3-HKA Analogs for the Treatment of Autoimmune Diseases

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# 3-HKA Analogs for the Treatment of Autoimmune Diseases

## Background & Unmet Need

- Autoimmune disease is the 4th largest cause of disability among women in the United States.
- Autoimmune disease has an incidence rate of 4% worldwide, or 300 million individuals, and increasing.
- IDO1 catalyzes the first, rate-limiting step of the kynurenine pathway, and is highly expressed in antigen-presenting cells (APCs) in inflammatory conditions dominated by interferon γ (IFN-γ).
- Targeting the kynurenine pathway may help control autoimmune and chronic inflammatory diseases, but which kynurenine to target remains unclear.
- **Unmet Need:** Improved understanding of kynurenine pathway to inform targeted therapy for autoimmune diseases.

## Technology Overview

- **The Technology:** Method to treat autoimmune diseases using 3-HKA and its analogs.
- **The Discovery:** 3-hydroxykynurenine (3-HKA) is a previously undescribed biogenic amine with anti-inflammatory and immunosuppressive capabilities *in vivo* and *in vitro*.
- **PoC Data:** 3-HKA inhibits the IFN-γ-receptor and NF-kB activation (pro-inflammatory cytokines) and decreases inflammatory T-cell proliferation in mouse models of psoriasis, nephrotoxic lupus, and Chron’s disease.
- IDO1 knockout (which thus abolishes 3-HKA production) leads to an increase in inflammation, and exacerbates psoriasis in mice models.
- The inventors also showed that 3-HKA is the most abundant Trp metabolite in multiple solid tumor types, suggesting antagonism of 3-HKA may have therapeutic applications in cancer immunotherapy.

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## Patents:
Provisional Application Filed

## Publications:

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## Cornell Reference:
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Technology Applications

• Development of 3-HKA and its analogs as potent treatments of autoimmune diseases
• Antagonism of 3-HKA may have therapeutic applications in cancer immunotherapy

Technology Advantages

• Demonstrated efficacy across multiple indications (psoriasis, nephrotic lupus, and Chron’s disease)
• 3-HKA is a naturally-occurring metabolite with no known toxicity

Supporting Data / Figures

Figure 1: A: 3-HKA treatment ameliorates psoriasis plaques in the imiquimod mouse model. B: 3-HKA decreases pro-inflammatory chemokines and cytokines in human dendritic cells, which are activated in psoriasis.

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3-HKA as a Treatment for Nephrotoxic Nephritis

Figure 5: 3-HKA treatment decreases nephrotoxic nephritis in mice. Mice were administered either nephrotoxic serum (N-Ab) or control (PBS). Mice treated with the 3-HKA showed lower levels of proteinuria and decreased increased serum urea nitrogen, which show reversal of renal dysfunction. The treatment also significantly improved the survival of mice given nephrotoxic serum.

AADC Enzyme Generates 3-HKA

Figure 6: AADC converts 3OH-L-kynurenine to 3-HKA. 3-OH-L-kynurenine was incubated with the AADC enzyme for 40 minutes. 3OH-L-kynurenine was converted to 3-HKA, indicating AADC is the likely enzyme generating the lateral derivate of 3-HKA.

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