**Exploring the anticancer potential of functionalized isoindigos : Synthesis, drug-like potential, mode of action and effect on tumor-induced xenografts.**

http://www.pharmacy.nus.edu.sg/staff/phagoml/main.html

Meisoindigo has been used as an indirubin substitute for the treatment of chronic myeloid leukemia (CML) for several years. In view of its poor solubility and erratic absorption, several investigations have focused on developing analogs with more desirable physicochemical profiles. Our group has investigated the structure activity relationship (SAR) of meisoindigo with respect to its antiproliferative activity on leukemic K562 cells and found that appending a phenalkyl side chain onto the lactam NH resulted in analogs that retained good activity. Furthermore, analogs in which the phenyl ring was substituted with a basic heterocycle were significantly more soluble than meisoindigo while retaining acceptable antiproliferative profiles. The most promising analog (E)-1-(2-(4-methylpiperazin-1-yl)ethyl)-[3,3'-biindolinylidene]-2,2'-dione (**5-4**) is more potent than meisoindigo across a panel of malignant cells, with at least 40 times greater solubility than meisoindigo, little or no tendency to aggregate in solution and capable of significantly extending the life-spans of animals with K562 induced xenografts. Mechanistically, it induced apoptotic cell death and disrupted the progression of K562 cells from the G1 to G2 phase. Taken together, our findings highlight the feasibility of addressing the physicochemical deficits of the isoindigo scaffold by systematic modifications which was achieved without overt loss of growth inhibitory activity.