2024稃偄嬶胑湠蒼娩鐨募娩蚼盫裥旜　蒼煀碨娩胞蒼煀鑢畣III

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開發小分子藥物治療抗藥性肺癌

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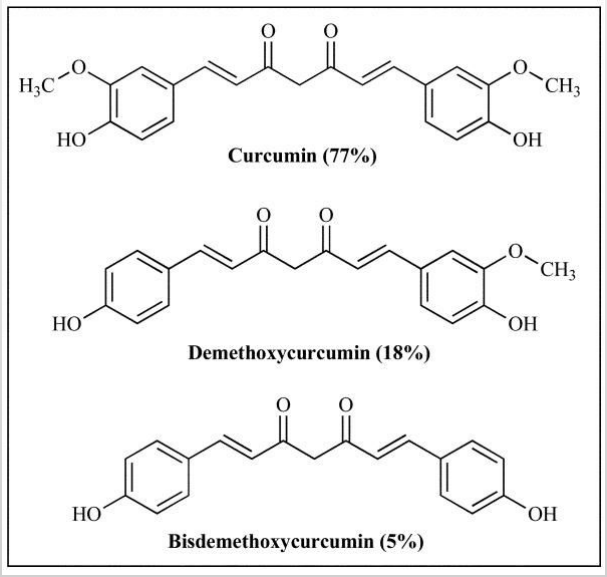
中國醫藥大學 藥學系副教授

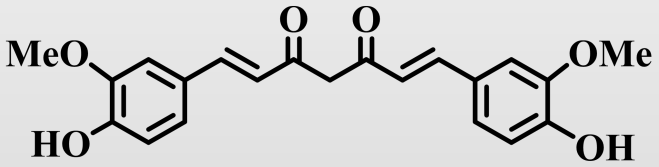
2024/11/17

Turmeric (C. longa L. 薑黃) is a herbal medicine used for the treatment of a large variety of illnesses, such as inflammation, infectious diseases, and gastric, hepatic, and blood disorders.

Major components of Turmeric (curcuma longa)

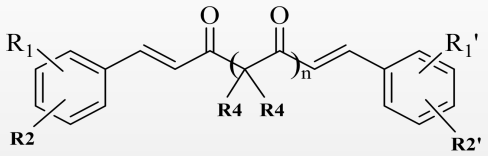


- **Curcumin (Major component)**

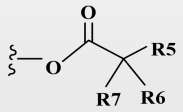


1. Low potency (anticancer; anti-inflammation, anti hyperlipidemic effects and etc.)
2. Poor PK profiles (low solubility, poor absorption, rapid metabolism, rapid systemic clearance)
3. Pan-assay interference compounds

Derivatives of curcuminoids and use thereof as an anticancer agents



R1, R2, R1', R2' = H, OH, OR,



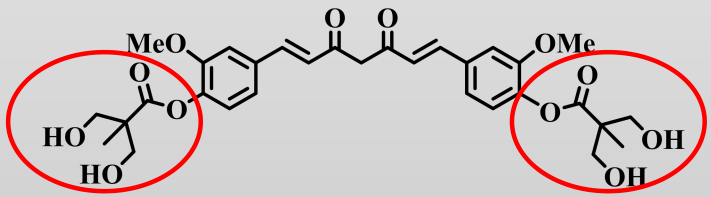
R4 = H, alkyl R5, R6, R7 = H, OH, alkyl [at least one R5, R6, R7 is -(CH2)mOH]

n = 0~3, m = 0~3

Aims of the modification

1. **Higher potency**
2. **Improved PK properties**
3. **Specific MOA**

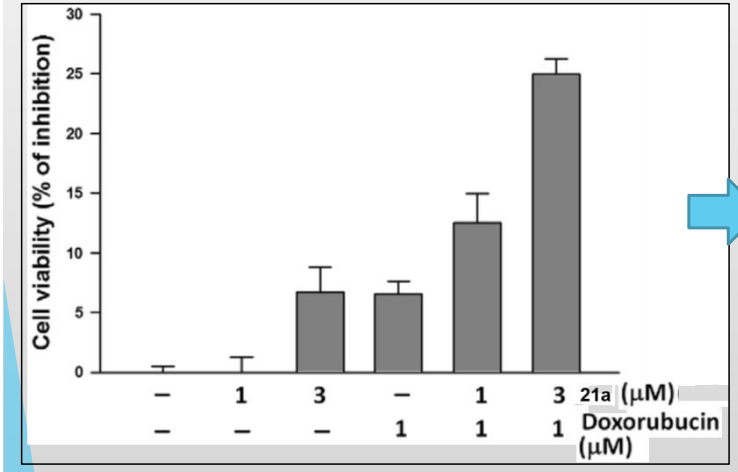
2,2-bis(hydroxymethyl)propionate curcumin (21a)

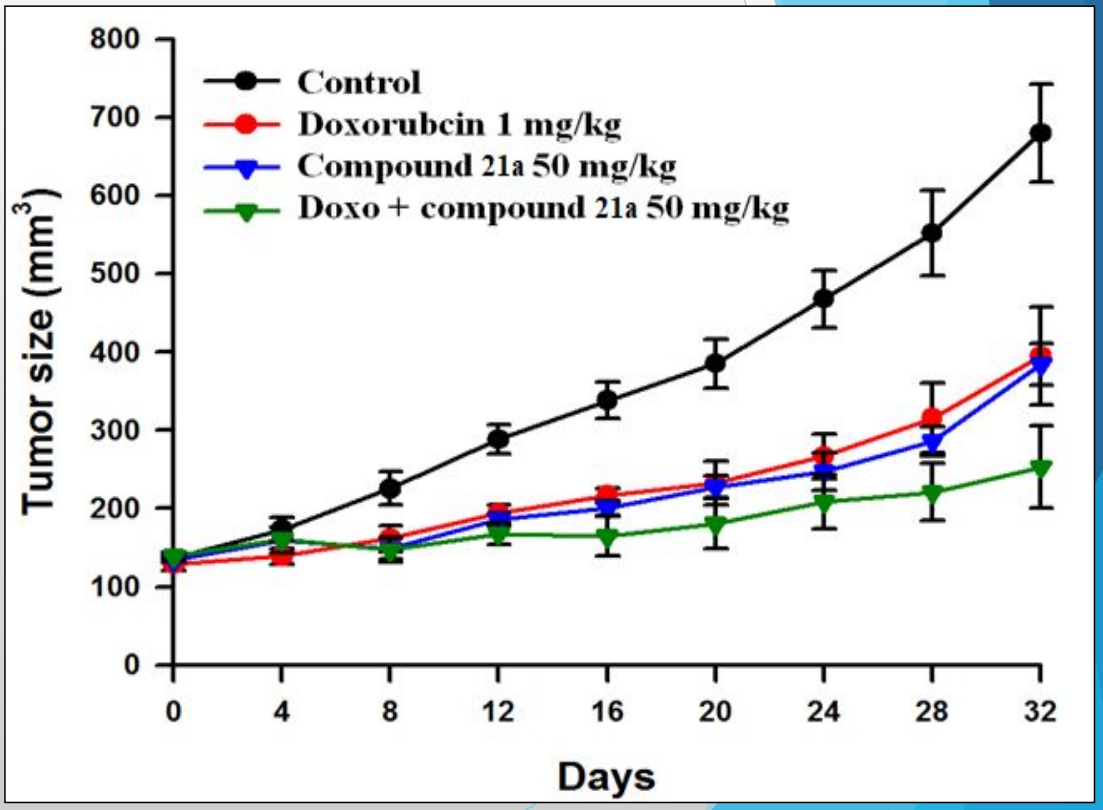


- **~10-fold more potent than the parent curcuminoids against colon, prostate and breast cancer cell lines**
- **Combining 21a with doxorubicin potentially can achieve a synergistic effect in a MDA-MB-231 TNBC xenograft model**

New bis(hydroxymethyl) alkanoate curcuminoid derivatives exhibit activity against triple-negative breast cancer in vitro and in vivo
Eur. J. Med. Chem. **2017**, *131*, 141-151

Antitumor activity of 21a combined with Doxorubicin

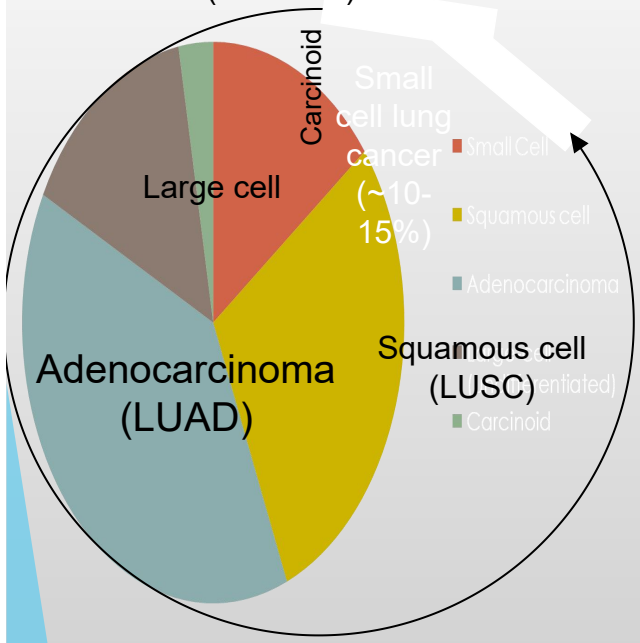




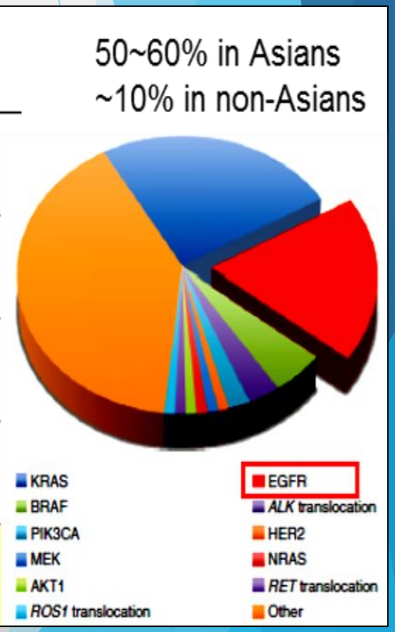
Phenotypes of Lung Cancer

Non-small cell lung cancer (NSCLC) (~85-90%)

Lung cancer is one of the most common and serious types of cancer



Patients/year	Advanced NSCLC patients	**EGFR mutation case (%)**	**EGFR TKI resistance (%)**
Taiwan	~11,300	~5,100 (40-45)	~5,100 (40-45)
Japan	~68,500	~29,100 (40-45)	~29,100 (40-45)
U.S.	~131,000	~16,300 (10-15)	~16,300 (10-15)
Europe	~224,000	~28,000 (10-15)	~28,000 (10-15)
Global	~1,240,000	**~372,000**	**~372,000**

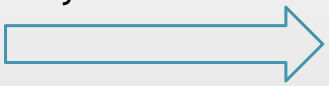


The Major hurdles for NSCLC treatment

EGFR tyrosine kinase inhibitor, TKI (FDA approved)

Generation	1		2	3
	Reversible		Irreversible	T790M mutant selective, irreversible
Drug	Gefitinib	Erlotinib	Afatinib	Osimertinib
US approved	2003	2004	2013	2015

Several months to 1.5years

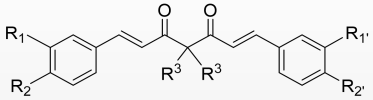


Drug resistance

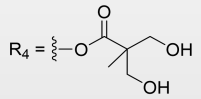
Could the new small molecules developed by our team overcome the TKI-resistance in lung cancer?

Diarylheptanoid 35d overcomes EGFR TKI resistance by inducing hsp70-mediated lysosomal degradation of EGFR in EGFR-mutant lung adenocarcinoma, *J. Biol. Chem.*, **2023**, *299*, 104814-104830

Screening of derivatives against EGFR-mutant TKI-resistant LUAD cells

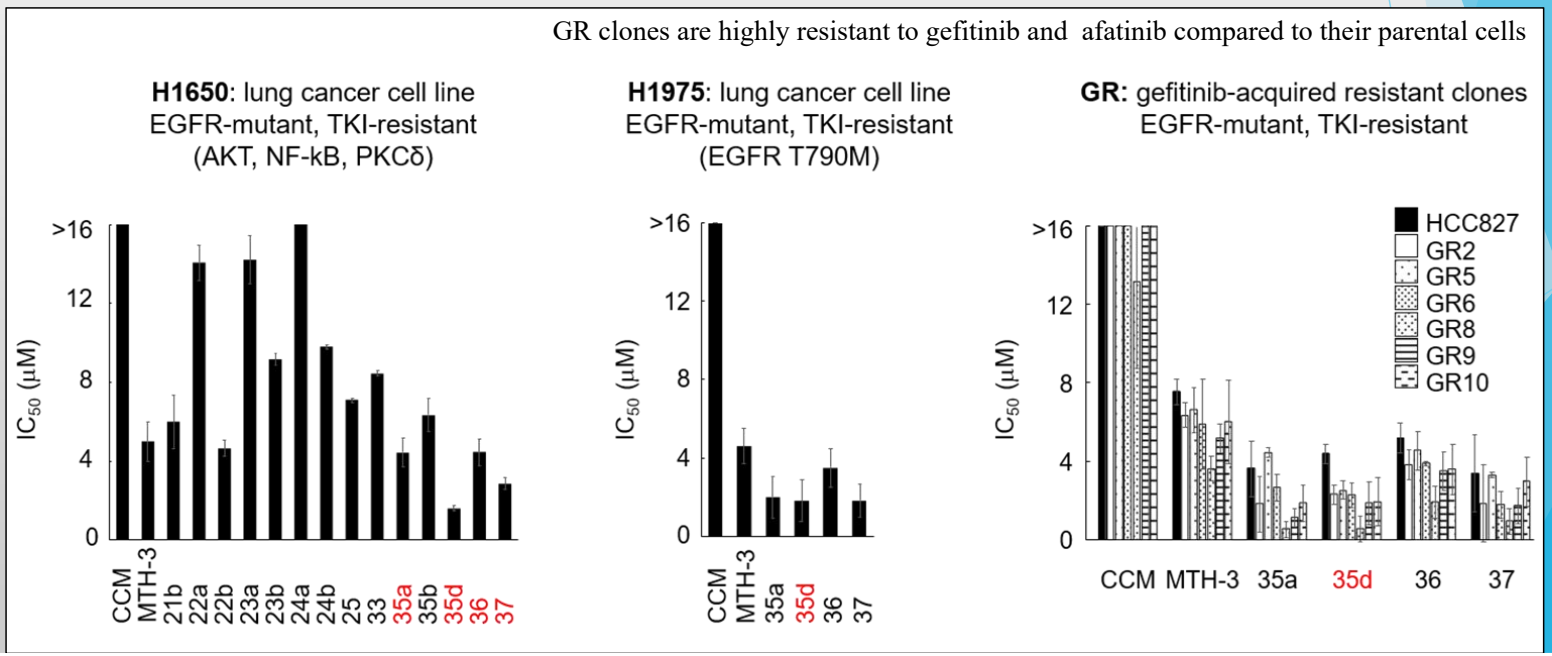


35a, R_1, R_1' = OCH_3, R_2, R_2' = R_4, R_3 = Me
35b, R_1, R_1' = OCH_3, R_2, R_2' = R_4, R_3 = Et
35d, R_1, R_1' = OCH_3, R_2, R_2' = R_4, R_3 = Propargyl
36, R_1, R_1' = H, R_2, R_2' = R_4, R_3 = Me
36, R_1, R_1' = R_4, R_2, R_2' = OCH_3, R_3 = Me

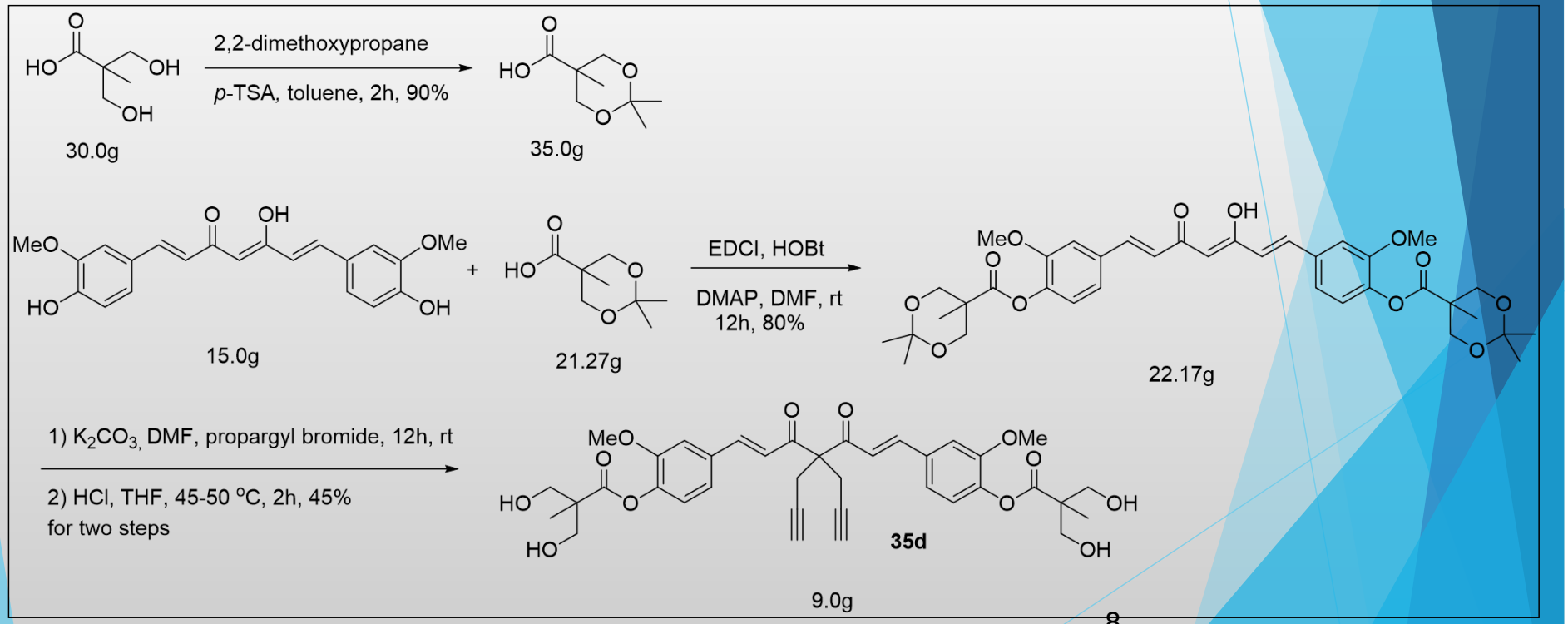


CCM=薑黃素Curcumin;
Diarylheptanoid derivatives (**21b、22a、22b、23a、23b、24a、a25、33、35a、35b、35d、36、37**)

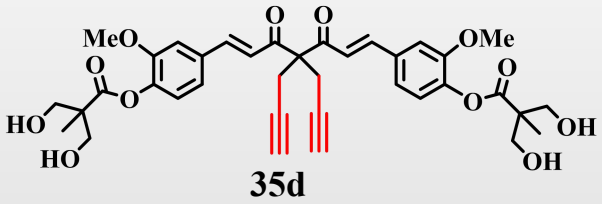
GR clones are highly resistant to gefitinib and afatinib compared to their parental cells



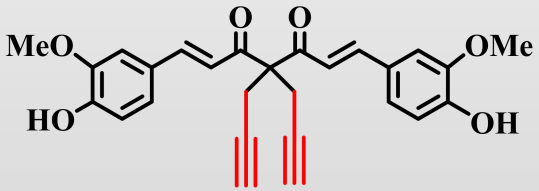
Synthetic procedure of 35d



Preliminary PK study of 35d



35d



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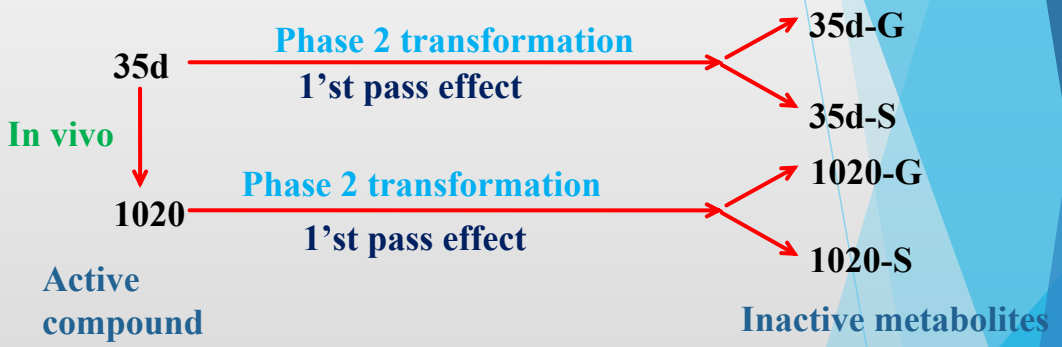
Metabolic pathway of 35d



Toxicology study of 35d

Single dose

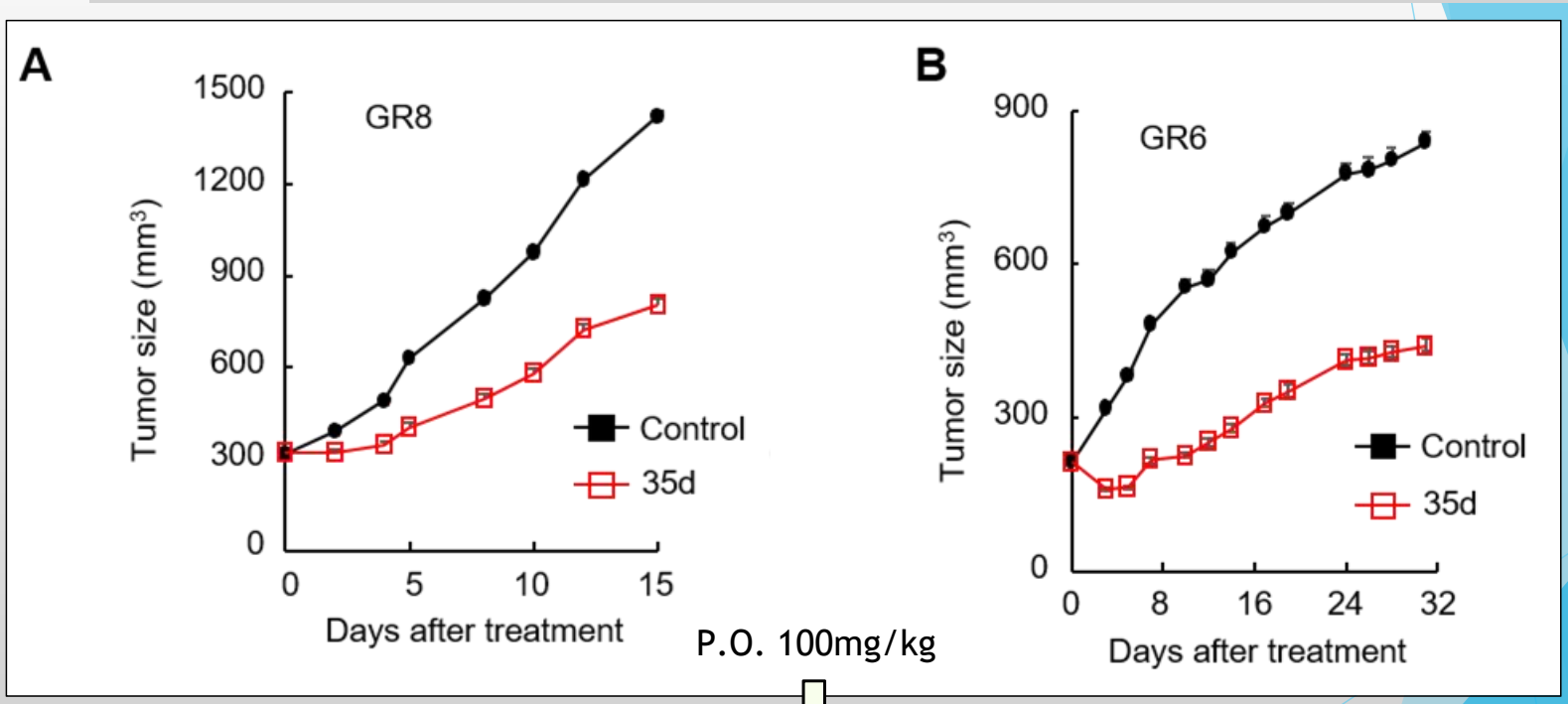
Treatment Groups	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)	Compound Concentration (mg/ml)	Number of Male rat	Dose Frequency	Route	Survival	Survival Rate	Vehicle
1	Vehicle	---	20	---	#1	Once	P.O.	1/1	100%	5% EtOH + 10% Tween-80 + 85% saline
2	Compound N7	600	20	30	#2	Once	P.O.	1/1	100%	
3	Compound N7	500	16.7	30	#3	Once	P.O.	1/1	100%	
4	Compound N7	400	13.3	30	#4	Once	P.O.	1/1	100%	
5	Compound N7	300	10	30	#5	Once	P.O.	1/1	100%	
6	Compound N7	200	6.7	30	#6	Once	P.O.	1/1	100%	
7	Compound N7	100	3.3	30	#7	Once	P.O.	1/1	100%	

Repeat dose

Treatment Groups	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)	Compound Concentration (mg/ml)	Number of Male rat	Dose Frequency	Route	Survival	Survival Rate	Vehicle
1	Vehicle	--	20	--	#1, #3, #4, #13, #16	Day 1- Day 14	P.O.	5/5	100%	5% EtOH + 10% Tween-80 + 85% saline
2	Compound N7	600	20	30	#9, #10, #11, #12, #15	Day 1- Day 14	P.O.	5/5	100%	
5	Compound N7	300	20	15	#5, #6, #8, #17, #18	Day 1- Day 14	P.O.	5/5	100%	

The hematology of the animals in the repeat dose group indicated that **35d** didn't cause adverse effects.

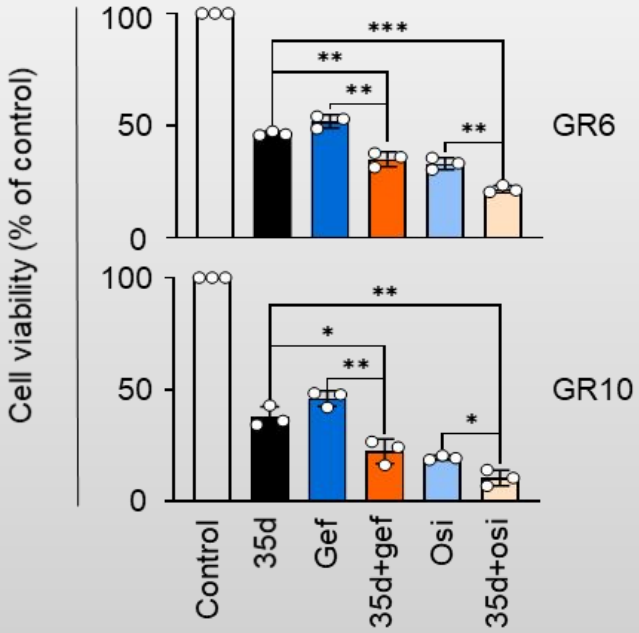
Collateral sensitivity of diarylheptanoid 35d to TKI-resistant tumor cells in *in vivo* studies

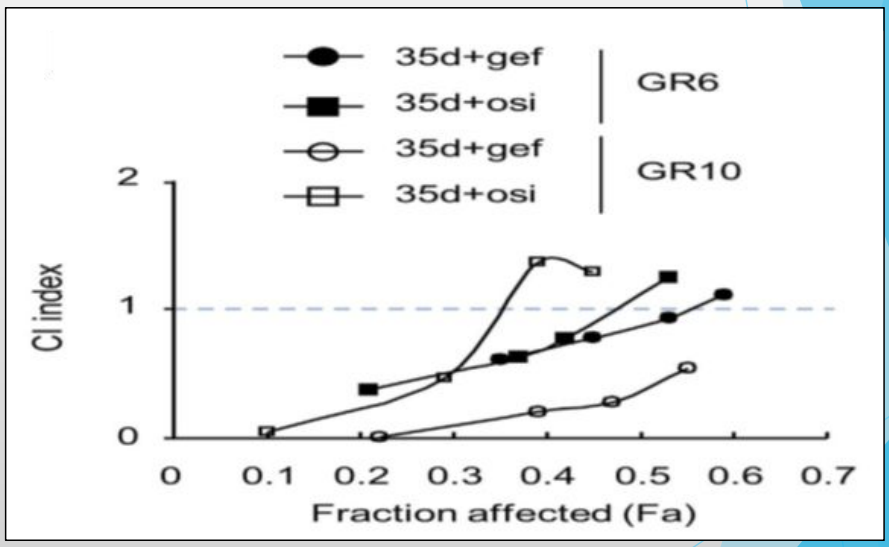


P.O. 100mg/kg

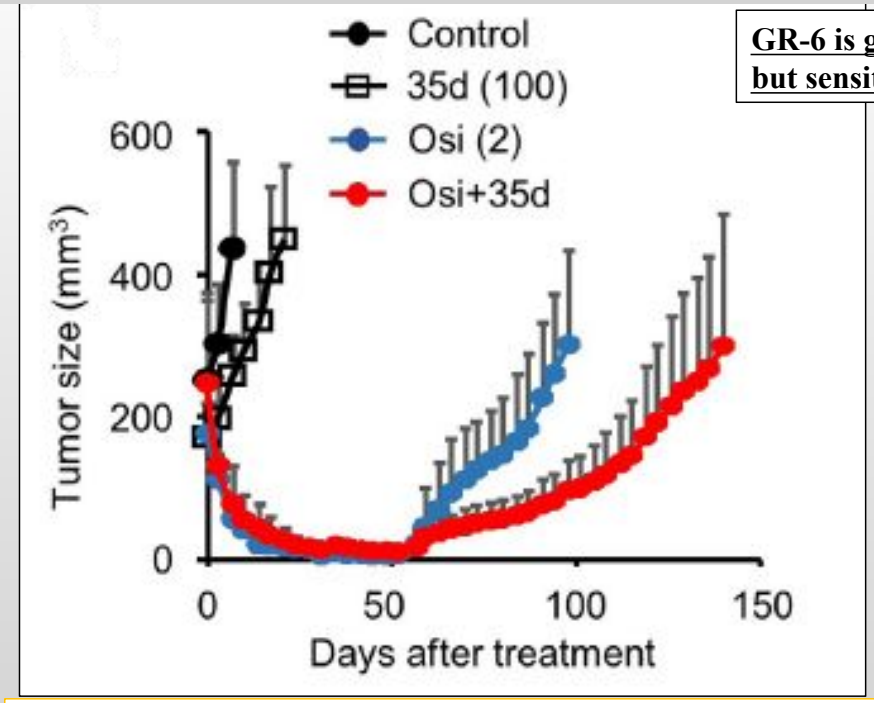
Try drug combination

Combination study of 35d and TKIs in gefitinib-resistant lung cancer





Combination of 35d and osimertinib suppressed GR6 tumor re-growth after osimertinib treatment

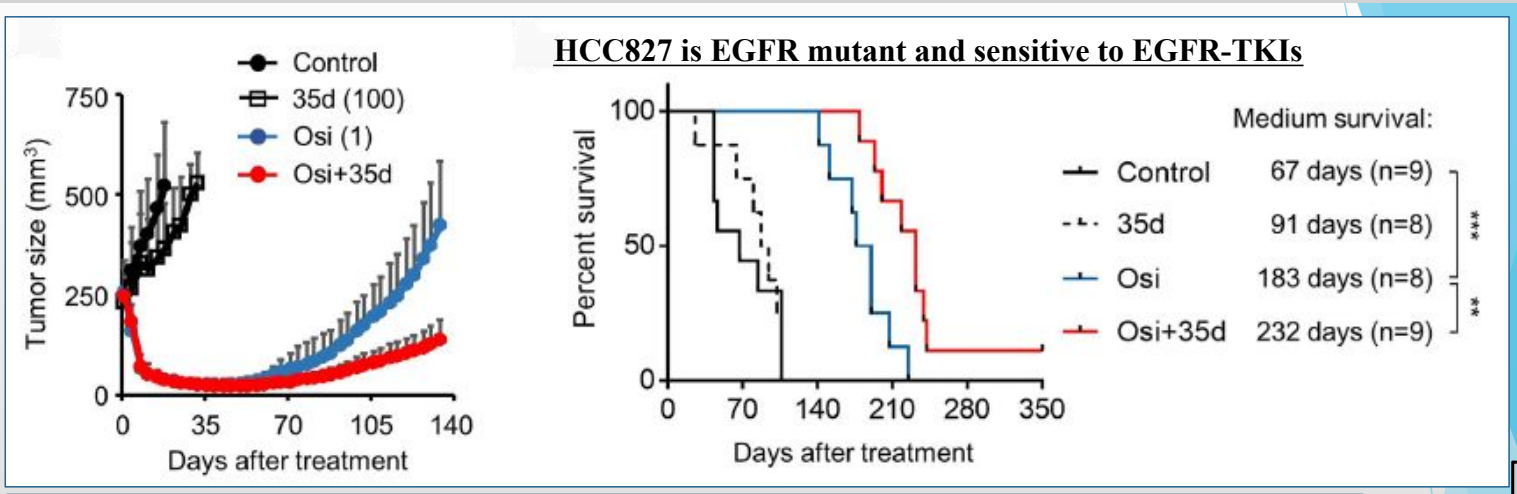


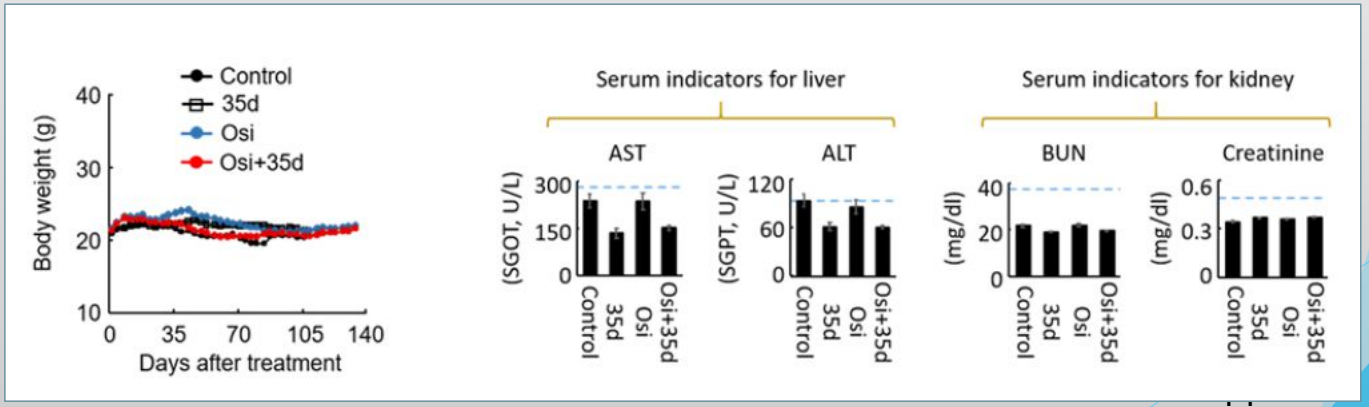
GR-6 is gefitinib-resistant but sensitive to osimertinib

GR-6 developed resistantace after around 60 days of osimertinib treatment

Combination of 35d significant delayed the osimertinib resistance

Combination of 35d and TKI suppressed tumor re-progression after acquiring TKI-resistance

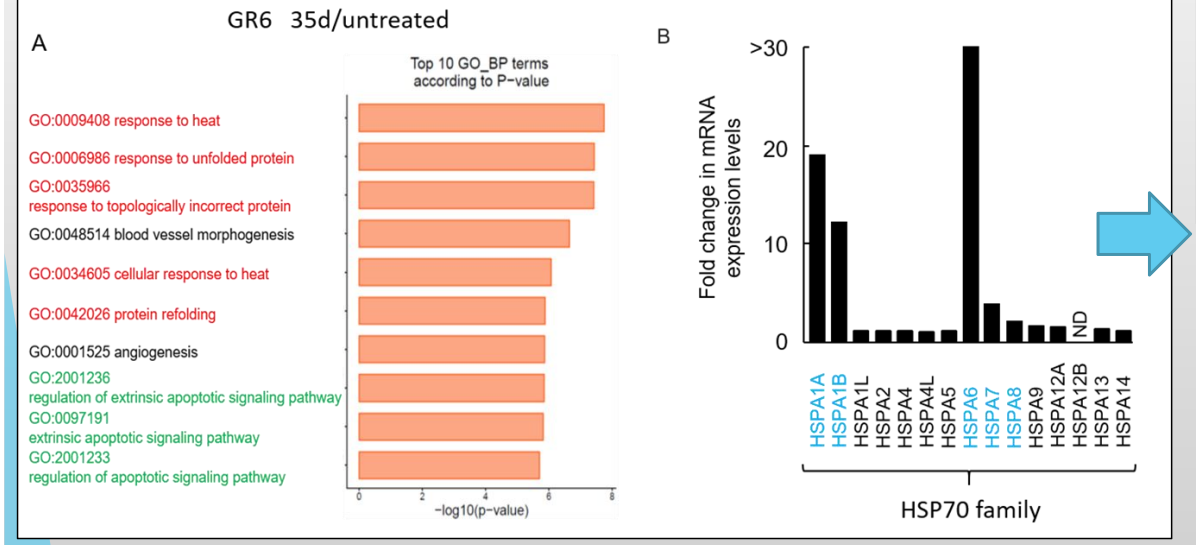




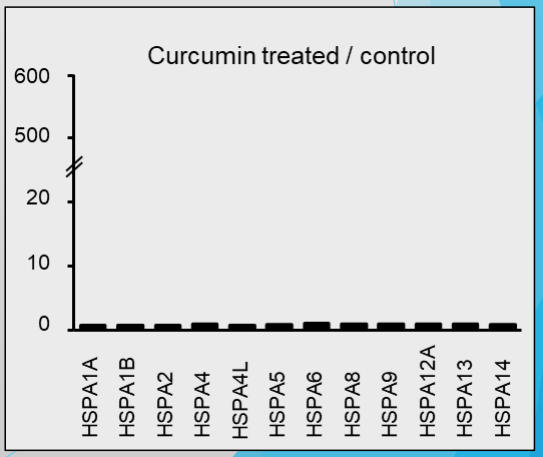
Combination of 35d significant delayed the osimertinib resistance

Investigation of MOA

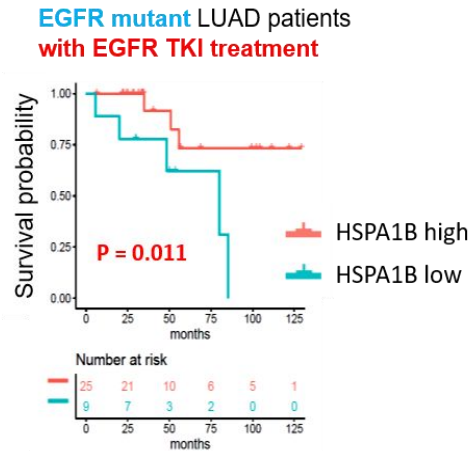
Global transcriptional analysis by RNA-seq revealed inductions of heat response and apoptosis by diarylheptanoid 35d



Cancer Lett. **2018**, *424*, 84-96.



HSPA1B (heat-shock protein70, HSP70) was significantly associated with good OS of EGFR-mutant lung cancer patients treated with TKI



Nature genetics, *52*, pages177–186 (2020)


nature genetics

ARTICLES

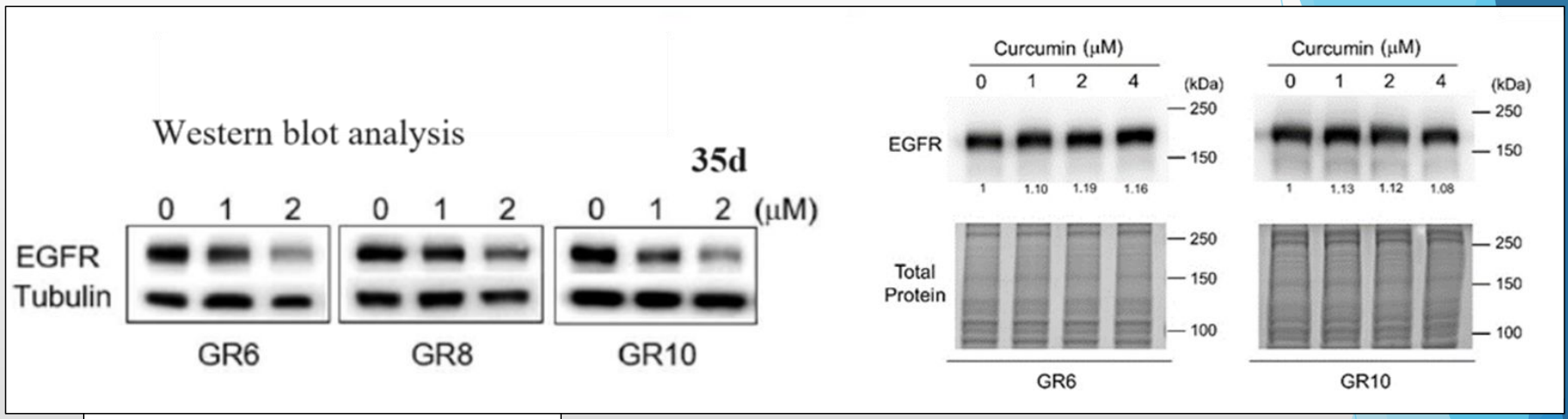
https://doi.org/10.1038/s41588-019-0569-6

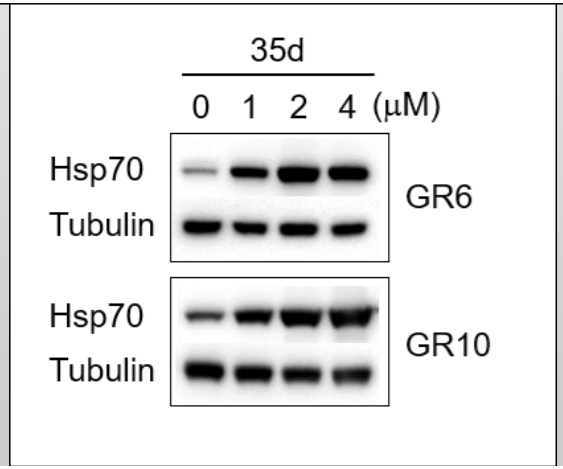
Genomic landscape of lung adenocarcinoma in East Asians

Jianbin Chen[1], Hechuan Yang[1,2], Audrey Su Min Teo[1], Lidyana Bte Amer[1], Faranak Ghazi Sherbaf[1], Chu Quan Tan[1], Jacob Josiah Santiago Alvarez[1], Bingxin Lu[1], Jia Qi Lim[1], Angela Takano[3], Rahul Nahar[1], Yin Yeng Lee[1], Cheryl Zi Jin Phua[1], Khi Pin Chua[1], Lisda Suteja[4], Pauline Jieqi Chen[1], Mei Mei Chang[1], Tina Puay Theng Koh[5], Boon-Hean Ong[6], Devanand Anantham[7], Anne Ann Ling Hsu[7], Apoorva Gogna[8], Chow Wei Too[8], Zaw Win Aung[9], Yi Fei Lee[1,10], Lanying Wang[9], Tony Kiat Hon Lim[3], Andreas Wilm[1], Poh Sum Choi[1], Poh Yong Ng[1], Chee Keong Toh[4], Wan-Teck Lim[4,11], Siming Ma[1], Bing Lim[1], Jin Liu[12], Wai Leong Tam[1,10,13,14], Anders Jacobsen Skanderup[1], Joe Poh Sheng Yeong[3,11], Eng-Huat Tan[4,9], Caretha L. Creasy[15], Daniel Shao Weng Tan[1,4,16]*, Axel M. Hillmer[1,17]* and Weiwei Zhai[1,2,10,18]*

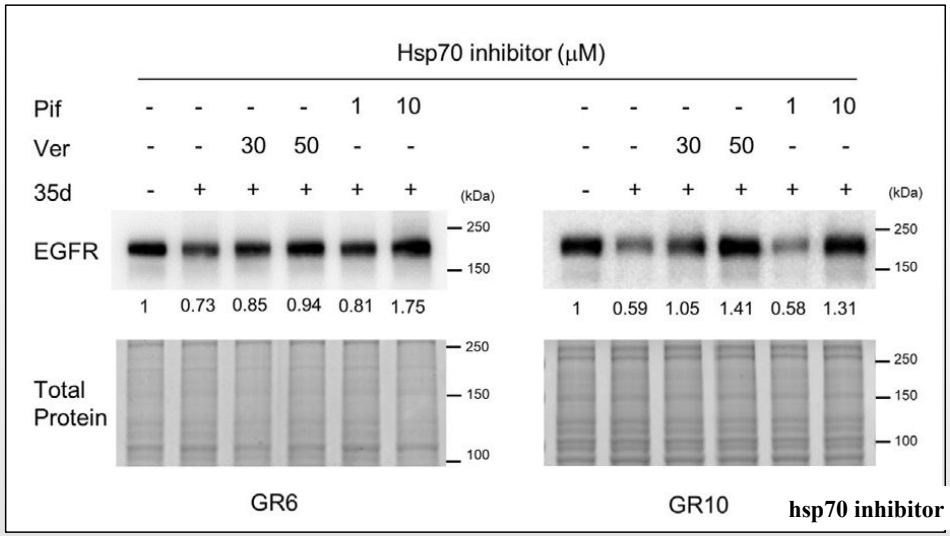
★ Patients with high HSP70 expression in TKI treatment had higher OS

35d suppressed EGFR protein in GR cells



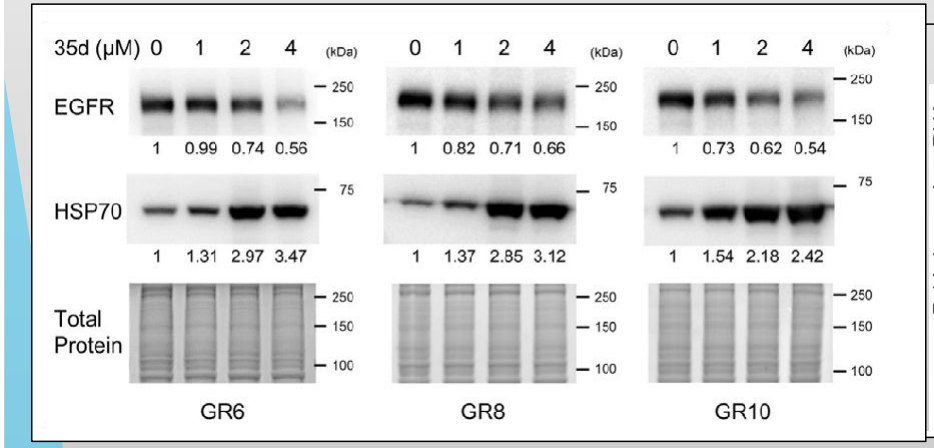


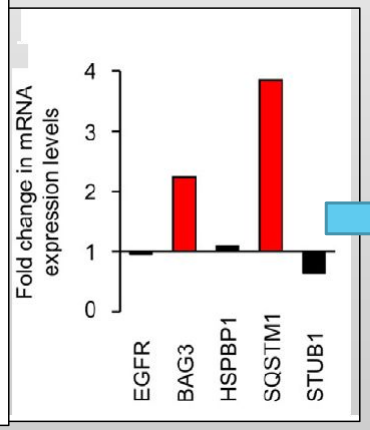
35d upregulated HSPA1B gene expression and reduced EGFR protein expression. **35d** may reduce EGFR expression by activating hsp70-mediated pathways.



Inhibition of hsp70 by pif and ver reversed **35d**-induced reduction of EGFR expression in GR6 and GR10 cells, indicating that 35d led to suppression of EGFR protein through hsp70-mediated pathways.

hsp70 inhibitor ver-155008 (ver) and pifithrin (pif)

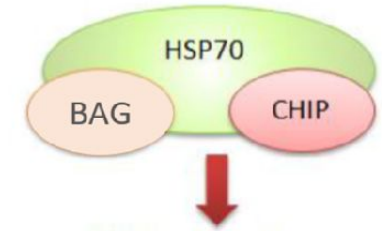


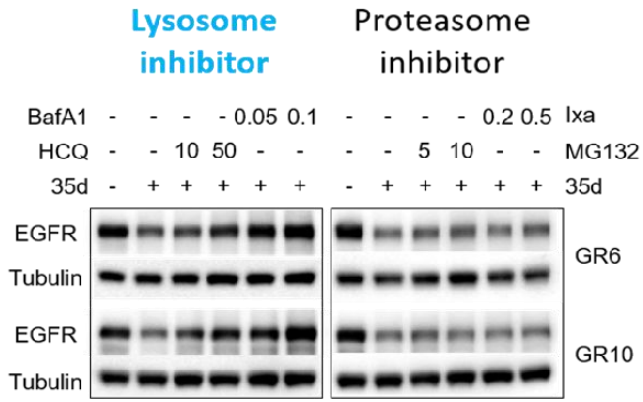


35d reduced EGFR protein expression, but not mRNA expression, suggesting that 35d may lead to EGFR protein degradation through induction of hsp70 pathway.

35d activates Hsp70 and causes EGFR degradation through proteasome pathway

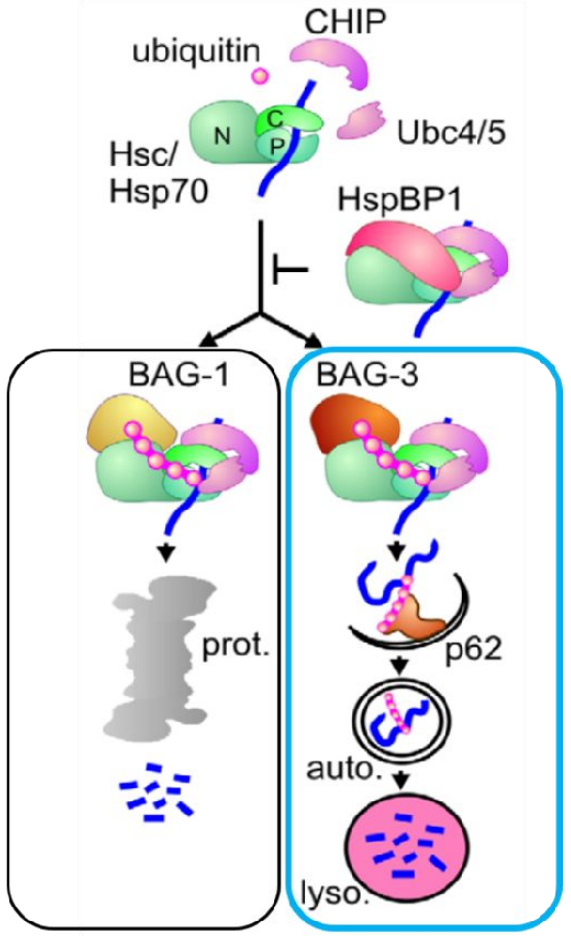
Hsp70 complex was reported to involve lysosome or proteasome pathways as major degradation systems in the cells.

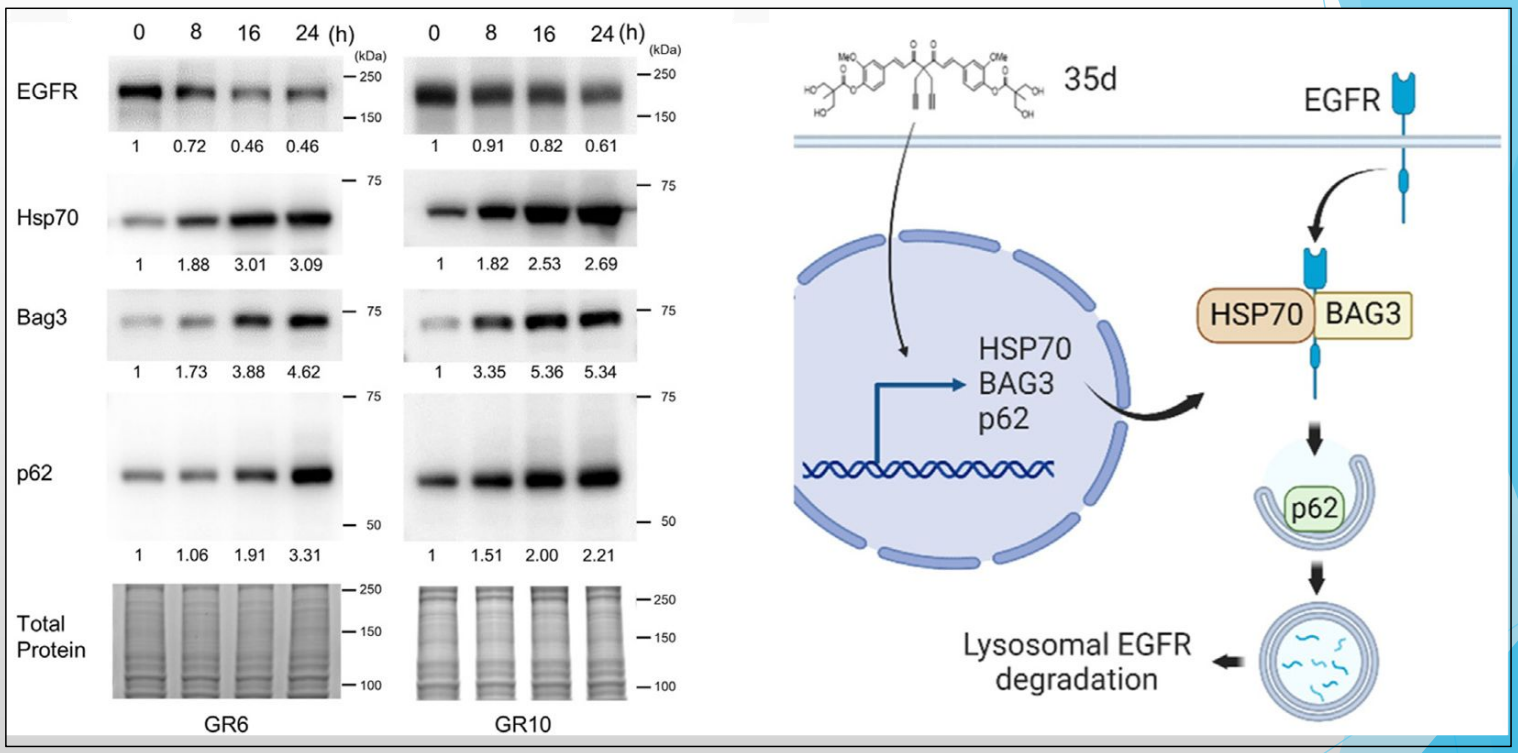




*lysosome inhibitors hydroxychloroquine (HCQ) and bafilomycin A (bafA)
*proteasome inhibitors MG132 and ixazomib (ixa)

CHIP (C-terminus of HSP70/HSC70 interacting protein): a ubiquitin ligase





Treatment of **35d** upregulates the expression of hsp70 complex components, hsp70, bag3, and p62, which lead to EGFR protein degradation through lysosome dependent pathway.

Potential clinical application of 35d

35d-osimertinib combination could be used in EGFR-mutant LUAD patients who have acquired resistance to prior-line TKIs or as a first-line therapy for naïve patients in the future.

Global patent portfolio

嫟儀勤磋	嫟儀琊覢嵋旗	嫟儀牉訒蕡	雯訒撼时	嫟儀嬗嗢儇/列嚶
新穎類薑黃素衍生物及其做為抗癌藥劑的用途	20170603	TWI731096B	20210621	台灣
Novel Derivatives of Curcuminoids and Use Thereof as an Anticancer Agent	20170602 20170602 20170602 20170602 20170602 20170602 20170602 20170602	US10787413 B2 AU62/349208B2 CA3029459B2 EP3433225B1 KR2127852B1 JP6940527B2 CN109689608A IN400493A	20200929 20190828 20210907 20210317 20200630 20210906 20220216 20220630	美國 澳洲 加拿大 歐盟 韓國 日本 大陸 印度
Bis(hydroxymethyl) alkanoate diarylheptanoids for use in treating lung cancer	20211214	PCT/CN2021/137647	WO2022/127751	美國; 澳洲; 加拿大; 俄羅斯; 韓國; 日本; 大陸; 巴西; 墨西哥
醫藥組合物治療肺癌之用途	20211214	TW1798994B	20230411	台灣

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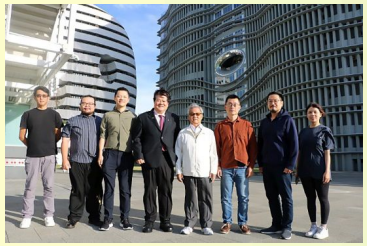
Min-Tsang Hsieh (Associate professor, department of pharmacy, CMU)
Pei-Chih Lee (Assistant professor, graduate institute of cell biology, CMU)
Yu-Chi Hou (Professor, department of pharmacy, CMU)
Yi-Ting Chiang (Associate professor, department of pharmacy, CMU)
Ling-Chu Chang (Associate investigator, CMUH)



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3. China Medical University hospital

Technology transfer

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