ANTITUMOR GOLD (III) COMPLEXES WITH OLIGOPEPTIDES FUNCTIONALIZED WITH SULFUR DONORS AS IMPROVED SYSTEMS FOR INTRACELLULAR TRANSFER AND DELIVERY

Technology Overview - PCT/EP 2009/053296

Some of the most widely employed drugs to treat several types of cancer are platinum based coordination compounds (e.g. Cisplatin, Carboplatin). Despite high effectiveness, the therapy is severely hindered by clinical problems such as severe side effects and frequent occurrence of either intrinsic or acquired resistance to the treatment.

University of Padua and CRO have designed highly innovative gold-peptido derivatives with an enormous potential as anticancer agents because of noticeable in vitro and in vivo antitumor activity toward different kind of tumours, lack of cross-resistance with cisplatin and reduced adverse side-effects (i.e. negligible nephrotoxicity, very low acute toxicity).

In addition, there is a potential enhanced bioavailability through the di-/tripeptide-mediated cellular internalization by exploiting peptide transporters which represent an excellent target for the delivery of pharmacologically-active compounds.

Advantages

These new gold(III) complexes provide an evaluable alternative to cisplatin and other metal-based antineoplastic agents for the following characteristics:

- In vitro citotoxicity at micromolar concentration on several sensible and resistant to cisplatin human tumor cell lines,
- Significant in vivo anticancer activity (test on breast xenograft tumors have shown up of 90% of growth inhibition),
- Lack or very low renal and systemic toxicity,
- Improved intracellular drug transfer and delivery via peptido-mediated cellular internalization,
- Easy to obtain and stable under phisiological conditions.
**Development Stage**

Anticancer activity and nephrotoxicity have been extensively evaluated by in vitro and in vivo tests. The mechanism of action underlying their activity is currently under investigation. Compounds were proved to be highly reactive toward some biologically-relevant macromolecules: they trigger cell death by activating both apoptotic and non-apoptotic pathways. They are able to alter some mitochondrial functions, such as membrane potential and permeability conditions, strongly inhibit the activity of the selenoenzyme thioredoxinreductase (TrxR), and increase ERK-1/2 phosphorylation. Moreover, the proteasome has been recently identified as a major in vitro and in vivo target for these gold(III) derivatives, potently reducing proliferation in different highly metastatic and invasive breast cancer. These gold(III) compounds might therefore exert their activity by inhibiting TrxR activity and stimulating production of ROS, which then oxidize and inactivate the proteasome and/or other molecules involved in the ubiquitin/proteasome pathway. They are worthy of further preclinical investigations aimed at their recognition as suitable candidates for clinical trials.

**Looking for**

Industrial partners interested in:
- assignment or license agreements,
- supporting the development phase (enter the compounds in clinical trials),
- their future commercialization.

**More Information**

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