Using Platinum (IV) STAT3 Inhibitors to Enhance Immune Cell Antitumor Activity

This patented antibody drug conjugate technology is a method of enhancing the antitumor activity of an immune cell, in particular a neutrophil, NK cell, or TIL with a platinum (IV) STAT3 inhibitor linked to an antibody for a surface marker on the immune cell. Additionally, a patented method of treating tumors is covered where a TIL is contacted with a platinum (IV) STAT3 inhibitor ex vivo. The platinum (IV) STAT3 inhibitors CPA-1, CPA-7 and IS3 295 are specifically described in the patent.

COMMERCIAL OPPORTUNITY

- The antibody drug conjugate (ADC) market is expanding, and has recently been bolstered by two FDA approved therapies, Kadcyla (Genentech) and Adcetris (Seattle Genetics), which generated $1.2B in worldwide sales in 2015. Kadcyla is Herceptin bound to the drug DM1, a microtubule-targeted cytotoxic agent for the treatment of breast cancer, and Adcetris is an anti-CD30 antibody bound to Monomethyl auristatin E, a microtubule-targeted cytotoxic agent for the treatment of Hodgkin lymphoma. Both Pfizer and Seattle Genetics also have ADCs in Phase III clinical trials, while Abbvie Inc. acquired Stemcentrx for $5.8B based on promising results of its ADC therapeutic that has now passed through Phase II trials.
- The marketplace for cancer immunotherapy is attractive. Antibody based immunomodulators, such as Bristol Myers Squibb's Yervoy and Opdivo produced more than $2B in sales worldwide in 2015. Additionally, Keytruda (Merck) generated $352 million in sales in the first nine months of 2015.
- STAT3 inhibitors are being developed by numerous companies, including GLG Pharma, Boston Biomedical and Otsuka Pharmaceuticals. These compounds are small molecule inhibitors for the treatment of various types of cancers, including breast, chronic lymphocytic leukemia (CLL), colorectal, gastric, and other solid tumors.
- The platinum (IV) compounds CPA-1, CPA-7 and IS3 295 have been reported to potentially block the DNA binding activity of STAT3. IS3 295 blocked STAT3 DNA-binding activity with an IC50 of 1.4 uM. In mouse in vivo studies, 5 mg/kg of CPA-7 caused the regression of CT26 colon cancers.

TECHNOLOGY

The patent covers two methods: First, the method of enhancing anti tumor activity of an immune cell, where the immune cell is a neutrophil, an NK cell or a tumor-infiltrating lymphocyte, comprising contacting the immune cell with a platinum (IV) STAT3 inhibitor, where the STAT3 inhibitor is conjugated to an antibody specific for a surface marker of the immune cell. Second, an ex vivo method of killing a tumor cell or inhibiting tumor growth in a subject comprising contacting an isolated tumor-infiltrating lymphocyte with a platinum (IV) STAT3 inhibitor, and administering the tumor infiltrating lymphocyte to the subject, wherein the STAT3 inhibitor enhances the ability of the tumor infiltrating cell to kill the tumor cell or inhibit tumor growth in the subject. The patent also covers the platinum (IV) compounds CPA-1, CPA-3, CPA-7 and IS3 295.

PUBLICATION/PATENT

- U.S. Patent Number 7,951,374 B2 granted to Drs. Yu, Jove, Kortylewski, and Pardoll on May 31, 2011.
- Manuscript published in *Nature Medicine* on November 20, 2005.

CONTACT

Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

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