治療抗藥性癌症的小分子藥物

藥物化學營研討會

08/05/2021

中國醫藥大學

謝閔滄 副教授

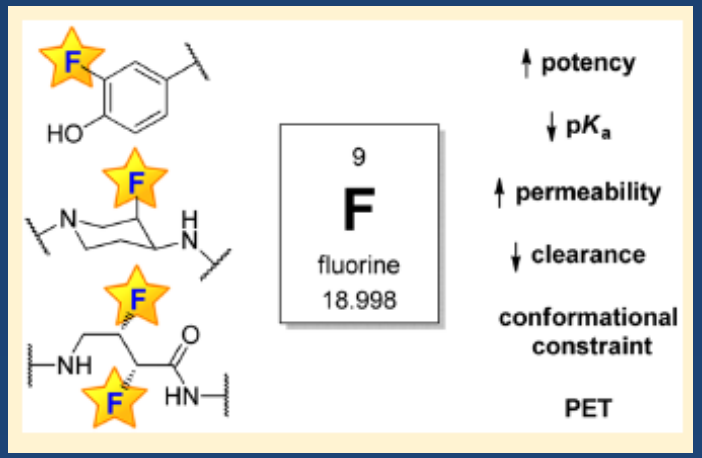
Our lab

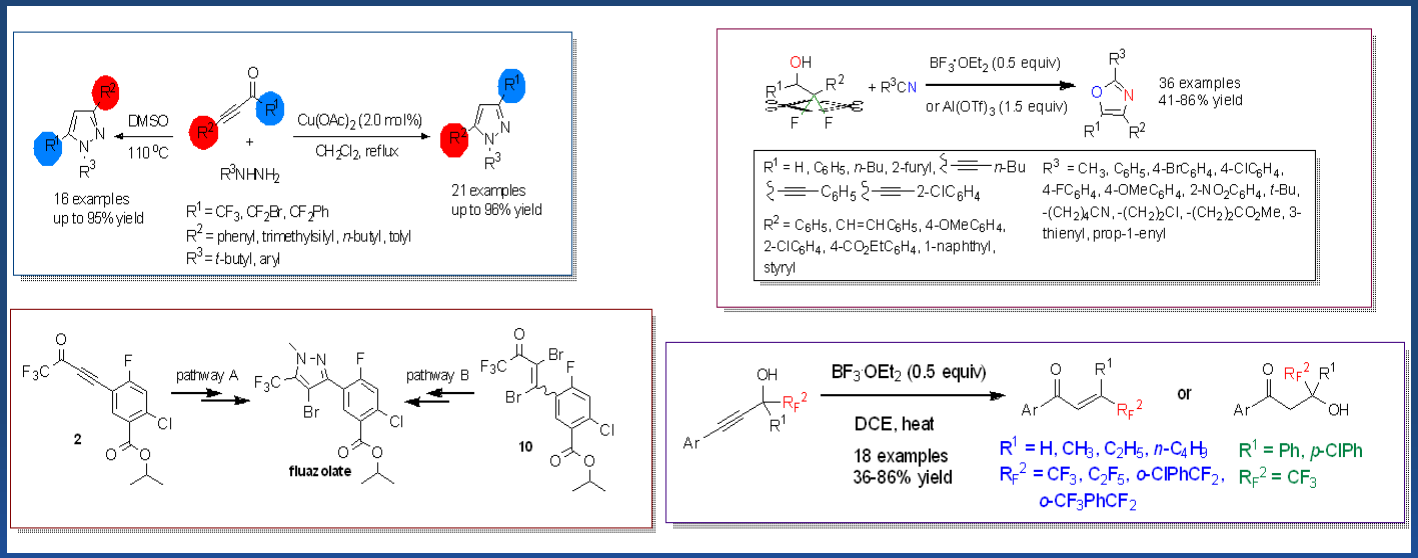
Culture room

Warehouse

Our research

實驗室近年的研究方向分為兩部份:
(1) 新穎之有機氟化物合成方法開發及應用：此研究是開發有效率的方法合成含有氟原子的藥物活性分子





1. *ADVANCED SYNTHESIS & CATALYSIS* · **2015**, 683-689.
2. *TETRAHEDRON* · **2016**, 5880-5885.
3. *ADVANCED SYNTHESIS & CATALYSIS* · **2018**, 1605-1610.
4. *SYNLETT* · **2019**, 356-360.
5. *EUROPEAN JOURNAL OF ORGANIC CHEMISTRY,* **2020**, 5207-5210.

(2) 活性天然物結構修飾開發可治療抗藥性癌症的小分子藥物：此部份研究是由實驗室成員進行藥物分子結構修飾、體外活性試驗、動物抗腫瘤活性評估以及藥物動力學評估找出抗癌候選藥物

癌腫瘤抗藥性的成因

1. 腫瘤異質性: 腫瘤母細胞進行複製與分裂的過程中，產生的子細胞因為基因變異產生差異化，造成新生腫瘤癌細胞在生長速度、轉移程度及藥物感受性逐漸與原生癌細胞產生差異，新生癌細胞對藥物感受性可能較原生細胞弱，即是產生抗藥性。

2. 物理性屏障: 癌細胞可以降低腫瘤內血液流動來減少接觸抗癌藥物的機會，或是調控膜蛋白ABC-transporter（ATP-Binding cassette transporter）的表現，ABC-transporter可透過與ATP結合，水解ATP來獲得能量，將藥物排出細胞，使得作用在細胞內受體的藥物濃度不足以殺死細胞。

3. 調整免疫系統和改變癌腫瘤微環境: 癌腫瘤所處周圍的環境稱為腫瘤微環境(tumor microenvironment)，內含血管、炎性細胞、免疫細胞、成纖維細胞、細胞外基質細胞和各種訊息分子。腫瘤與腫瘤微環境進行交互作用，癌細胞釋出訊息分子調控周邊腫瘤微環境，促進腫瘤血管新生和激發免疫耐受性，使原本應該對抗癌細胞的免疫巨噬細胞，反倒變成有助腫瘤生長的腫瘤相關巨噬細胞。

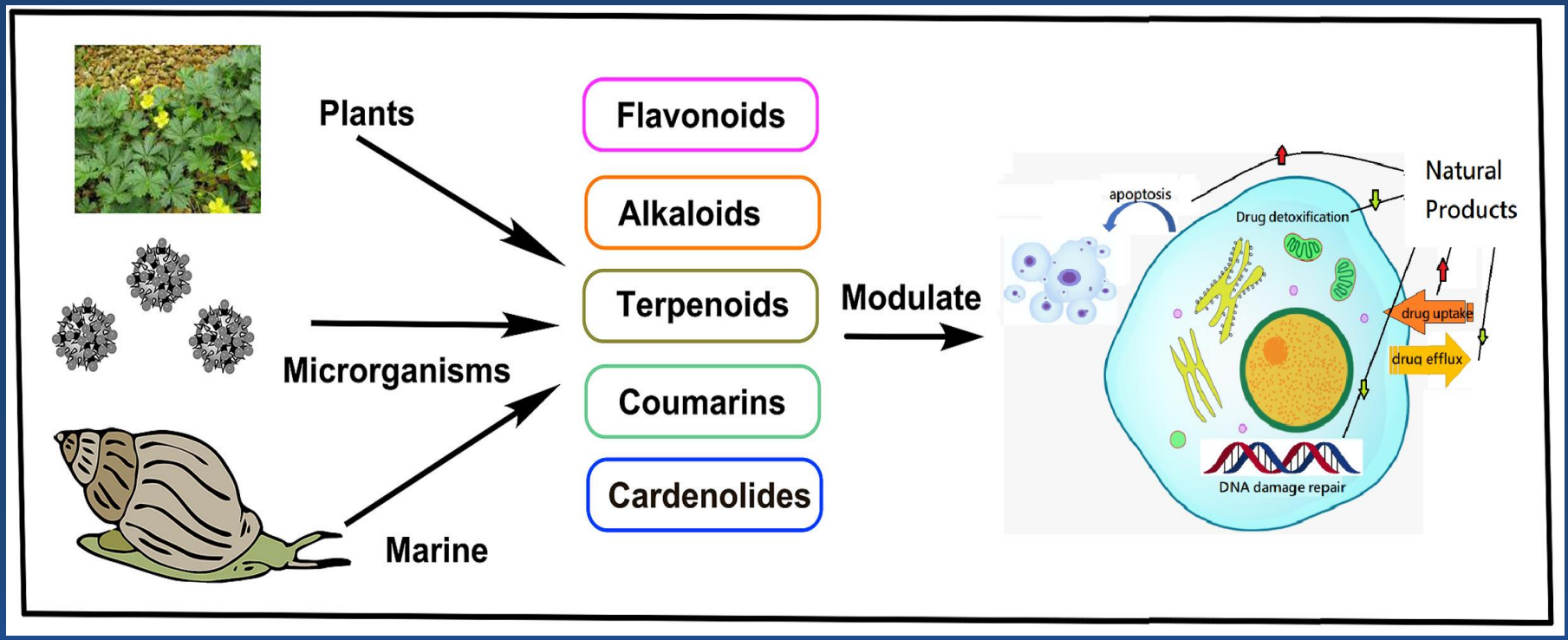
4. 無藥可及的基因驅動因子: 抑制致癌驅動基因突變 (oncogenic driver mutation) 的藥物雖然已獲得成功，但仍有許多重要的致癌或抑制癌症基因 (如MYC, RAS或TP53) 沒有標靶藥物，在治療過程中一旦致癌驅動基因發生突變，原有療法便無法抑制新生癌細胞生成。

5. 癌細胞使藥物失去活性: 長期使用抗癌藥物後，具活性的藥物則可能因為癌細胞發展出使藥物失去活性 (加速藥物代謝) 的酵素而喪失活性，癌細胞即獲得抗藥性。

6. 增加DNA修復能力以及抑制癌細胞的細胞凋亡機制: 化療以及放射性療法會增加癌細胞以及正常細胞基因不穩定性，標靶療法的影響較微弱但癌細胞仍會產生早期的適應性反應和藥物長期使用後的抗藥機制。化療或標靶療法多是造成癌細胞DNA損傷或是引發癌細胞凋亡機制讓癌細胞死亡，因此當基因變異使得癌細胞獲得更好的DNA修復能力或是癌細胞凋亡機制被抑制，藥物便失去作用。

"A view on drug resistance in cancer" *Nature*, **2019**, *575*, 299-309.

Natural products to treat drug resistance in cancer



"Natural products as multidrug resistance modulators in cancer"
European Journal of Medicinal Chemistry, **2019**, *176*, 268-291

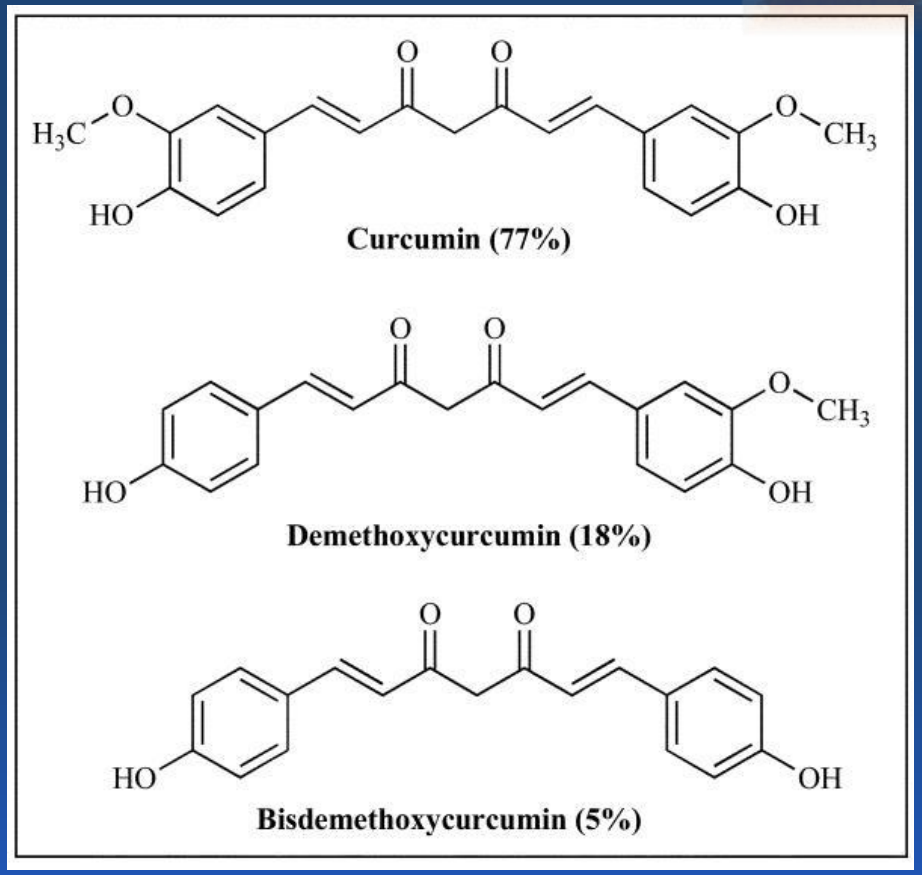
Major components of Turmeric (curcuma longa)

Curcuminoid

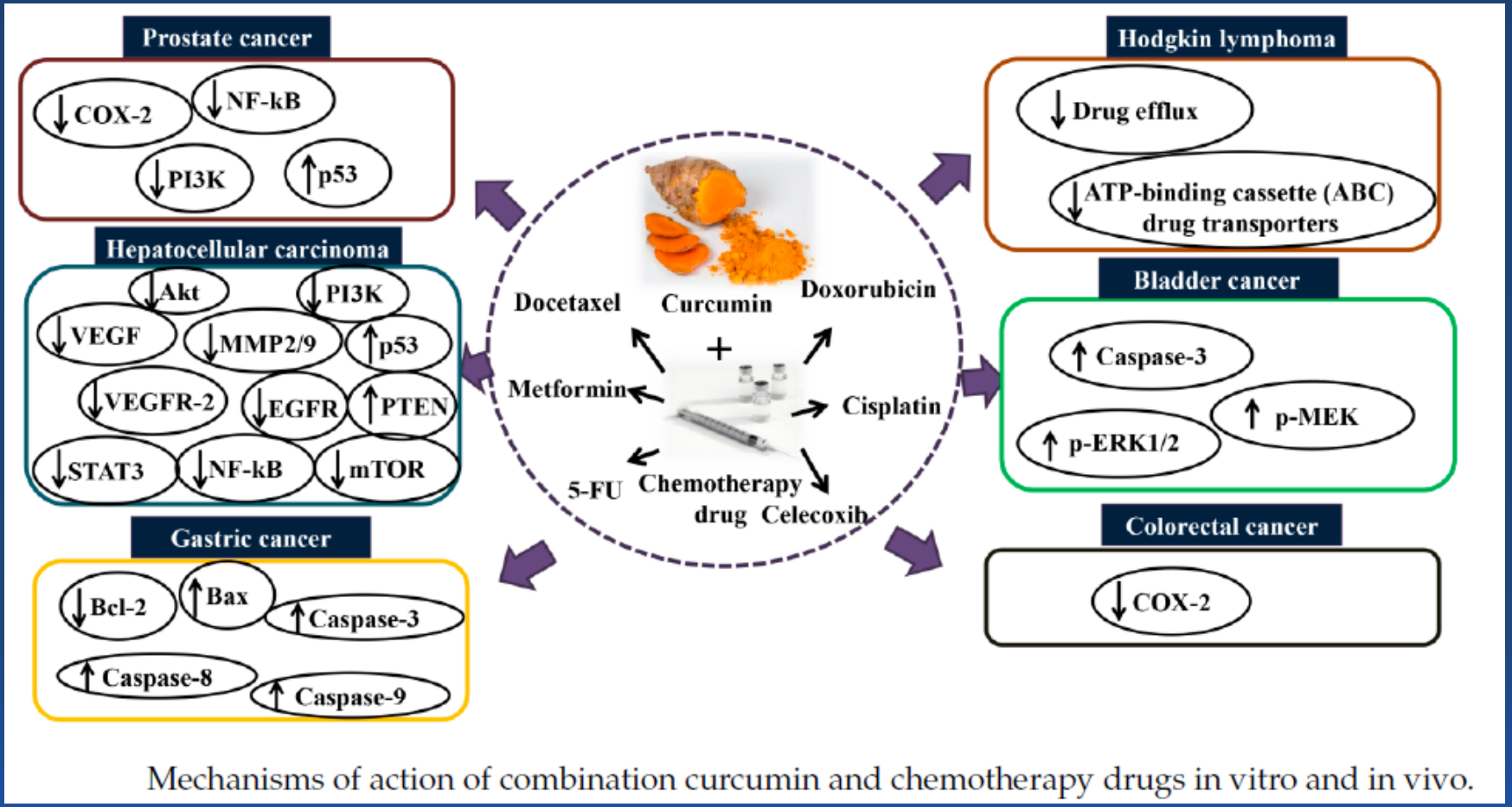
Curcumin I
The most studied component

Curcumin II

Curcumin III



*Studies on curcumin and curcuminoids XXXI. Symmetric and asymmetric curcuminoids: stability, activity and complexation with cyclodextrin". Int J Pharm. 2007, **338**, 27–34*

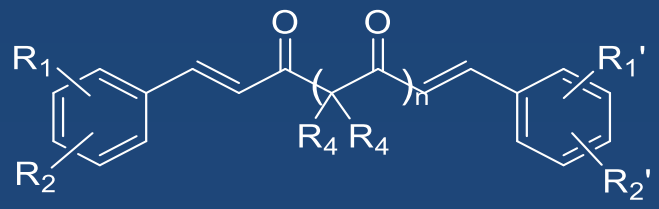


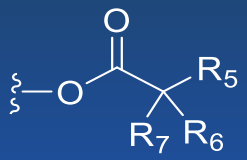
Mechanisms of action of combination curcumin and chemotherapy drugs in vitro and in vivo.

"Curcumin Combination Chemotherapy: The Implication and Efficacy in Cancer"
***Molecules* 2019, *24*(14), 2527**

New small molecule drugs: bis(hydroxymethyl) alkanoate diarylheptanoids

1. **Derivatives themselves show moderate to weak in vitro/vitro anticancer activity against breast, colon, prostate and lung cancer cell.**
2. **When combined with clinical drugs for the treatment of drug-resistant cancer, a synergistic effects were realized.**



R_1, R_2, R_1', R_2' = H, OH, OR, 

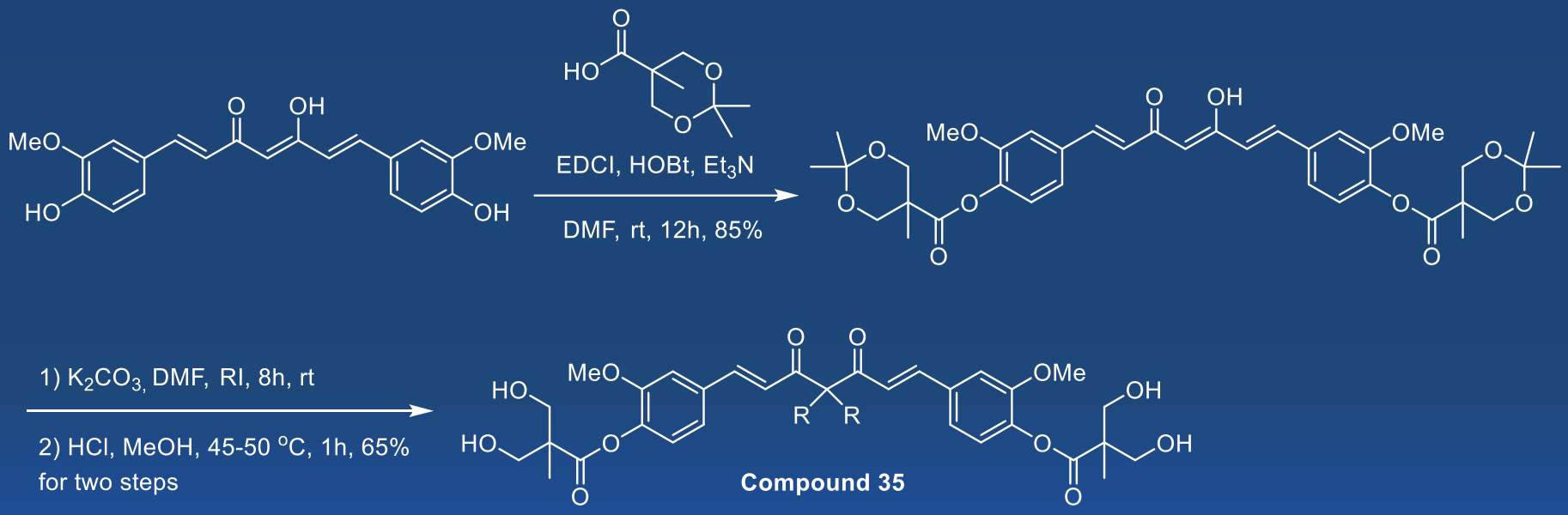
R_4 = H, alkyl R_5, R_6, R_7 = H, OH, alkyl [at least one R_5, R_6, R_7 is $-(CH_2)_mOH$]

n = 0~3, m = 0~3

Fig 1. General structure

Synthetic procedure of diarylheptanoid 35

The bis(hydroxymethyl) alkanoate diarylheptanoids are synthesized in high yield by relatively easy 3-4 steps synthetic procedures. The synthesis procedure is illustrated in scheme 1 using 35a as an example.



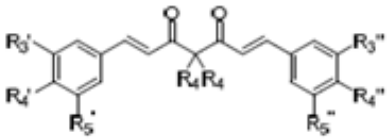
Scheme 1

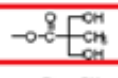
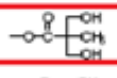
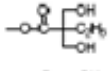
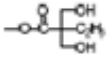
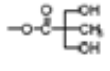
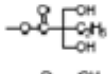
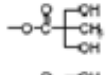
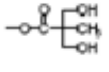
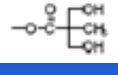
In vitro studies

Growth Inhibitory Activity of Target compounds against MDA-MB-231, HCT-116, PC-3, CAR and HT29 cell lines

Selected examples of in vitro study

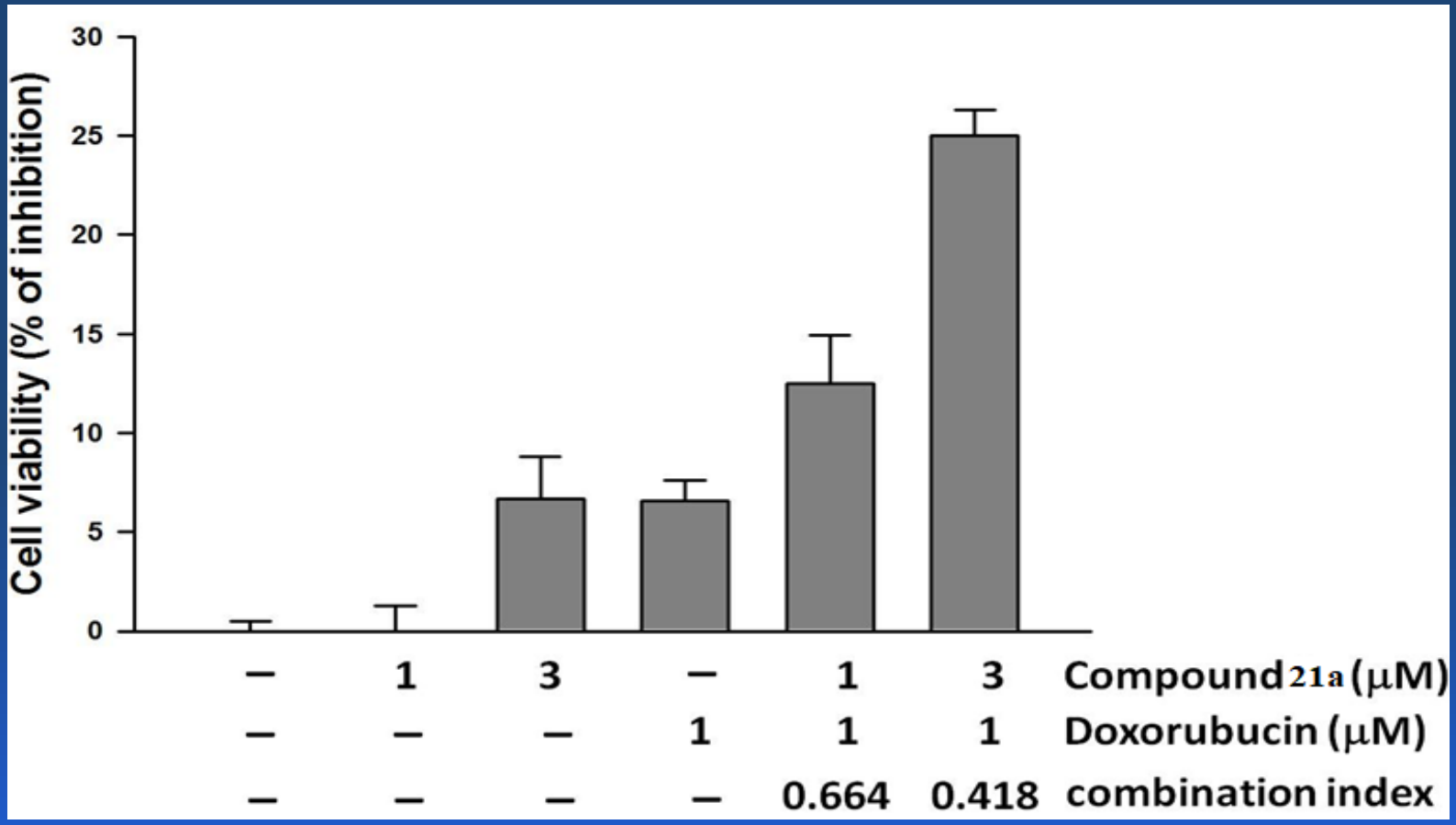
Table 1A. The IC_{50} of curcumoid derivatives in cell viability of MDA-MB-231 breast cancer cell



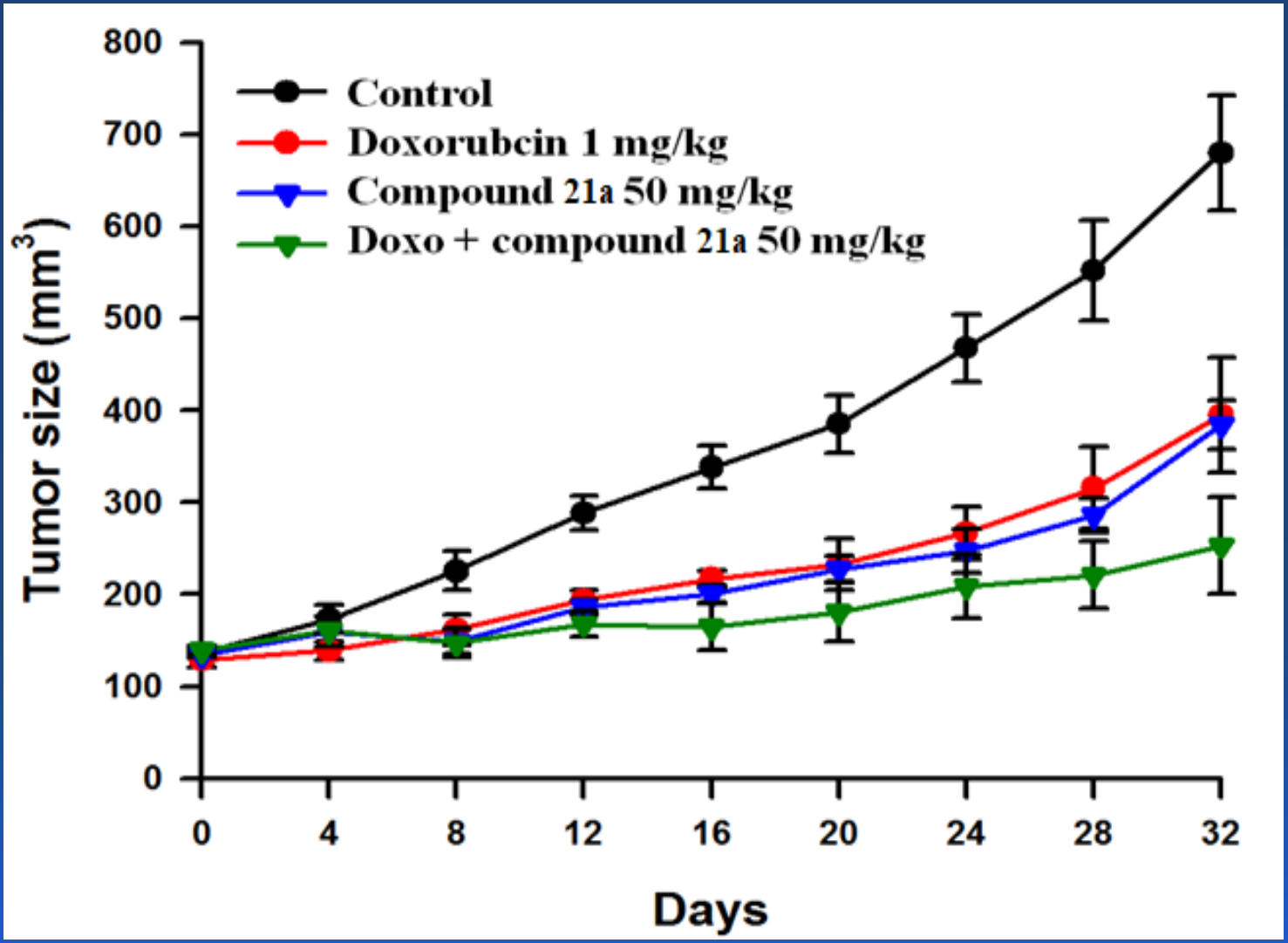
Compound	R_3'	R_3''	R_4'	R_4''	R_4	R_5', R_5''	$IC_{50}^{a,b}$ (μM)		
							24 hours	48 hours	72 hours
Curcumin	OCH_3	OCH_3	OH	OH	H	H	38.77 ± 3.35	22.05 ± 2.97	16.23 ± 0.24
Bisdemethoxy-curcumin	H	H	OH	OH	H	H	>100	26.92 ± 0.19	27.53 ± 0.42
1	OH	OH	OCH_3	OCH_3	H	H	>100	6.93 ± 0.06	6.55 ± 0.29
21a	OCH_3	OCH_3			H	H	5.37± 1.22	3.06 ± 0.18	2.67 ± 0.18
22a	OCH_3	OCH_3			H	H	4.71 ± 0.29	2.56 ± 0.18	2.00 ± 0.16
21b	OCH_3	OCH_3		OH	H	H	13.18 ± 1.20	9.97 ± 1.12	5.94 ± 0.78
22b	OCH_3	OCH_3		OH	H	H	14.55 ± 2.42	7.55 ± 0.86	4.66 ± 0.34
23a	H	H			H	H	26.66 ± 1.85	7.82 ± 0.56	6.74 ± 0.54
23b	H	H		OH	H	H	19.52 ± 1.82	5.27 ± 0.57	1.33 ± 0.05

Synergistic effect of 21a

21a was used in combination with Doxorubicin to treat MDA-MB-231 cell and resulted inhibitory activity was shown below, in which the presence of synergistic effect was observed



In vivo Antitumor Activity of 21a Combined with Doxorubicin in Xenograft Model



80 % inhibition
N = 5

開發小分子藥物治療抗藥性肺癌

肺癌治療概況

根據衛福部統計，在台灣每年約有13,000人罹患肺癌，9000人死於肺癌，在美國每年約有234,000人罹患肺癌，154,000人死於肺癌，**全世界癌症人口約有20%是肺癌患者，肺癌無論是在歐美日先進國家、或是發展中以及低開發的國家，其死亡率皆高**。在台灣的肺癌患者約有85-90%為非小細胞癌患者，EGFR突變可使用臨床標靶治療用藥EGFR抑制劑（Fig. 2）

第一代	第二代	第三代
First genertion (target WT EGFR)	Second generation (irreversible inhibitors of EGFR and HER 2)	Third generation (EGFR mutant-specific, irreversible inhibitors)
Erlotiniba	Neratinib	AZD9291 (AstraZeneca)
Gefitinib	Afatiniba	Osimertinib 泰格莎
Icotinib	Dacomitinib	Tagrisso®

Fig. 2

EGFR 突變（EGFR 19del或L858R /T790M/C797S）

使用第一或第二代EGFR抑制劑，平均9個月至1年左右就會面臨EGFR突變產生抗藥性，之後使用第三代標靶藥物Tagrisso 繼續治療，1到2年後即可能再失效。由此而知，**藥物產生抗藥性是目前肺癌治療的一大問題**

常見抗藥機制包括：EGFR T790M mutation、HER2 amplification、MET amplification 、以及小細胞的組織學轉化等等

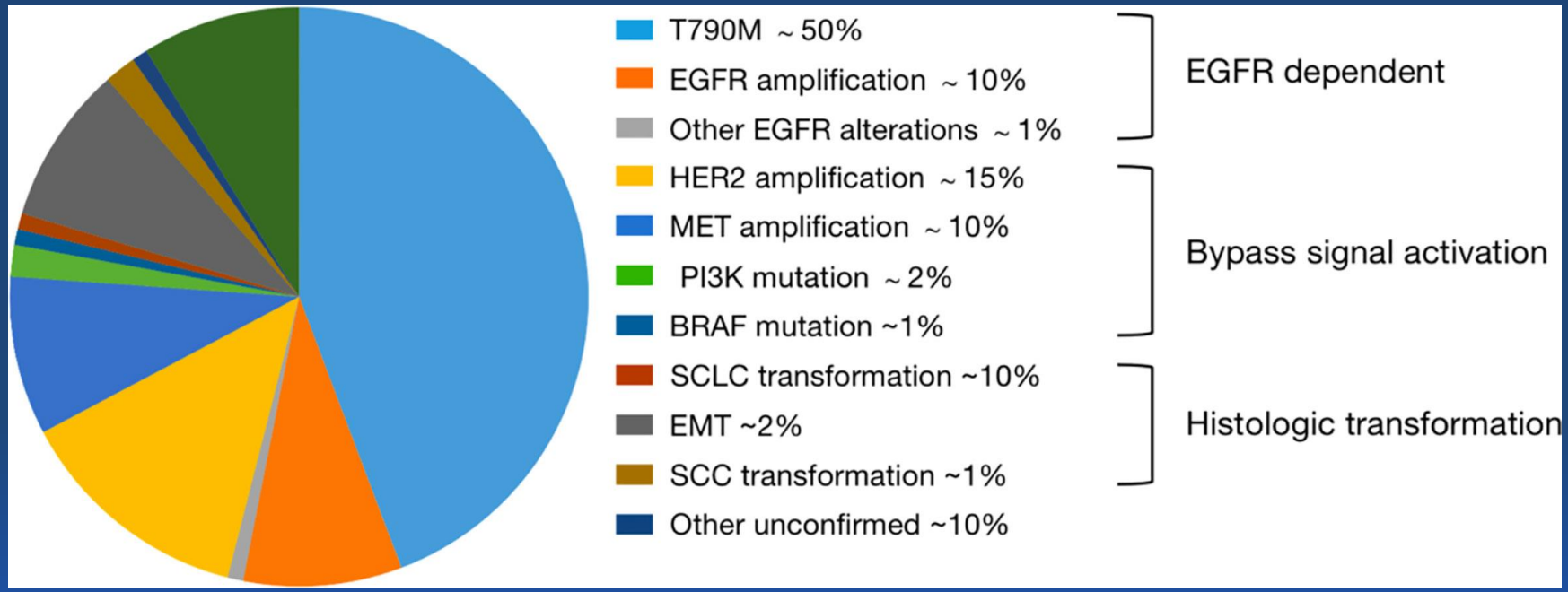
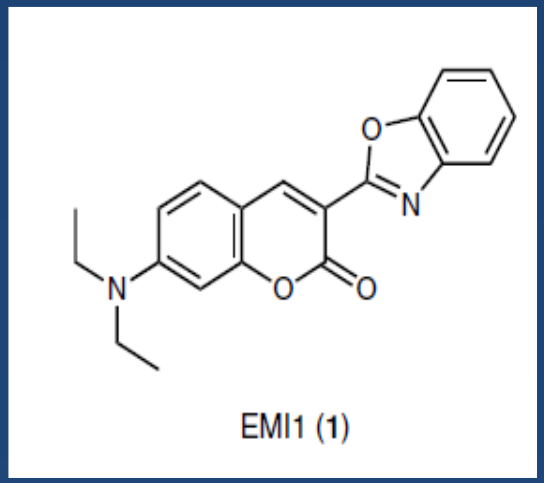


Fig. 3

"Development of EGFR TKIs and Options to Manage Resistance of Third-Generation EGFR TKI Osimertinib: Conventional Ways and Immune Checkpoint Inhibitors." *Front. Oncol.* **2020**, 602762

Selected synthetic small molecules that inhibit EGFR mutant lung cancer cell growth



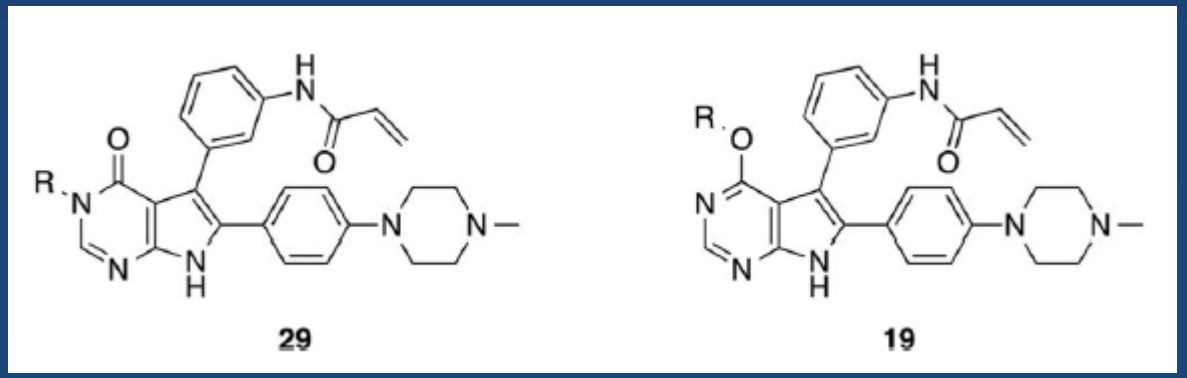


Fig. 4 **IC50 = 10-100 nM**

"A drug discovery platform to identify compounds that inhibit EGFR triple mutants" *Nature cancer*, **2021**, 377-391.

"Inhibition of osimertinib-resistant epidermalgrowth factor receptor EGFR-T790M/C797S" *Chem. Sci*.,**2019**,*10*,10789

In vitro growth inhibitory activity of diarylheptanoids against NSCLC cell lines

The anticancer efficacies of a series of diarylheptanoid derivatives was evaluated in several EGFR-mutant TKI-resistant NSCLC cells, including H1650, H1975 cell lines, and several HCC827 gefitinib-acquired resistant (GR) clones, which are 200-fold more resistant to TKI than their parental HCC827 cells.

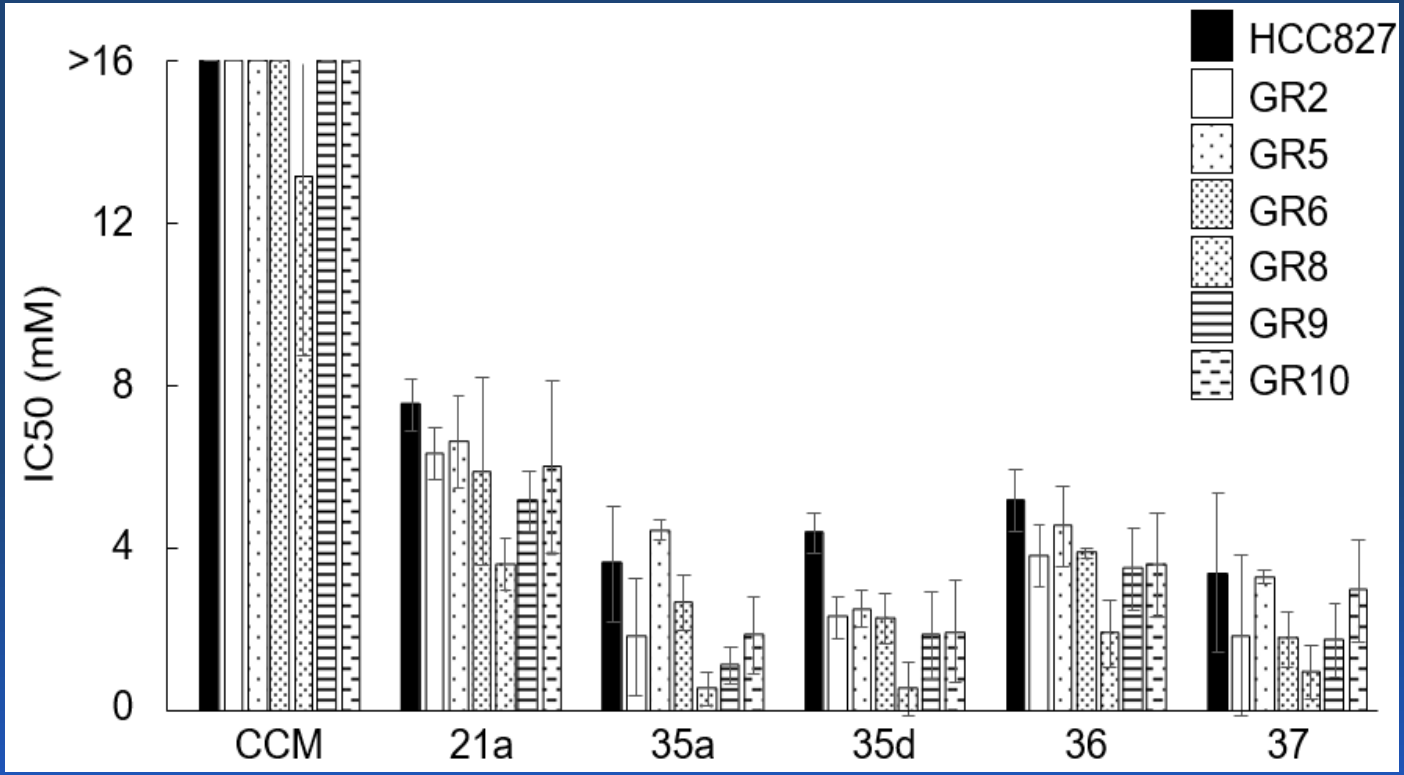
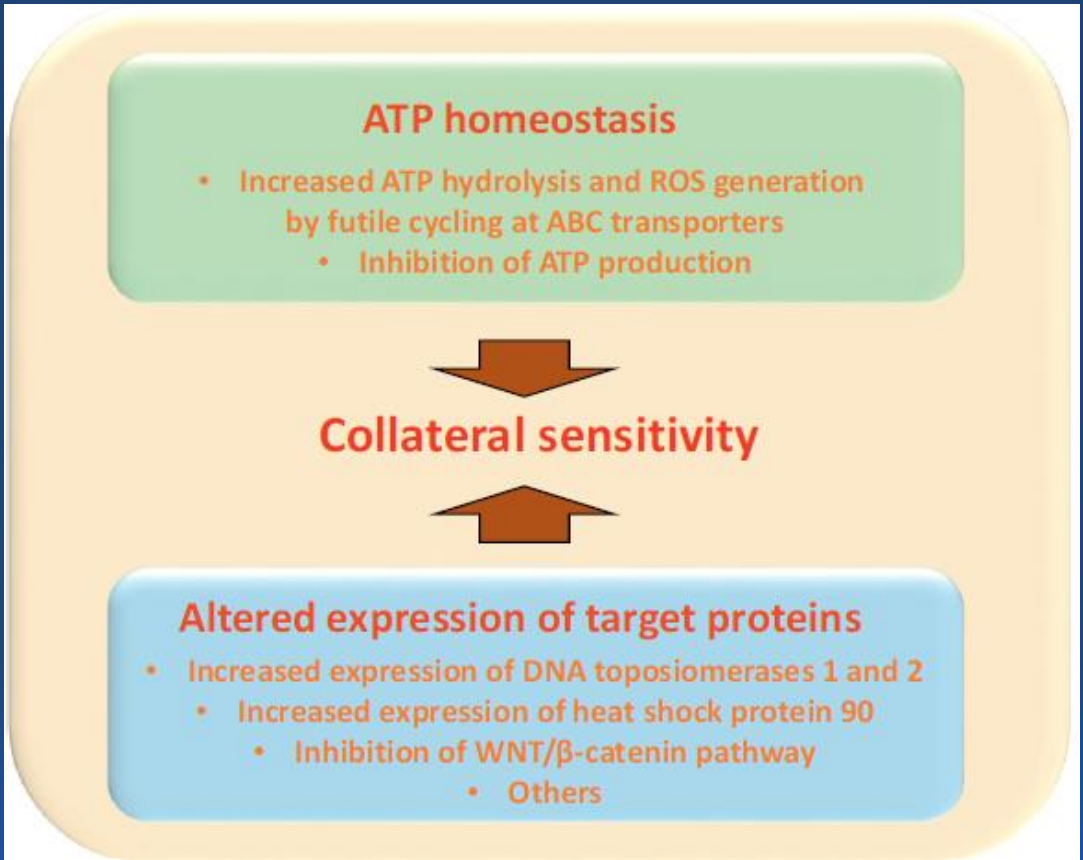


Fig. 5

Mechanisms associated with collateral sensitivity in drug resistant cancer



"Collateral sensitivity of natural products in drug-resistant cancer cells"
Biotechnology Advances **2020**, *38*, 107342

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