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Mining gold to treat the untreatable: Design, Synthesis and Characterization of Gold Based Nucleosidic Compounds

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The current field of anticancer therapy is dominated by organic molecules[1]. However, after FDA approval of the platimum based drug Cisplatin in 1978 and its positive effects to treat testicular and ovarian cancer, there came an urge to design more metal based anticancer drugs which would be more selective, non-toxic to non-targeting cells and will have reduced side effects[2]. Following the success of Cisplatin, came the gold based anti-cancer drug Auranofin, which showed immunosuppressory properties as well[3, 4]. Gold's oxidation state +3 is similar in chemical configation as platinum and on the top gold complexes show anti-inflammatory and immunosupressory properties[5]. Therefore, there were several reports afterwards which emphasized the synthesis and use of gold based complexes as potential drugs against cancer[6, 7]. Most of the gold complexes described so far targets enzymes or proteins inside the cells[8, 9]. Gold complexes targeting DNA are rare[10].

In an article published in the current issue of the journal Maity et al. have described several gold bearing nucleosidic compounds. The base molecule of these compound is 6-Mercaptopurine which has well defined anti-inflammatory and cytotoxic capabilities. The gold provides anti-enzymatic function and the ribose sugar moiety makes it soluble. Using synthetic chemistry, several compounds were generated whereas a few of the end compounds were further purified, crystallized and tested for their effects *in vitro* using multiple cells lines. The crystallized structure of one of the tested compounds showed a typical structure of gold-complexes further supporting their suitability as a promising gold-based prodrugs.

Together, the design of the compounds resulted in water soluble and cell permeable compounds which, in cell based assay showed cytotoxicity, cell death and inhibition of cellular enzyme. To note, one of the compounds, 8a in particular showed cytotoxity for all the cell lines tested and even had LD_{50} value for leukemia cells in the nanomolar range. There are only a few gold based compounds available which targets DNA synthesis. Interestingly the author showed that 8a affects cell viability by interfering with nucleotide metabolism and by indirectly inhibiting DNA synthesis in non-adherent cancer cell lines. In contrast, in adherent cancer cell lines, it induces apoptosis by accumulation of subG1 DNA population. Furthermore, the author also showed that treatment of the cells with compound 8a alters the mitochondrial integrity in them.

One of the key enzymes that gets upregulated in cancer is thioredoxin reductase (TrxR)[11, 12]. Because gold compounds exert their effects on cancer cells by modulating mitochondrial biology, TrxR is often targeted by gold complexes which inhibit the enzyme[13, 14]. In an *in vitro* assay using rat liver TrxR, compound 8a was able to reduce the enzyme in a concentration dependent manner. This suggests that that the synthesized compound might impose its effects on cancer cell line by inhibiting mitochondrial TrxR.

The elegant study showed by Maity et al. characterized a gold based nucleosidic compound that was able to show, at least in cell based assays anti-cancer properties. Of course, follow up studies should be conducted and possibly include i) testing the selectivity of this compound in non-cancerous cell lines ii) examining and testing for other possible targets of the compound such as kinases and iii) minimizing any unwanted side effects and finally iv) testing to see if any anti inflammatory properties other than just cytotoxicity.

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