



**Method of Improving Drugs with Anti-Retroviral and Anti-Cancer Activity** (*Harmut M. Hanauske-Abel, NJMS 04-39, 04-46*) *Therapeutic*

**Background**

This invention relates to a method of inhibiting the generation of infections viral progeny, or suppressing the proliferation of malignant cells, which comprises interrupting the eIF5A-dependent cellular pathway essential for cellular proliferation. eIF5A is a eukaryotic translation initiation factor 5A, an intracellular protein with two isoforms. eIF5A requires posttranslational modification in order to become biologically active. It has been shown to be over-expressed in cancers and is thought to play an essential role in virally-induced proliferation of cells. This protein is unique in that it contains hypusine, a lysine derivative, which is formed by posttranslational hydroxylation, catalyzed by the non-heme ferrous dioxygenase deoxyhypusine hydroxylase (DOHH). The active site architecture of DOHH can be characterized by an active site cage entombed inside the apoenzyme ('fireplace-with-chimney' model). This invention relates to the discovery that the 'chimney' segment of the DOHH active site can accommodate large hydrophobic moieties which can serve as an anchor for a smaller inhibitor in the 'fireplace' segment of DOHH thereby significantly improving the efficacy of the inhibitor.

**Description of the Technology**

This invention discloses a method used to obtain a suppressive effect on the proliferation of cells occurring within a non-metastatic or metastatic malignancy. The preferred embodiment of the pharmacologically relevant DOHH inhibitor is a compound of a disclosed formula or a derivative thereof with a hexane backbone and a hydrophobic anchor as (C<sub>5</sub>-C<sub>12</sub>) alkyl, (C<sub>3</sub>- C<sub>12</sub>) cycloalkyl, or a hydrophobic aromatic moiety. Other side chains can be hydrogens; alkyl, alkenyl, alkynyl or alkoxy groups; or a peptide or a peptidomimetic moiety containing 10 to 50 carbon atoms particularly positioned on the hexane ring. The disclosed formula for the proposed pharmaceutical agent has been shown to have an improved efficacy as compared to the currently existing DOHH inhibitors.

**Application**

The compounds of this invention can be used in systemic or topical application as anti-neoplastic agents in combination with existing anti-cancer drugs of various clinically introduced chemotypes, as well as, a part of cancer treatment protocols also comprising surgery and radiation.

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