SCST Colloquium Report

Speaker: Prof wen Shin Li
Title: Therapeutic challenges and opportunity in Drug discovery
Date & Time:21/04/2021
Location: Online

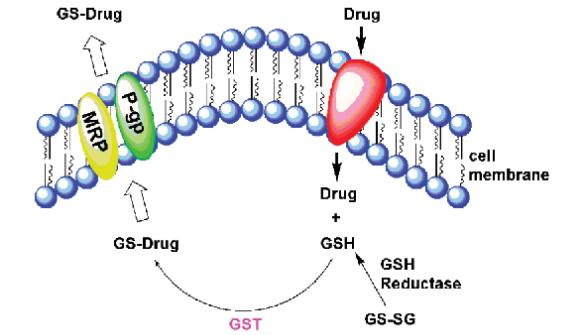
Student Name:

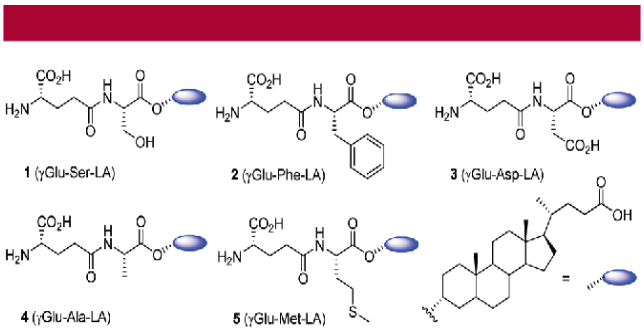
Student ID No.:

Prof Wen Shin li spoke about drug discovery, organic synthesis and future prospect in his lecture. He explained various areas of drug discovery such as molecular targeting, chemotherapy in anticancer agent, Drug resistance, Drug Delivery and cell imaging and immunotherapy.

Drug resistance is the major cause of reduction in drug efficacy and plays a vital role in the success or failure of cancer therapy. Due to drug resistance, chemotherapeutic agents such as cisplatin, thiotepa, chlorambucil, doxorubicin are mostly used in cancer treatment. To overcome drug resistance in cancer cells Prof Wen, Shin Li and co-workers developed an efficient glulathione s-transferase inhibitor and investigated it for therapeutic use.

The compound (3)γGlu-Asp- LA shows the most active compound with IC50 of 3.6 and 1.4 µM against GSTA2 and GSTP1-1, respectively. The inhibition characteristics of compound 3 were evaluated by steady-state kinetics analysis in the presence of different concentrations of GSH. The type of inhibition they observed for compound 3 indicates that substrate (GSH) and inhibitor simultaneously compete for the same active site (G-site). Taken together, the results serve to explain why LA -based analogs, γGlu-aa (amino acid)- LA, represent a new alternative use for GSH in GST inhibitor design. They conducted SAR study in which they made systematic variations in





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compound 3. By replacing aspartic acid with another group, the potency changed drastically, suggesting that the γ-glutamyl moiety of GSH is very important in the recognition of GST. In the presence of compound 3, cytotoxicity in vitro study shows that the inhibition of cell viability by cisplatin against MCF -7 is increased by 640% (decrease in IC -50 value by 6.4-fold) and against MDA-MB-231 is increased by 270% (decrease in IC -50 value by 2.7-fold). Viability inhibition of thiotepa was enhanced by compound 3 (25 to 50 μM) by up to 170-320% against MCF -7 and by up to 180-270% against MDA-MB-231. Thus, the cell line was advantageously resistant to cisplatin and, to a lesser extent, to thiotepa compared to the MDA-MB-231 cell line. This study

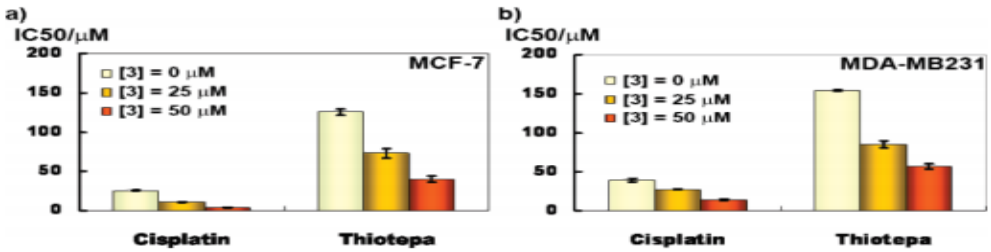

Figure 4. Synergetic effects of compound **3** on cell viability of human breast cancer cells MCF-7 and MDA-MB231.

demonstrates that the negligible effect of comp-3 on proliferation inhibition in the range 0-50 μM. Through the full study, it proves that the antitumor efficacy of cisplatin/thiotepa in breast cancer cells is through blocking the pathway of GST-mediated drug resistance and not through a direct anti-proliferative/cytotoxic effect.

They developed lead compound (3) showed synergistic effect with chemotherapy drugs against two breast cancer cell lines by inactivating GST isoenzymes .The extension of this approach will serve to explore high-affinity GST inhibitors, which is of great value for pharmacological and clinical application.

Reference:

Overcoming the Drug Resistance in Breast Cancer Cells by Rational Design of Efficient Glutathione S-Transferase Inhibitors. *Li, W. –S.; Lam, W. S.; Liu, K. –C.; Wang, C. –H.; Chang, H. C.; Jen, Y. C.; Hsu, Y. –T.; Shivatare, S.; Jao, S. –C* ***Organic Lett*****. 2010, *12*, 20.**

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