

Scientists at the Chinese University of Hong Kong (CUHK) have designed a unique approach to identify biologically active compounds and combining them within a platinum-based framework for treating cancer. This platform technology provides an opportunity to commercialize a new series of anti-tumor agents with selectivity to liver cancers.

BACKGROUND

There are currently only two platinum-based compounds that are marketed and clinically used worldwide as anti-tumor drugs: **cisplatin** and **carboplatin**. Platinum-based compounds are among the most active chemotherapeutic agents available. They are effective against a multitude of cancers. However, their clinical usage is hindered by toxic side effects, and by the emergence of drug resistance.

CUHK has adopted an "East meets West" approach to develop new compounds which are expected to:

- Eliminate cross-resistance;
- Possess high potency;
- Induce minimal side effects; and
- Possess good aqueous solubility.

Design Objectives: A new drug with selectivity against liver cancer.

Design Philosophy: Mechanism-based approach to cellular targets.

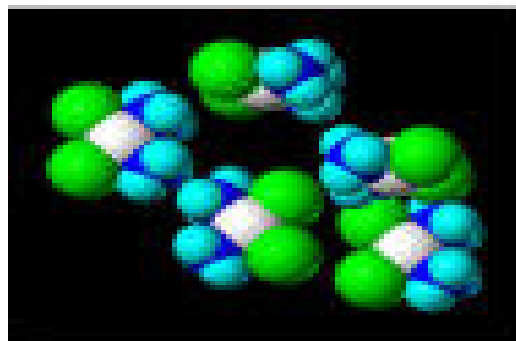
METHODOLOGY

- Integrate a biologically active compound (BAC) together with a well-established anticancer drug entity to resemble a cisplatin framework for the treatment of cancer; can also serve as a releasing agent in delivering the active compound.
- Identify BAC with known therapeutic value in the treatment of liver cancer.
- The BAC is a single entity that can be properly characterized using modern analytical techniques.
- Resulting platinum-compound containing the BAC remains a single chemical entity that can also be readily characterized.

MECHANISM

Features of the mechanism for activity include:

- The BAC has been identified as demethylcantharidin, a chemically modified form of cantharidin, which was originally isolated from *Mylabris* or blister beetle.



- Cisplatin framework interferes with DNA alkylating action by blocking DNA replication upon binding.
- Demethylcantharidin is known to inhibit protein phosphatase 2A (PP2A), rich in the liver cytosol, and disrupts the cell growth cycle and the mechanism of the nucleotide excision repair (NER) proteins.

BENEFITS

Blending the properties of demethylcantharidin into a novel platinum complex has led to a series of compounds with anti-tumor activity towards cancers of the liver, lung, and colon, as well as leukemia, lymphoma, naso-pharyngeal carcinoma, and cervical tumors. The approach forges the dual mechanism of cytotoxic action, thereby creating a role to overcome platinum resistance. (All other platinum drugs operate with a single cytotoxic action mechanism). The compounds also exhibit the following properties:

- Excellent in vitro anti-tumor activity.
- Selectivity towards liver cancer in vivo (nude mice).
- Lower acute toxicity.
- Improved solubility (favors easier formulation).
- Demonstrated & favorable pharmacokinetics.

INTELLECTUAL PROPERTY

- US Patent 6,110,907.
- Chinese Patent No.: ZL 97 1 02796.X.
- Chinese Patent No. ZL 97 1 02797.8.
- New PCT application filed.

The inventors have also published several papers in various scientific journals.

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