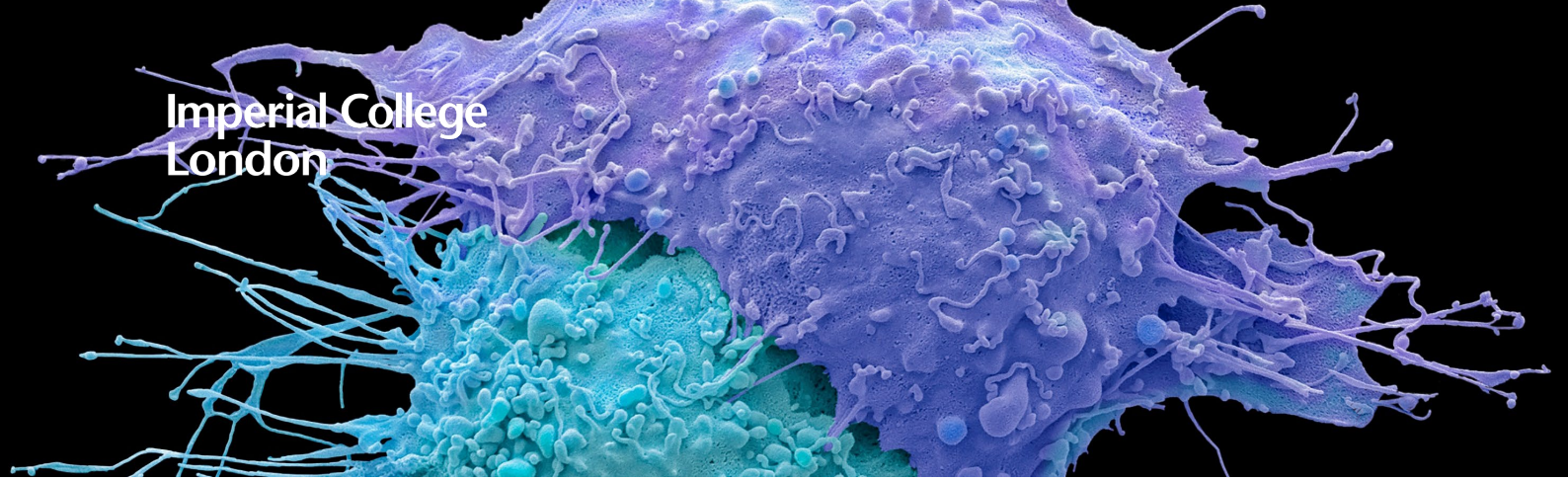

Dual DNA-PK/AKT inhibition for the treatment of platinum-resistant cancer

Novel compounds with dual DNA-PK/AKT inhibitor activity for the treatment of platinum-resistant cancers.

Proposed use

The dual inhibitors can be used to treat patients that indicate innate or acquired resistance to platinum-based drugs, such as cisplatin, or used as first line treatment in combination with platinum-based drugs to prevent the emergence of drug resistance and prolong survival of cancer patients.

Problem addressed

Platinum-based treatments, e.g. carboplatin and cisplatin, are commonly used to treat various cancers. Whilst initial response to these agents is high, emergence of platinum resistance is common. Ovarian, breast and lung cancers commonly progress as platinum-resistant cancers and display low survival rates. Recent evidence indicates that platinum-resistant cells can be present in primary tumours prior to chemotherapy treatment.

Platinum exposure induces AKT-dependent survival and DNA damage response in clinically platinum-resistant but not sensitive ovarian cancer cells. AKT relocates to the nucleus of cancer cells where it is phosphorylated at Serine473 by DNA-PK and this activation inhibits platinum-induced apoptosis, rendering platinum-based drugs ineffective. Inhibition of DNA-PK or AKT re-sensitises cisplatin-resistant ovarian cancer cells to platinum-based chemotherapy. Re-sensitisation is associated with prevention of AKT-mediated BAD phosphorylation.

Technology overview

Novel ATP-competitive inhibitors with dual inhibition of DNA-PK and AKT isoforms (pan-AKT) show efficacy in platinum-resistant ovarian cancer cells. Inhibition of DNA-PK/AKT restores platinum sensitivity in a panel of clinically resistant ovarian cancer cell lines. The use of dual DNA-PK/AKT inhibitors in platinum-resistant cancers or use in combination with platinum-based agents is a novel and effective approach to tackling cancers that have few treatment options post development of resistance.

Benefits

- The first known dual DNA-PK and AKT inhibitors
- A treatment for drug resistant cancers that currently lack treatment options
- Efficiently targets a common survival pathway in cancer
- Potentially applicable to any cancer type that employs AKT- and DNA-PK-dependent survival response
- Could potentially be used in combination with chemotherapeutic platinum-based agents to prevent the emergence of platinum-resistant tumours.
- Tested in panel of platinum sensitive and resistant epithelial ovarian cancer cell lines.

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Intellectual property information

Patent protecting the novel dual-DNA-PK/AKT inhibitory compounds and their use in platinum-resistant cancers and in combination with platinum-based chemotherapy or other chemotherapies, targeted agents and immune-oncology agents in cancer has been filed. The technology is available for exclusive licensing for further development, commercialization and/or collaborations with the inventor team.

Link to published paper(s)

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