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Advancing the Arizona State University Knowledge Enterprise

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Compounds to Modulate Retinoid X Receptors

The human retinoid X receptors (RXRs) function as transcriptional regulators, often in partnership with members of a larger nuclear receptor family of transcription factors. RXR agonists have been shown to modulate RXR transcription and activate or repress various biological pathways and effect therapeutic results for various conditions.

There are a few RXR agonists that are known such as CD3254, Bexarotene, Bexarotene analogs, and LGD100268. Bexarotene (Targretin®) is one of the more recognized compounds and is used to treat cutaneous T-cell lymphoma (as well as off label to treat other types of cancer). Recent research may show significant potential in its use for treatment of Alzheimer's disease. However, Bexarotene treatment has some side effects, namely hypothyroidism, hyperlipidemia, and cutaneous toxicity, which may be due to its activation of RXR in several different tissues.

Researchers at Arizona State University have developed a portfolio of RXR agonists, which are more potent analogs and derivatives of Bexarotene, CD3254, LGD100268 and Tamibarotene. These analogs have a higher selectivity for the retinoid X receptor versus the retinoic acid receptor (RAR) and can be uncoupled from drastic lipid changes and thyroid axis variations. Additionally, in astrocytes and microglia, the Bexarotene analogs increase expression of ApoE and highly lipidated HDLs, which then promote clearance of amyloid beta in the brain.

These new analogs may provide viable and efficacious alternative treatment options for cancer, Alzheimer's disease (AD), Parkinson's disease (PD), schizophrenia, and other neurodegenerative diseases. Further, animal testing suggests that the improved PK and triglyceride profiles make these compounds compelling therapeutic candidates.

Potential Applications

- Anti-cancer treatment

o CTCL, colon, breast, lung, pancreatic, skin, ovarian, bladder, kidney, head and neck cancers, leukemia and others

- May be useful in treatment of AD & other neurodegenerative diseases
- May be useful in treatment of RXR-pathway related diseases
- May be useful in treatment of diseases associated with dopamine deficiency

o PD, schizophrenia, depression, and other psychotic disorders

- May be useful in treatment of non-insulin dependent diabetes mellitus

Benefits and Advantages

- Several analogs demonstrate higher affinity/activation for RXR than Bexarotene
- Higher efficacies/potency/specificity may allow for lower doses thus alleviating some side effects
- Improved side effects than parent compounds
- May stimulate gene expression better
- Some compounds may be less toxic than parent compounds and produce statistically lower triglyceride levels
- Improved PK characteristics

For more information about the inventor(s) and their research, please see Dr. Wagner's directory webpage Dr. Marshall's laboratory webpage Dr. Jurutka's department webpage