Small molecule transthyretin ligands for the treatment of dry Age-related Macular Degeneration and orphan Stargardt Disease

Age-related Macular Degeneration (AMD) is the leading cause of blindness in developing countries. AMD occurs in both dry (atrophic) and wet (exudative) forms, with dry AMD accounting for the majority of all AMD cases. However, there are currently no FDA-approved therapies for this disease. Dry AMD is caused by degeneration of photoreceptor cells in the central part of the retina, due to the buildup of cytotoxic lipofuscin bisretinoids, such as A2E, in the eye. This technology describes several small molecule inhibitors that disrupt the formation of A2E. These compounds could be used to treat dry AMD, as well as other degenerative eye diseases related to the buildup of lipofuscin bisretinoids, including orphan Stargardt disease and Best disease.

Effective in vivo activity from already FDA-approved small molecule therapeutics

This technology describes several small molecule inhibitors that disrupt the formation of cytotoxic bisretinoids responsible for the degeneration of rod and cone cells in the retina. Bisretinoid production is fueled by serum retinol, which is delivered to the retina by a complex composed of retinol binding protein 4 (RBP4) and transthyretin (TTR). This technology identifies several transthyretin (TTR) ligands that act as allosteric antagonists of retinol-dependent RBP4-TTR interaction, effectively lowering concentrations of serum retinol and limiting its delivery to the retina. This partially reduces the concentration of visual cycle retinoids, and in doing so reduces the production of cytotoxic bisretinoids in the eye. Furthermore, some of the small molecules embodied by the invention are already FDA approved for other diseases, so clinical toxicity issues are already known.

The small molecules described by this technology are demonstrated to be effective in both in vitro assays and in vivo in a murine model.

Lead Inventor:

Konstantin Petrukhin, Ph.D.
Applications:

- Therapeutic for ocular diseases caused by lipofuscin build-up
- Therapeutic for dry age-related macular degeneration
- Therapeutic for Stargardt disease
- Therapeutic for Stargardt-like macular dystrophy
- Therapeutic for Best disease
- Research tool for characterization of the vision cycle

Advantages:

- Describes a library of transthyretin-specific compounds and their mechanism of action that decrease the amount of toxic lipofuscin buildup.
- Some molecules are already FDA approved for other indications

Patent Information:

Patent Pending (US 20150057320)

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Related Publications:


Inventors

Konstantin Petrukhin