

Licensing Opportunity



Improved cancer treatment by inhibiting homologous recombination with hyperthermia and sensitizing cancer cells to DNA double-strand breaks inducing agents

- Extended use of PARP -1 inhibitors in different cancer type
- Improved efficacy of cancer treatment in patients undergoing chemotherapy, radiation therapy and PARP-1 inhibitors
- Reducing effective dose of chemotherapeutics

Therapy | Oncology; PARP-1 inhibitor; Hsp90 inhibitor; Hyperthermia; DSB

2011

Background

Many currently applied anti-cancer strategies are based on cytotoxicity of DNA double-strand breaks (DSBs) induced by ionizing radiation or, indirectly, by chemical agents. However, efficient DSB repair mechanisms protect (cancer) cells from the genotoxic effects of DSBs, reducing the effectiveness of the treatment. Two major DSB repair pathways have been described in mammalian cells: homologous recombination (HR) and non-homologous end joining. HR utilizes intact homologous DNA sequences - usually the sister chromatid in post-replicative chromatin - to faithfully restore DNA breaks. Major HR factors include the DNA strand exchange protein RAD51 and the recombination mediators BRCA2, XRCC3 and RAD54. Inhibition of DSB repair processes potentiates the cytotoxic effects of induced DSBs. Methods for disrupting DNA DSB repair pathways are rapidly gaining importance in anti-cancer therapy.

The Technology

Hyperthermia (HT) is a type of cancer treatment in which the affected body tissue is exposed to high temperatures (up to 43°C). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to non-heated, surrounding normal tissue. By killing cancer cells and damaging proteins and structures within cells, HT may reduce tumor volume. Additionally, HT is known to make cancer cells more sensitive to other forms of cancer therapy, such as radiation- and chemotherapy, and to sensitize cancer cells to certain anticancer drugs.

In Vitro Data

AMC scientists have now demonstrated, in vitro, that the combination of HT and inhibition of HSP90 greatly sensitizes cells to PARP-1 inhibitors and to ionizing radiation. The combination of HT and inhibition of HSP90 can be applied in patients undergoing chemotherapy, radiation therapy and therapy using PARP-1 inhibitors.

In Vivo Data

Xenograft studies have shown that HT in combination with PARP-1 inhibitors reduces tumor growth in mouse and rat. HT in combination with Hsp90- inhibitors also reduce tumor growth, but the largest effect is seen for triple treatment with HT, PARP-1 inhibitors and Hsp90-inhibitors.

R&D Status

Currently pre-clinical trials are being set up to assess the critical parameters for tumor growth in xenograft models and to assess the efficacy of HT treatment in combination with other anti-cancer therapies. Clinical studies will be initiated simultaneously.

Applications

Cervical cancer, vulvar cancer, locoregional breast cancer, head/neck tumors, rectal cancer, melanoma, anal carcinoma, vaginal carcinoma.

Intellectual Property

Patent nr. : US 13/144,079; EP 10700073.9; CN 201080007285.1; also filed in Canada and India.

Patent nr. WO2010NL50016

Publication date: 2010-07-22

Inventors

Dr. Przemyslaw Krawczyk, Cell Biology and Histology, AMC

Dr. Jacob A. Aten, Cell Biology and Histology, AMC

Prof. Dr. Roland Kanaar, Molecular Radiation Biology, Erasmus MC

Dr. Jeroen Essers, Molecular Radiation Biology, Erasmus MC

Key publications

1. Krawczyk PM, Eppink B, Essers J, Stap J, Rodermond H, Odijk H, Zelensky A, van Bree C, Stalpers LJ, Buist MR, Soullié T, Rens J, Verhagen HJM, O'Connor MJ, Franken NAP, ten Hagen TLM, Kanaar R, Aten JA. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. P NATL ACAD SCI USA 2011
2. Bergs JWJ, Krawczyk PM, ten Cate R, Rodermond H, Borovski T, Medema JP, Aten JA, Franken NAP. Inhibition of homologous recombination by mild hyperthermia shunts early double strand break repair to non-homologous end-joining in G2 phase cells.. INT J MOL MED 2010;26:suppl 1-123.