

## ANALOGUES OF WITHANOLIDE E SENSITIZE CANCER CELLS TOWARD APOPTOSIS

### SUMMARY

There is a need to develop compounds that can sensitize cancer cells to apoptosis inducing ligands, such as poly I:C and TRAIL. In collaboration with the University of Arizona, NCI investigators discovered a series of compounds in the withanolide family that synergistically enhance the response of cancer cells to treatment with an apoptosis-inducing ligand. The NCI seeks licensing and/or co-development research collaborations for development of withanolide E analogues for the treatment of cancer.

### REFERENCE NUMBER

E-051-2016

### PRODUCT TYPE

- Therapeutics

### KEYWORDS

- TRAIL, TLR3 ligands, apoptosis, immunotherapy
- withanolide

### COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

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### DESCRIPTION OF TECHNOLOGY

The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) protein has been a target of interest in cancer therapy because it plays a large role in inducing cell apoptosis in cancer cells but not in normal cells. Although TRAIL has been reported to successfully target certain tumor cells which are resistant to traditional chemotherapy or radiation, TRAIL resistance has also been widely observed. Similarly, Toll-like receptor (TLR) 3 ligands such as poly I:C have also been reported to promote apoptosis in certain cancer cells, though the apoptotic signaling in most cancer cells was weak and was only significant following longer term incubations. Thus, there is a need to develop compounds that can sensitize cancer cells to apoptosis inducing ligands, such as poly I:C and TRAIL.

In collaboration with the University of Arizona, NCI investigators have discovered a series of compounds in the withanolide family that synergistically enhance the response of cancer cells to treatment with an

apoptosis-inducing ligand. The compounds each show a 4-10 fold increase in potency compared to withanolide E alone in promoting death ligand-mediated cancer cell death. One biotinylated analogue in particular is at least 15 fold more potent than withanolide E in promoting apoptosis in human melanoma cells when used in combination with either poly I:C or TRAIL. A selection of active compounds were tested in xenograft models of human melanoma in mice and showed decreased tumor growth and tumor regression in these animal models.

## POTENTIAL COMMERCIAL APPLICATIONS

- Potential therapeutic for the treatment of cancer either alone or in combination with an apoptosis inducing agent such as TRAIL receptor or TLR 3 agonists by directly promoting tumor cell apoptosis.
- Possible indirect enhancement of cancer immunotherapy due to release of cancer cell antigens in the presence of the powerful immune-adjuvant effects of TLR3 agonists.

## COMPETITIVE ADVANTAGES

- Withanolide E derivatives enhance the anti-cancer activity of known apoptosis inducing ligands such as TRAIL or poly I:C and may be used to enhance efficacy of TRAIL receptor or poly I:C agonists that are currently under development.

## INVENTOR(S)

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## DEVELOPMENT STAGE

- Pre-clinical (in vivo)

## PUBLICATIONS

1. Tewary P., Gunatilaka A.A. and Sayers T.J. (2016) Using natural products to promote caspase-8-dependent cancer cell death. *Cancer Immunol Immunother.* doi:10.1007/s00262-016-1855-0

## PATENT STATUS

- **U.S. Provisional:** US Provisional Application No. 62/292,974, entitled "Method of Sensitizing Cancer Cells to The Cytotoxic Effects of Apoptosis Inducing Ligands in Cancer Treatment," filed February 9, 2016

## RELATED TECHNOLOGIES

- [E-050-2010 - Use of Cucurbitacins and Withanolides for the Treatment of Cancer](#)

## THERAPEUTIC AREA

- Cancer/Neoplasm