Nanoparticle based formulation of copper diethyldithiocarbamate, an anticancer metabolite of disulfiram, for treatment of cancer

Introduction:
Repurposed disulfiram (trade name Antabuse), an old alcohol-aversion drug, is effective against diverse cancer types in multiple preclinical studies. Recently, we identified ditiocarb-copper complex (termed as CuET) as the metabolite of disulfiram which is formed in the human body that is responsible for the anti-cancer effects. This metabolite is preferentially accumulated in tumors where it compromises p97-segregase dependent turnover of proteins and other regulatory and stress-response pathways, making it selective and efficient anticancer agent. Because of its very low solubility in water (<0.5 ng/ml) and other biocompatible solvents, the CuET cannot be used as an anticancer agent directly.

Technology (invention) description:
We have developed a new formulation of CuET, shifting its water solubility by more than 8 orders (>100 mg/ml). This formulation is based on formation of nanoassemblies (nanoparticles) which are very stable, and contain CuET embedded in a polymeric excipient. The excipients include a plethora of water soluble biocompatible polymers and also proteins. The size of individual particles can be modulated within the range 5-150nm. Dispersion of such nanoparticles behaves similarly to true solution and can be applied in-vivo intraperitoneally, intravenously and for some formulations also orally. For the nano-assembly formation, immunoglobulins can also be used, introducing additional feature of targeted delivery of the particles. Importantly, CuET delivered in the nanoparticle formulation form penetrates through blood-brain barrier. Our new formulations are highly stable, compatible with freeze-drying and easy to manufacture.

Advantages over existing solutions:
Currently, the only way of CuET in-vivo dosing is based on metabolism dependent conversion of its precursors (disulfiram and copper). This reaction is by its biological nature very hard-to-define giving various yields of the active compound.
In contrast, the described nano-particle based CuET formulation allows precise dosing. Moreover, the size of the particles can be manipulated to increase its tumor absorbing properties by enhanced permeability and retention (EPR) effect. Finally, the excipients forming the CuET-nano assembly can be chosen to selectively target particular cancer cells and personalize composition of nanoparticles for given individual.

Development status:
Fully mastered production process of the CuET nanoparticles scalable for inductrial production. Compound stability data. Preclinical stage – *in vitro* and *in vivo* testing for antitumor effects, pharmacokinetics, toxicology.

Publications:
Skrott, Z., M. Mistrik, K. Andersen, S. Friis, D. Majera, J. Gursky, T. Ozdian, J. Bartkova, Z. Turi, P. Moudry, M. Kraus, M. Medvedikova, J. Vaclavkova, P. Dzubak, I. Vrobel, P. Pouckova, J. Sedlacek, A. Miklovicova, A. Kutt, J. Mattova, C. Driessen, Q. Dou, J. Olsen, M. Hajduch, B. Cvek, R. Deshaies, J. Bartek. Alcohol-abuse drug disulfiram targets cancer via p97 segregase adaptor NPL4. Nature. 2017, 552(7684), 194-199. ISSN 0028-0836. IF: 40.137. PMID: 9211715

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