

**Contact:**

Harl Tolbert,
techtransfer@roswellpark.org,
716-845-1060
www.roswellpark.org/commercialization

TAK1 Inhibitors as Anti-Cancer Agents

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Keywords: TGF- β , TAK1, 5(Z)-7-oxozeaenol, therapeutic, cancer, other.

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking partners to help co-develop TAK1 inhibitors as potential anti-cancer agents.

Summary: Transforming Growth Factor- β -Activated Kinase 1(TAK1) inhibition is a 20 mechanism to down-regulate cancer growth. Transforming growth factor- β 1 (TGF- β 1) cytokine regulates the composition of extracellular matrix (ECM), matrix proteolysis, and inflammatory responses. TGF- β 1 suppresses tumor growth at early stages of cancer, whereas, at late stages, TGF- β 1 promotes tumor spreading by through angiogenesis.

Interference with TGF- β -activated protein kinase 1 (TAK1) activity alters TGF- β 25 interactions with MMP-9 and the metastatic potential of cancer cells. Thus, there is a need to identify improved TAK1 inhibitors useful in cancer treatments.

Technology: TAK1 is a member of the MAPKKK family, is a key mediator of proinflammatory and stress signals. Activation of TAK-1 by proinflammatory cytokines and T and B cell receptors induces the nuclear localization of nuclear factor κ B (NF-Kappa B) and the activation of c-Jun N-terminal kinase (JNK)/AP1 and P38, which play important roles in mediating inflammation, immune responses, T and B cell activation, apoptosis, and epithelial cell survival. Recently it was shown that the natural product 5(Z)-7-oxozeaenol can effectively inhibit TAK-1 activity, thereby lessening the extent of these cancerous growths. The inventors have created a library of synthetic analogues that surpass the activity of 5(Z)-7-oxozeaenol. In vitro studies reveal that a number of these synthetic analogues are not only sufficiently cytotoxic to tumor cells, but also relatively harmless to normal cell lines. These compounds have also been shown to reduce tumor growth in xenograft mouse models. Additional medicinal chemistry work is being conducted in order to optimize these novel compounds for therapeutic use.

Potential Commercial Applications:

- Formulation of compound can be used as a method for treating or preventing cancer.
- Compositions can be formulated for enteral, parenteral, topical, transdermal, or pulmonary administration.
- Compound can be used to treat broad array of different cancers, any that involve proliferative disorders as the primary tumor.

Competitive Advantages:

- TAK-1 activity can lead to metastasis and cancerous angiogenesis.
- Suppression of TAK-1 has been demonstrated by a novel set of synthetic analogues based on the natural product 5(Z)-7-oxozeaenol.
- Active agents can be administered simultaneously in the same dosage form or in separate dosage forms.

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Inventor: [Andrei Bakin, PhD](#), [Spandan Chennamadhavuni](#), [Huw M. L. Davies](#)