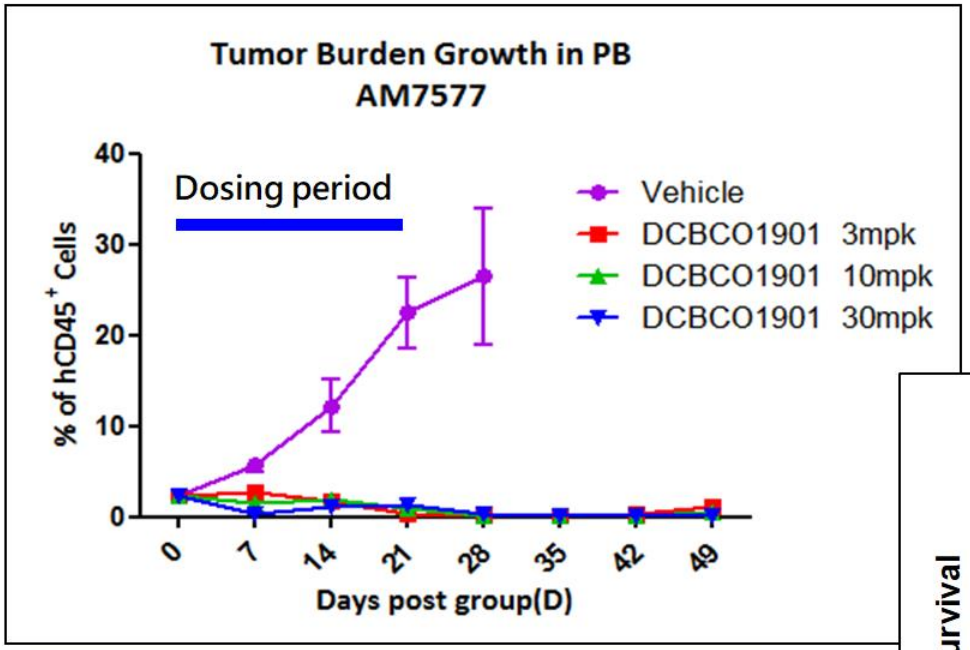
DCBCO1901 Can Achieve Complete Remission

Strain: Female NOD-SCID (n=10)

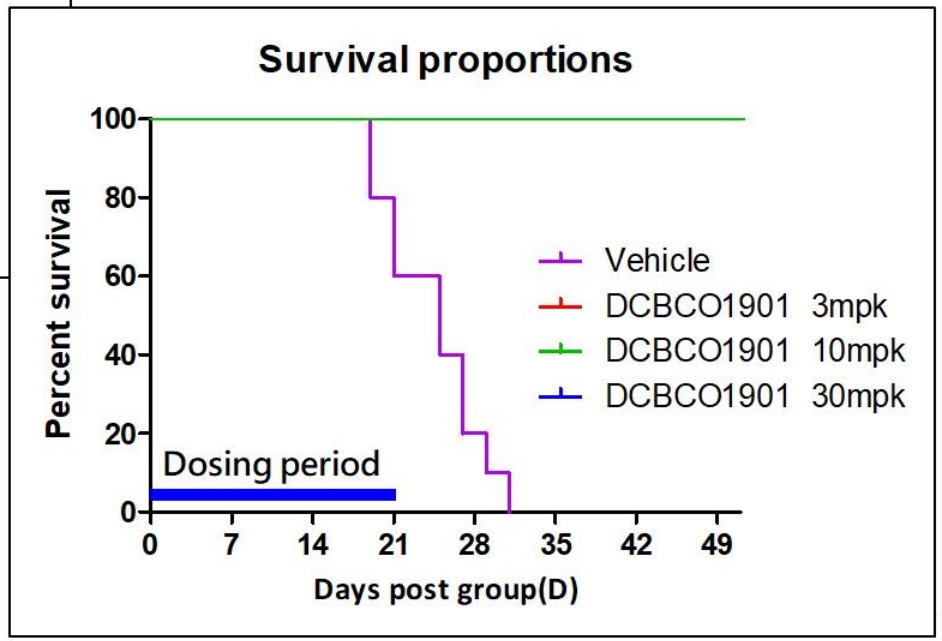
Model: AM7577 FLT3-ITD positive PDX model

Frequency: Once daily oral dosing for 21 days

Execution: CrownBio



The study was initiated at ~2% hCD45 positive cells detected in peripheral blood (PB).



No death or body weight loss was observed in all dosing groups after 28 days dose cessation

Competitiveness Analysis

Competitor	Problems of existing drug	Advantages of DCBC01901
Midostaurin (Rydapt®)	• Broad spectrum (high off-target activity) • Limited single-agent activity	• Highly potent & highly selective (nM vs. μM range selectivity in protein-based and cell-based assay) • Monotherapy & orally active
Quizartinib (Vanflyta®) Only in Japan	• QT prolongation • Hematological adverse effect • Short response duration (Secondary FLT3-TKD mutation mediated drug resistance)	• Highly potent & highly selective • High potency against FLT3 and FLT3 mutants
Gilteritinib (Xospata®)	• Toxic (Mortality at 20 mg/kg/day in rat, 5 mg/kg/day in dog in GLP tox study) • Hematological and liver adverse effect • Relative low CR (CR/CRh =21%)	• Highly potent & highly selective • Well-tolerance in preclinical tox study (No death was noted in rat with 1000 mg/kg/day dosing for 14 repeated dose)

- Patent status: US provisional patent had been filed
- Expected Progression: Complete IND enabling studies within the end of 2020

IP/Dev Status

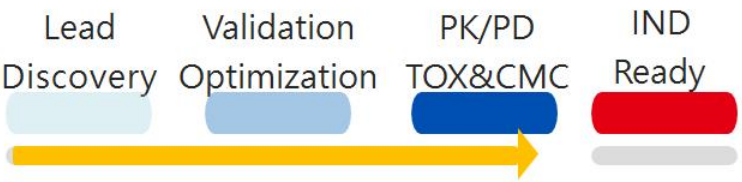
IP

US Provisional Patent Applied (62/891,097)

Partnership

Exclusive License

Development status



Summary and Contact

DCB's FLT3 Inhibitor DCBCO1901

- Novel chemical structure distinguished from known FLT3 inhibitors (provisional patent filed)
- Highly potent against FLT3 and FLT3 mutants (overcome FLT3-TKD mutation mediated drug resistant)
- Highly selective
- Monotherapy & orally active
- Well-tolerance in preclinical tox study
- Kilogram level scale-up process had been done
- GLP tox study is in progress.

BD Contact

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Thank you for your attention