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Influence of the Basal Cellular Level of Glutathione in Triggering MRP1-cells Death

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Drug Resistance Mechanism and Modulation

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MDR & ABC transporters

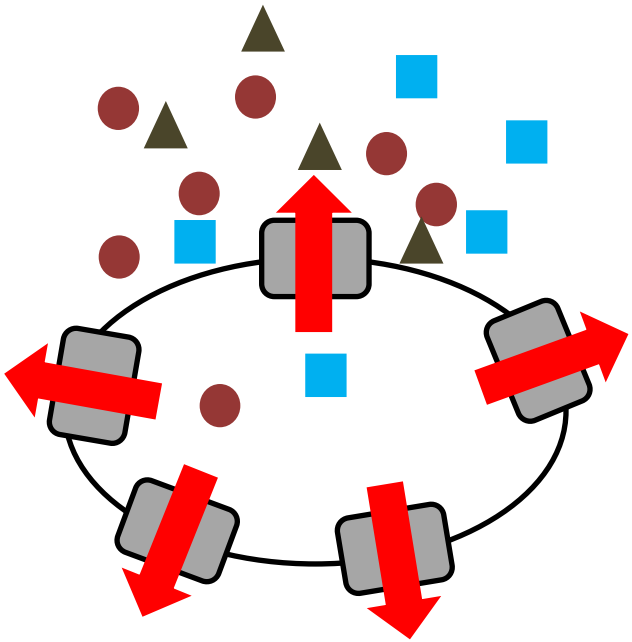
➢ What is Multi Drug Resistance within cancer cells ?

- Cross resistance to various chemotherapeutics
- Active efflux of antitumoral drugs out of cancer cells through overexpressed ABC transporters

-P-gp (ABCB1)

-BCRP (ABCG2)

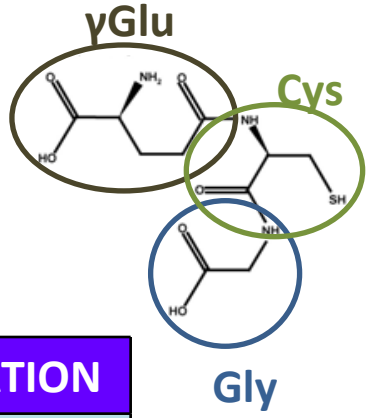
-MRP1 (ABCC1)



Overexpression: transport of drugs like chemotherapeutics

MRP1

- 190 kDa
- Transport of various substrates including glutathione

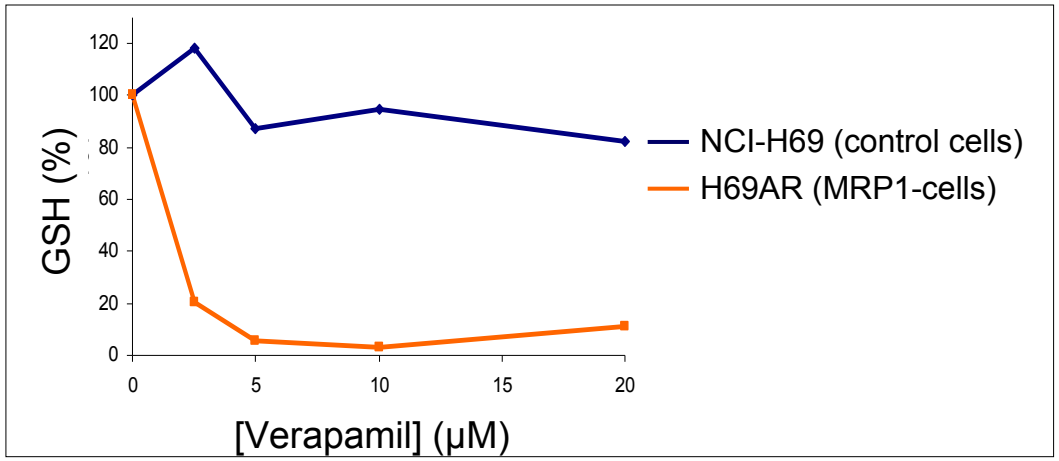


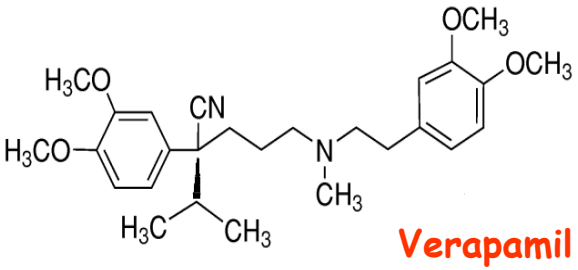
SUBSTRATES	PHYSIOLOGICAL LOCALISATION
• GSH et GSSG • LTC_4 • organic anions • glucuronate, sulfate or GSH conjugates of endo- and xenobiotics	TISSULAR: • ubiquitous • ++ in lung, testis, kidney, skeletal and cardiac muscles… • - in liver
	SUBCELLULAR: • basolateral

- Implicated in oxidative stress (through GSH transport), detoxification, inflammation

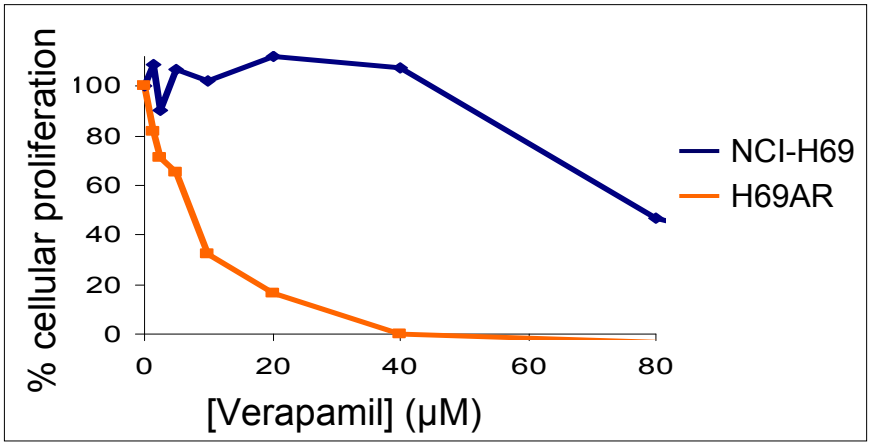
MRP1, GSH & MRP1-cells death

Total cellular glutathione after 3 h incubation with verapamil





Cellular proliferation after 72 h incubation with verapamil



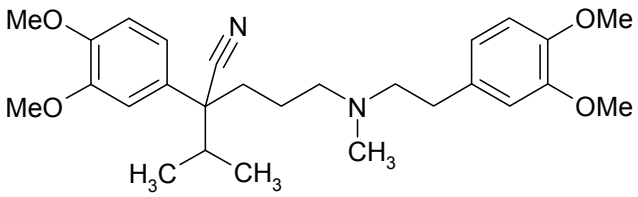
Selective cell death of tumoral MRP1-cells after stimulation of glutathione efflux

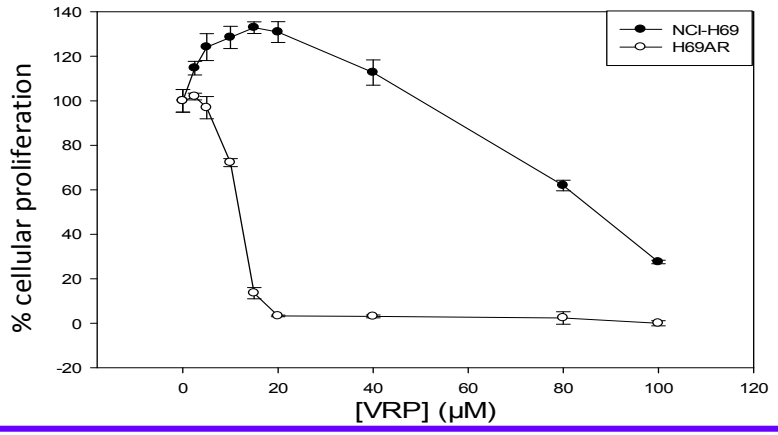
➔ **COLLATERAL SENSITIVITY**

3 « models » compounds

verapamil

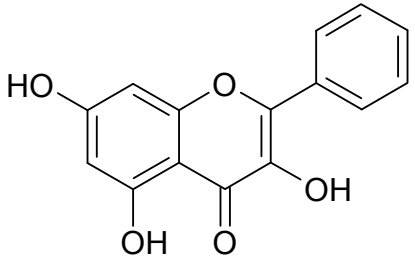
GSH efflux (20µM) = **75%**

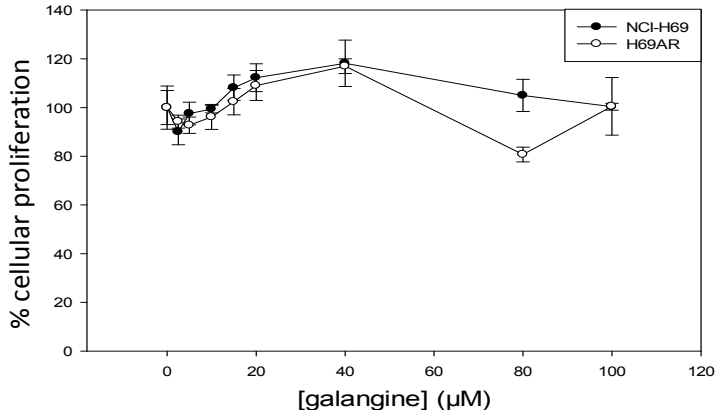




galangin

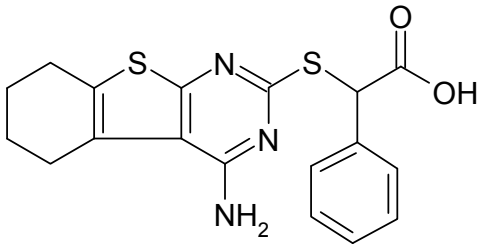
GSH efflux (20µM) = **85%**

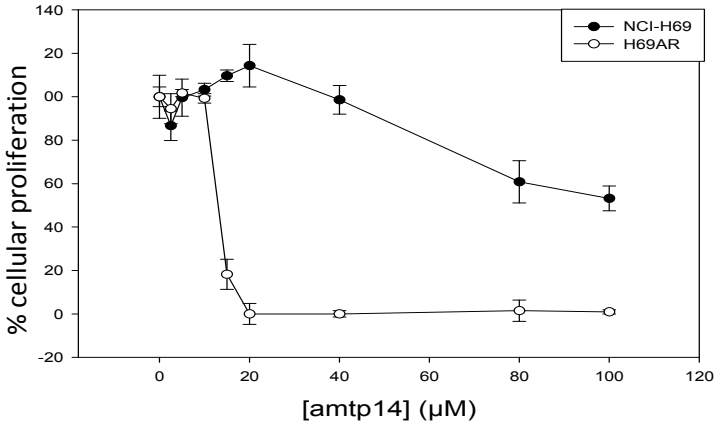




amtp14

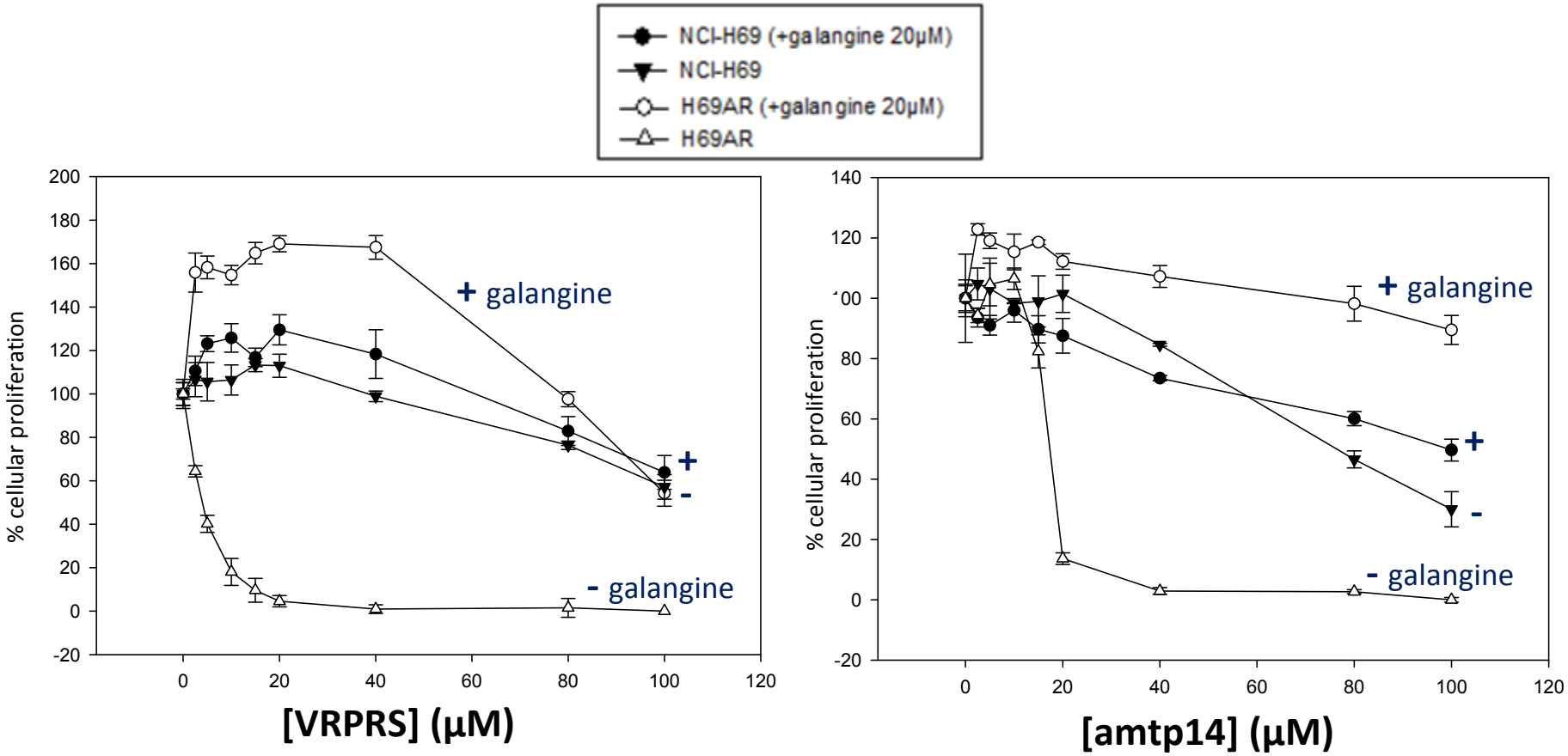
GSH efflux (20µM) = **28%**





Involvement of glutathione in triggering MRP1-cells death

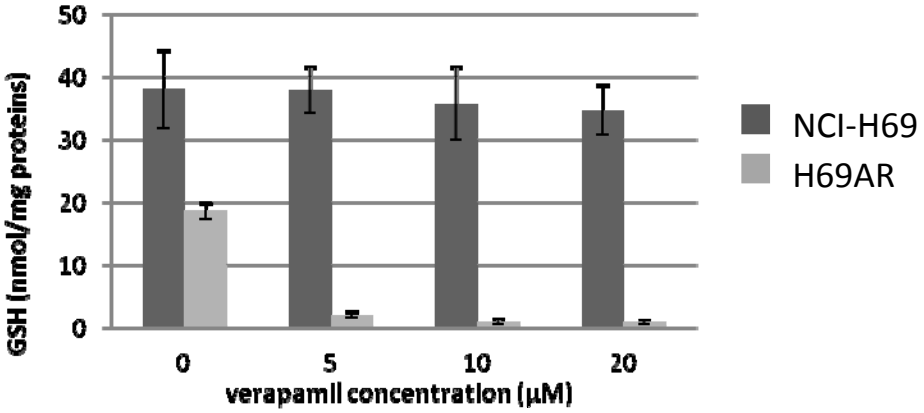
Does Galangin-triggered GSH efflux potentiate the cytotoxicity of verapamil or amtp14?



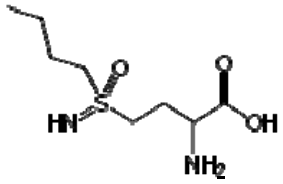
➔ **Galangin has a protective effect against the cytotoxicity of verapamil or amtp14.**

Involvement of glutathione in triggering MRP1-cells death

What is the involvement of basal GSH level in MRP1-cells death triggered by verapamil?

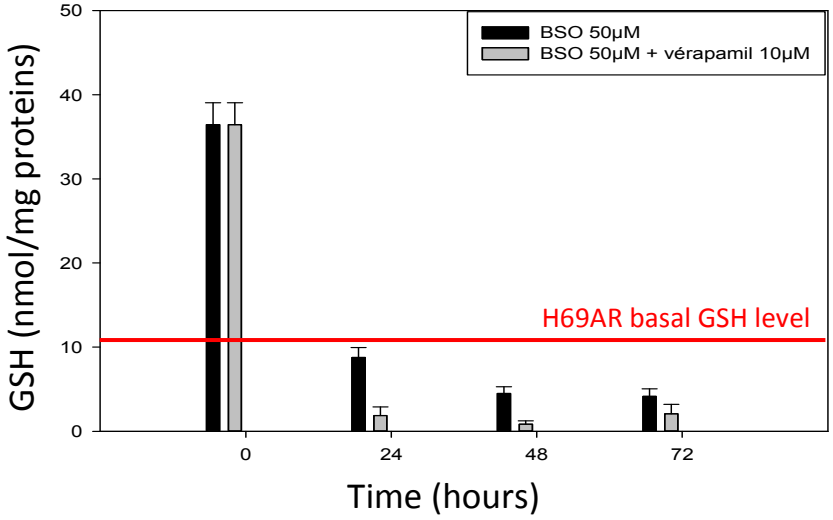


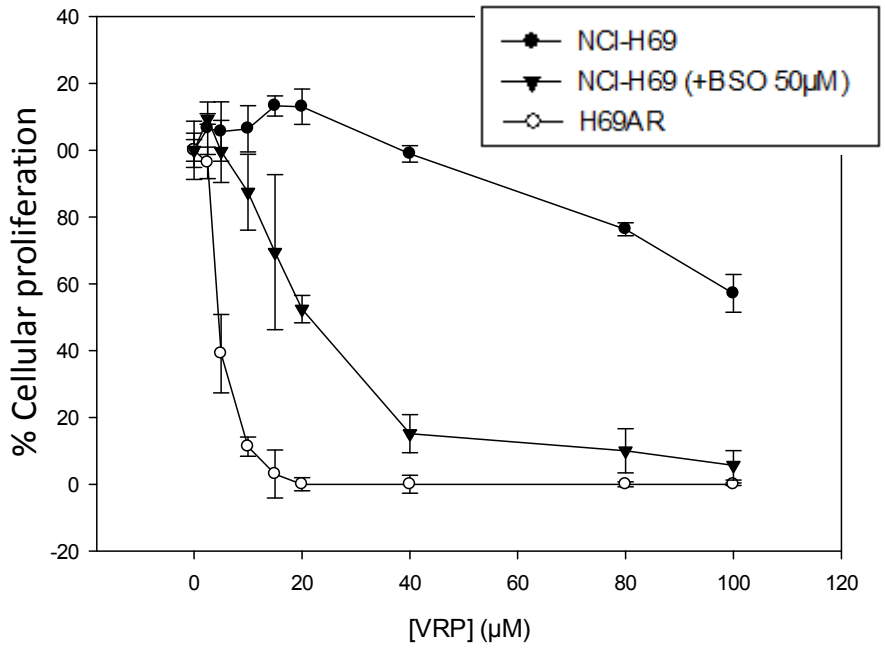
BSO= L-buthionine sulfoximine



γ-glutamyl-transferase inhibitor

Effect of BSO and verapamil on NCI-H69





➔ When the GSH basal level in NCI-H69 was brought to the same level as that of H69AR thanks to BSO, the verapamil effect was not equivalent in the two cell lines.

Conclusions

➔ Low basal glutathione level might be important for triggering death of H69AR, but the **depletion of GSH** has to be **achieved by MRP1**.

➔ The mechanism by which verapamil kills MRP1-cells is complex:

- verapamil kills MRP1-cells through GSH efflux: production of ROS? Galangin protects against cell death maybe through its antioxidant properties.

but

- amtp14 induces a collateral sensitivity for MRP1-cells without strong GSH depletion. Surprisingly, galangin also protects against amtp14-induced cell death. Is it the same mechanism than with verapamil?