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Repositioning the Old, Existing Copper-Binding Drugs for Cancer Treatment

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The conventional approach toward anti-cancer drug development is expensive and time-consuming. One approach to expedite this process and achieve more affordable means is to discover new uses of old, existing drugs, since their pharmacokinetics and pharmacological profiles have been well established [1]. Recent studies reveal anti-cancer activities of several approved copper (Cu)-binding drugs including disulfiram (an anti-alcoholism drug), clioquinol (a drug for treatment of Alzheimer's and Huntington's diseases) and ditiocarb (or diethyldithiocarbamate, a drug for treatment of HIV-1 infection) [2,3]. *In vitro* and *in vivo* studies have discovered a new mechanism in which these old drugs target and react with tumor cellular copper, forming complexes that act as potent proteasome inhibitors and apoptosis inducers in human cancer cells [4]. Extensive studies have strongly supported the idea that Cu could be used as a novel, selective target for human cancer therapies. First, Cu, but not other metals, is a co-factor essential for the processes of tumor angiogenesis [4,5]. Secondly, high tissue levels of Cu have been found in many types of human cancers, including breast, prostate, colon, lung and brain [4,6,7]. Thirdly, significant decrease in Cu levels in mammalian organs does not cause detectable side effects [8]. Finally, in clinical trials with patients suffering from metastatic cancers, use of the Cu chelator tetrathiomolybdate achieved the Cu-deficiency and stabilization of disease in a large portion of the patients, demonstrating the clinical feasibility [9]. It has been found that some organic Cu complexes can selectively inhibit the cancer cellular 26S proteasome activity, resulting in induction of apoptosis [10]. Furthermore, a Cu-binding ligand alone can induce proteasome inhibition and apoptosis in Cu-enriched human cancer cells that mimic *in vivo* situations of many human tumors [4,10]. Some of the Cu ligands tested include disulfiram, clioquinol and ditiocarb. All of them are able to interact with Cu, forming complexes with potent proteasome-inhibitory and apoptosis-inducing abilities in tumor cells *in vitro* and *in vivo* [4]. This identified mechanism of action of these approved Cu-binding drugs may be responsible for their observed anticancer activities.

The potential advantage for using these existing Cu-binding drugs for cancer therapies is apparent. Due to the fact that Cu concentrations are elevated in cancer but not normal cells [4,6,7], disulfiram, clioquinol and ditiocarb should have more selective effect against cancer and can bind the endogenous Cu in tumors to form a Cu-based proteasome inhibitor. Due to the difference of Cu levels in tumor and normal tissues [4,6,7], it is possible that these compounds may have little or no toxicity to normal cells while maintaining their anticancer activity. The studies using old Cu-binding drugs provided strong support for proof-of-concept of converting the pro-angiogenic cofactor Cu in cancer cells to the anti-angiogenic proteasome inhibitor and a cancer cell death inducer [4]. Identification of the new mechanism of action of the approved Cu-binding agents as potential proteasome inhibitors and anticancer drugs should have great significance in developing novel strategies for the treatment of human cancer. If successful, these old Cu-binding drugs could be immediately moved to anticancer clinical trials to determine their efficacy and toxicity. Since the drug development process can be burdensome replete with regulatory demands [1], the concept of repositioning of old drugs could represent a significant achievement in establishing positive momentum in generating further lead candidates in anticancer drug discovery.

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