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Apoptosis Inhibitors

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BACKGROUND

Although treatment of cancer through non-surgical methods such as chemotherapy and radiation has dramatically improved survival rates, these therapies are associated with a fair degree of toxicity. The deleterious effects are particularly due to inability of these treatment methods to target cancer cells specifically without affecting surrounding normal cells. The challenge therefore, has been to find methods of selectively protecting normal cells, while maintaining susceptibility of cancer cells to therapy.

Apoptosis triggered by chemotherapy and radiation is the most common cause of destruction of normal cells and is due to activation of a fully functional p53 protein present in these cells. p53 protein-induced transactivation of several genes involved in the apoptosis pathway leads to elimination of normal cells when exposed to anti-cancer agents. Therefore, therapeutic suppression of p53 directly or of its pathways leading to apoptosis, are attractive targets to prevent damage to normal cells during anti-cancer therapy. Earlier efforts in this area led to the isolation of a chemoprotectant, pifithrin that protected normal cells against radiation and chemotherapy-induced damage. However, this agent was not potent, was unstable and was not a specific inhibitor of p53-related apoptotic pathways. Hence, there is a clear need for new chemical inhibitors that are more robust, stable and specific as chemoprotectants of normal cells during anti-cancer therapy.

TECHNOLOGY DESCRIPTION

Researchers at the University of California have developed novel heterocyclic compounds that protect normal cells from apoptosis. These compounds are active in vitro in the nanomolar range and prevent apoptosis in cells treated with glucocorticoids or ionizing radiation. In addition, the compounds also significantly increase survival rates of mice irradiated with gamma rays with no observable toxicity.

ADVANTAGES

- ▶ Unique chemistry and stability under physiological conditions.
- ▶ Potent compounds active in nanomolar range with an IC50 several fold lower than other apoptosis inhibitors such as pifithrin.
- ▶ Demonstrated efficacy in animal models.

APPLICATIONS

- ▶ Wide range of clinical treatments where suppression of apoptosis of normal cells is desirable such as radiation and chemotherapy for human cancers to prevent side effects that include mucositis, hair loss, myelosuppression and diarrhea.
- ▶ Protection from apoptosis in heart and brain ischemia, peripheral limb protection in vascular disease and prevention of shock resulting from viral or bacterial infections, or burns.

STATE OF DEVELOPMENT

Synthesized product was formulated as a topical ointment, which was efficacious, in vivo (mouse), for healing of irradiation-induced skin damage (see Related Materials).

Research interests can be found at: http://cancer.ucsd.edu/Research/summaries/dcarson.asp

RELATED MATERIALS

- Nourmohammadi, A. et al., Synthesis and Formulation of a p53 Inhibitor to Control Side Effects of Cancer Radiotherapy, CallT2 Presentation, Sept. 22, 2009 09/22/2009
- ▶ Barchechath et. al. (2005) "Inhibitors of Apoptosis in Lymphocytes: Synthesis and Biological Evaluation of Compounds Related to Pifithrin-a" J. Med. Chem. 48:6409-6922. 01/01/2005

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OTHER INFORMATION

KEYWORDS

cancer, chemoprotectant, protectant, chemotherapy, apoptosis, radiation, radiation therapy, radiation protection, radioprotectant, p53, anti-cancer

CATEGORIZED AS

- Biotechnology
 - Other
- Medical
 - Disease: Cancer
 - New Chemical Entities,Drug Leads

RELATED CASES

2005-E50-0, 2000-E70-0

▶ Barchechath et. al. (2005) "Quinolinium salt as a potent inhibitor of lymphocyte apoptosis" Bioorg. & Med Chem Lett 15:1785-1788 - 01/01/2005

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