Validation of the human farnesyl pyrophosphate synthase (hFPPS) as a therapeutic target and design of pre-clinical candidates for the treatment of multiple myeloma and neurodegenerative diseases.

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Validation of the human farnesyl pyrophosphate synthase (hFPPS) as a therapeutic target and design of pre-clinical candidates for the treatment of multiple myeloma and neurodegenerative diseases.

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Research Abstract

The enzyme farnesyl pyrophosphate synthase (hFPPS) is responsible for the biosynthesis of farnesyl pyrophosphate (FPP), a key metabolite in the biochemistry and physiology of the human body. Abnormally high activity of hFPPS has been implicated in numerous cellular processes that are associated with cancer and the progression of neurodegenerative diseases, such as Alzheimer's. Recent clinical trials in prostate cancer have shown that zoledronic acid (ZOL, an hFPPS inhibitor) can decrease levels of tumor marker (PSA) while an increased disease-free survival was seen in breast cancer patients treated with ZOL. A landmark trial in Multiple Myeloma (MM) showed improved overall survival in patients treated with ZOL. Autopsy reports have shown high levels of hFPPS activity in the brain tissues of Alzheimer's patients. High levels of FPP in the brain have been shown to increase production of the protein phospo-Tau, which is strongly implicated in the death of neuronal cells in the brain. However, it is not known whether metabolic dysregulation of hFPPS is the cause of the Alzheimer's disease progression or whether it is a consequence of some, yet unknown factor. The goal of our research is to develop inhibitors of hFPPS that have good biopharmaceutical properties, so that we can properly investigate the role of the hFPPS blockade in cancer and the progression of the Alzheimer's disease. We have already designed "prototype" molecules that are potent and selective inhibitors of hFPPS, are able to block proliferation of MM cancer cells and decrease phospho-Tau levels in human immortalized neurons. These compounds exhibit superior pharmaceutical properties to those of the currently available drugs that target hFPPS (such as ZOL) and are less toxic

Further information available at:

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