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

Orally Active Hedgehog Inhibitor for Cancer Therapy

Institute of Pharmaceutics
Development Center for Biotechnology

Presenter : Ying-Shuan Lee, PhD
Mr. Tony Chung

Development Center for Biotechnology, DCB

400+

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

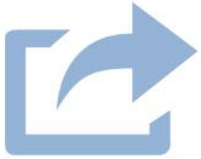
36

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
Mann-Yan Kuo, Ph.D.

National Taiwan University

E

Biology Project Leader
Ying-Shuan Lee, Ph.D.

STONY BROOK ESTABLISHED 1957 STATE UNIVERSITY OF NEW YORK

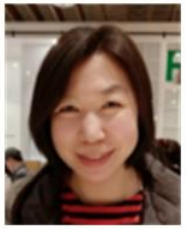
A

DMPK leader
Yih-Chiao Tsai, Ph.D.

TAIPEI MEDICAL UNIVERSITY 1960

M

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



Translational Cancer Research
Ling-Yueh Hu, Ph.D.

Hedgehog Inhibitor Targeting Vismodegib Acquired Resistance

Targeting tumors with dysregulated hedgehog pathway signaling

The landscape of resistant BCC is still emerging, driven by three FDA-approved products

Deregulated expression

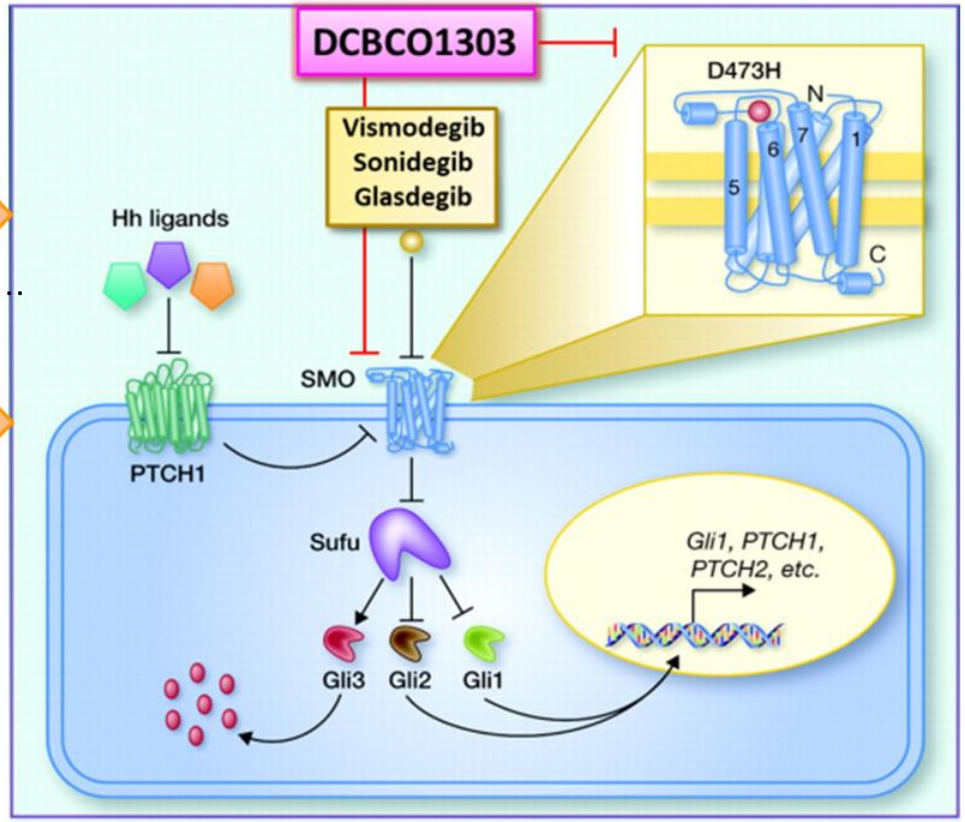
Cholangiocarcinoma, Esophageal…..

Mutations

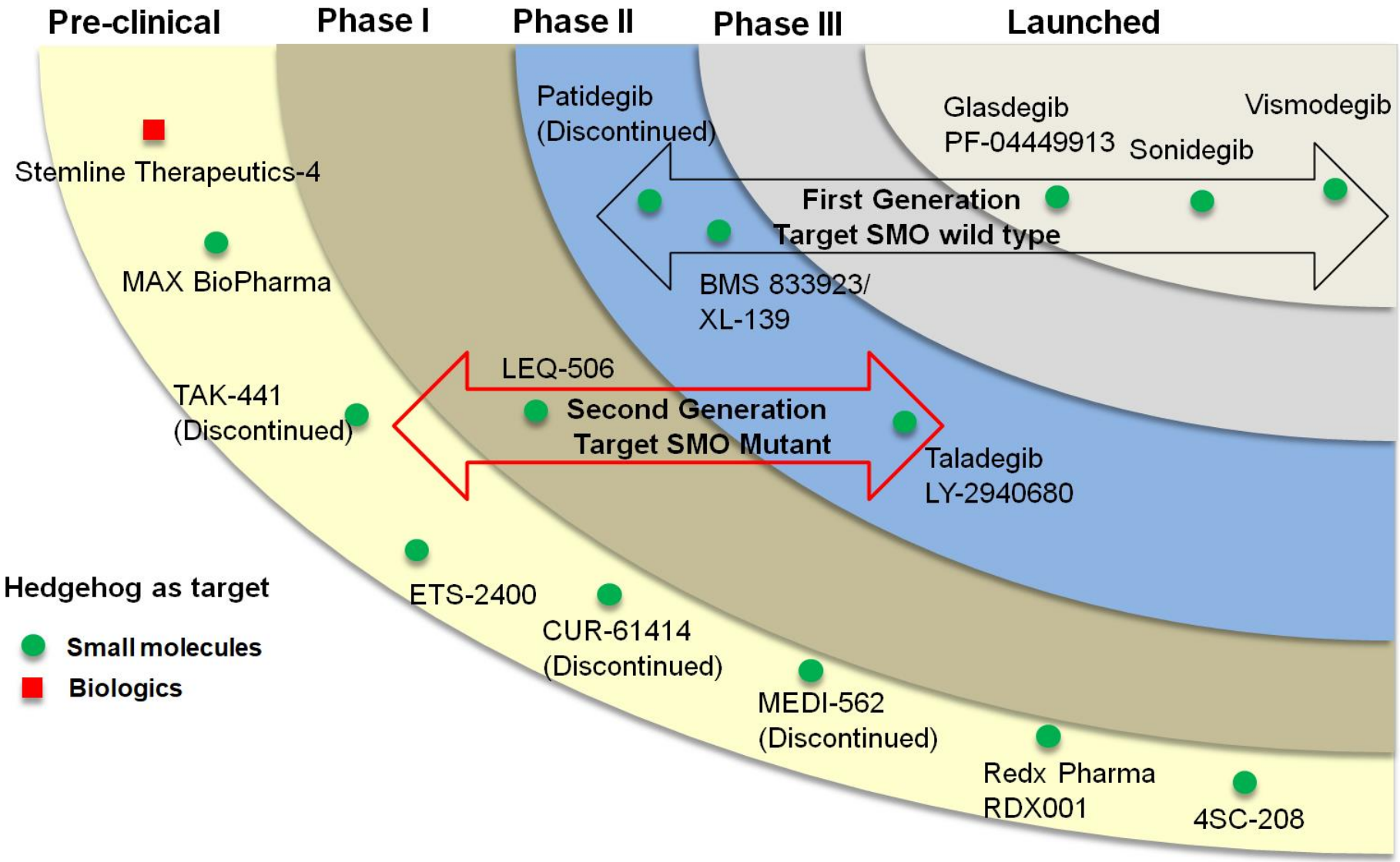
LOH of PTCH1

Activating mutation of Smo

BCC, Medulloblastoma…..



Competitive Landscape of SMOi



Highly Potent Hedgehog 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 [@ 1μM]	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	12 [a]
Glasdegib [b] (PF-04449913)	5					
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

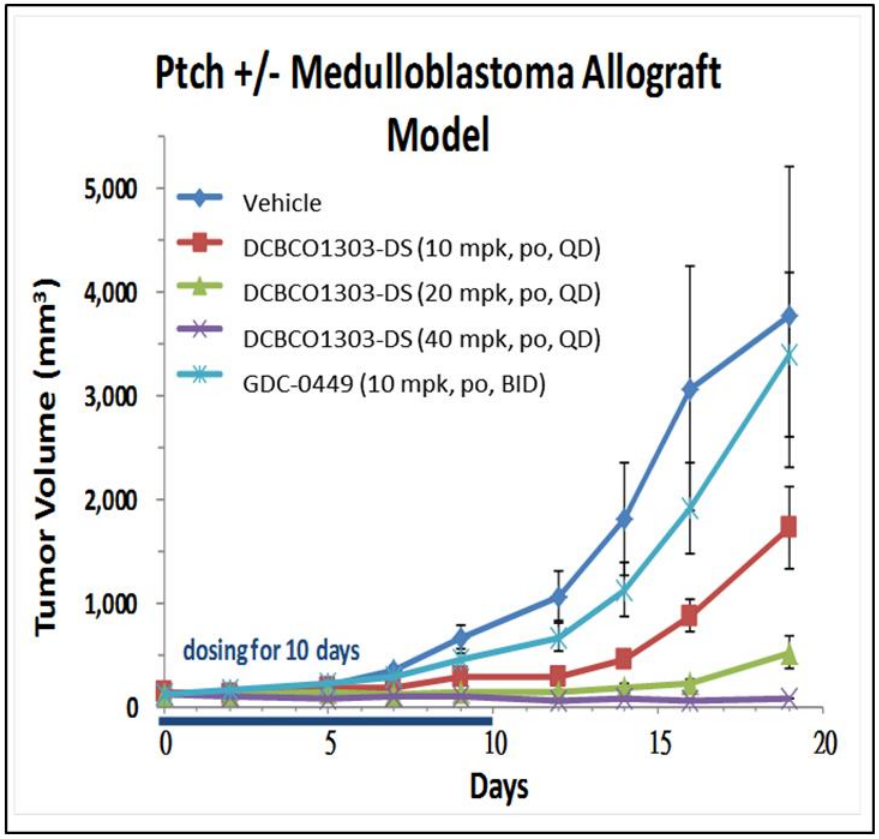
- DCB bioassay results

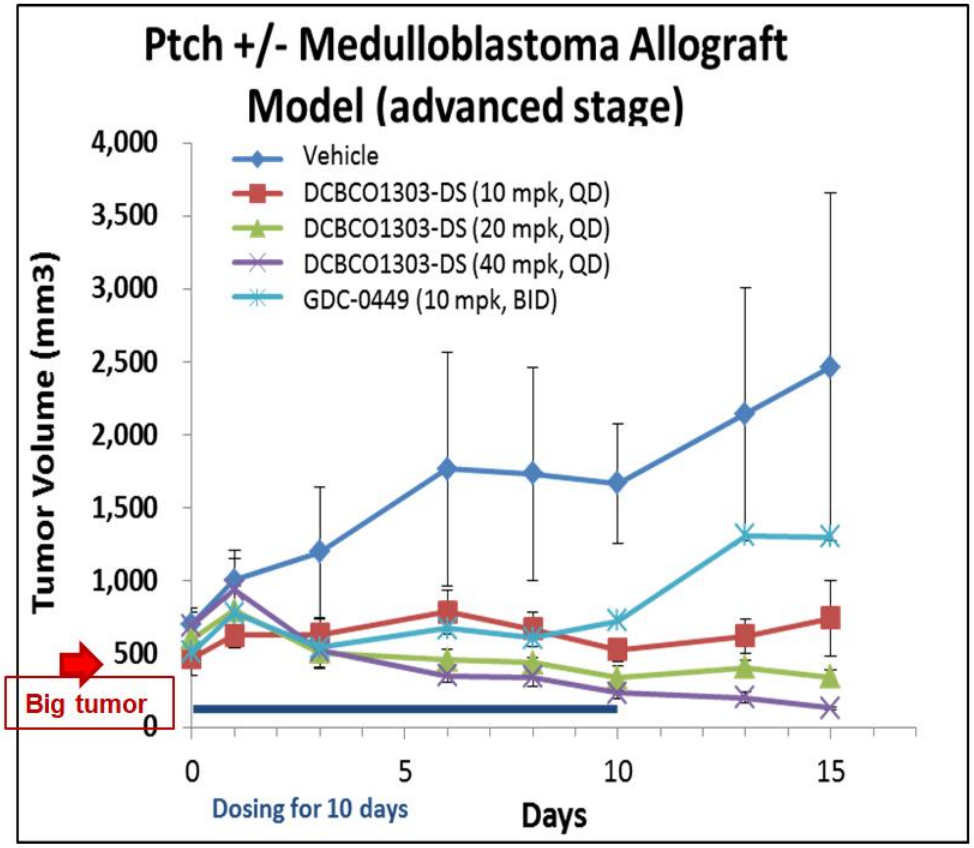
a. FASEB J. 29, 1817–1829 (2015)

b. combination 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

DCBCO1303 Has Superior in Vivo Pharmacological Properties over GDC-0449

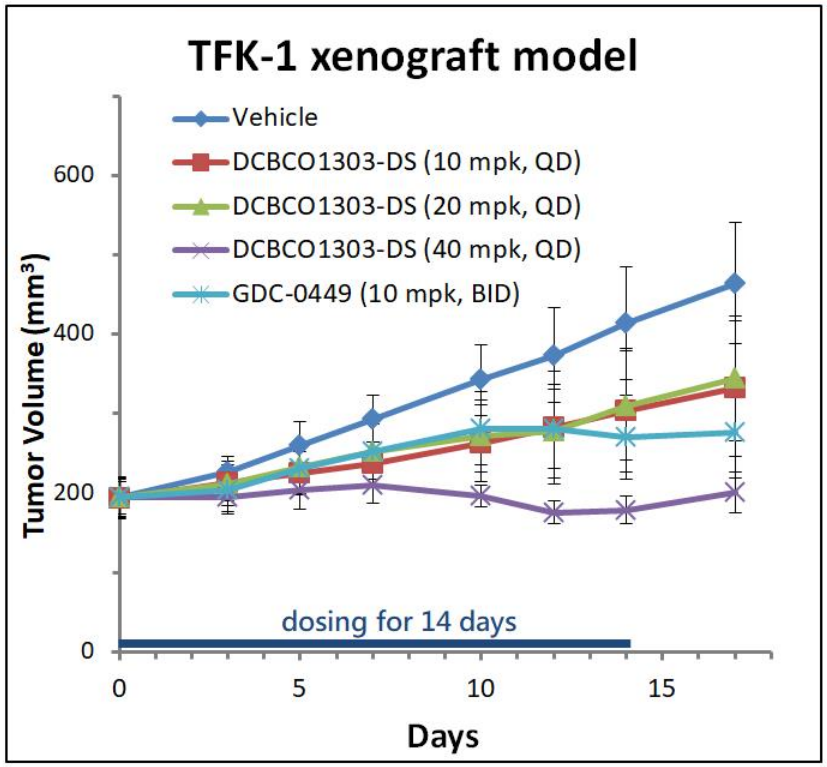
Highly effective in animal tumor model with hedgehog pathway mutation

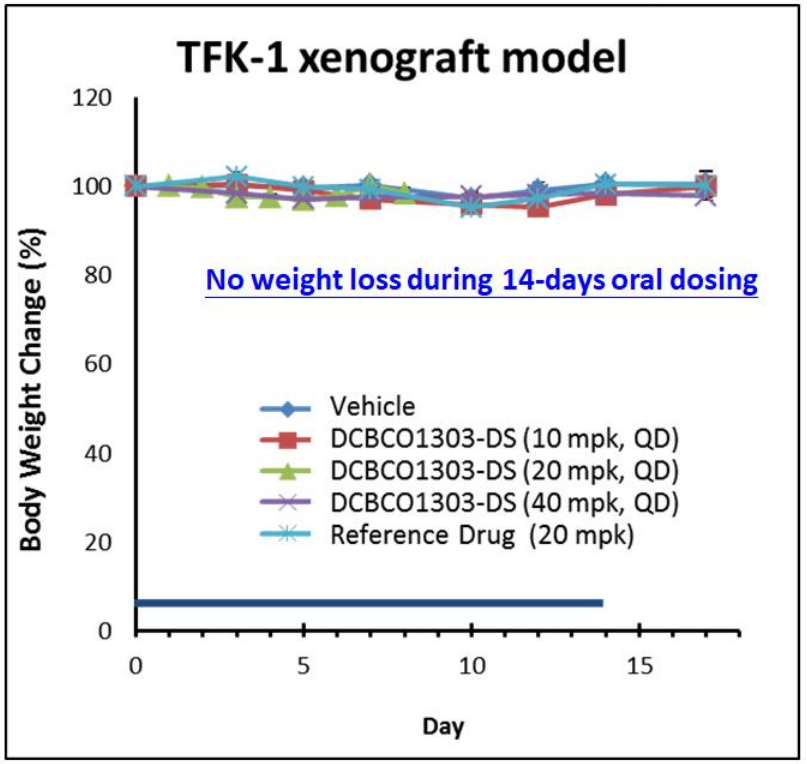




DCBCO1303 inhibited the Growth of Cholangiocarcinoma Xenograft

Highly effective 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

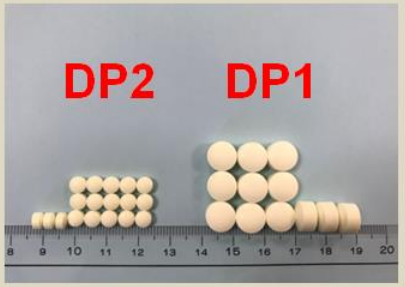
DCBCO1303 Drug Product - Tablets

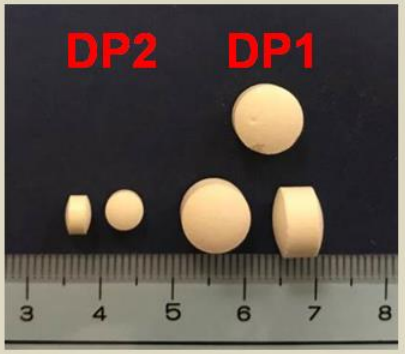
- ✓ Drug substance up to 10 Kg
- ✓ Scale up development of drug product for tablet formulation (prototype)

- ➢ DCBCO1303-DP1

- ➢ DCBCO1303-DP2

Packing Container for Drug Product





Different Dosage Strengths of Tablets

IP/Dev Status

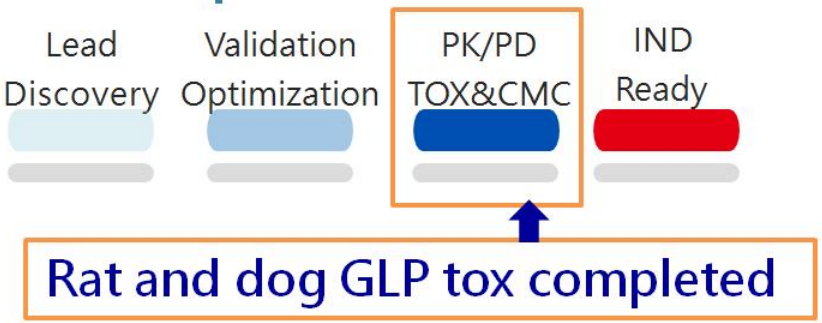
IP

Applied for US Provisional, PCT and Taiwan Patent

Partnership

Exclusive License

Development status



Expect in the Future

- Preclinical development for Hedgehog Inhibitor DCBCO1303
  - ✓ GMP batches scale-up for IND
- Indication expansion (PD study)
- Clinical plan for IND

Summary and Contact

Orally Active Hedgehog Inhibitor

- Tumor direct inhibition (Basal Cell Carcinoma, Cholangiocarcinoma….)
- Orally active small molecule
- Patent protected
- Low CYP inhibition potential
- GLP tox completed with acceptable safety profile
- Scale up development of clinical material production for tablet formulation (prototype)
- IND ready package

BD Contact

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Thank you for your attention