Weill Cornell Medicine

3-HKA Analogs for the Treatment of Autoimmune Diseases

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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 is increasing
- Current treatments that block inflammatory cytokines rapidly lose efficacy, with only 45% of patients still responding to therapy after ~2 years of treatment
- 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:** Treatments targeting the kynurenine pathway for autoimmune diseases

Technology Overview

- **The Technology:** 12 novel analogs of 3-HKA for the treatment of autoimmune diseases
- **The Discovery:** 3-hydroxykynurenine (3-HKA) is a previously undescribed biogenic amine with anti-inflammatory and immunosuppressive capabilities *in vivo* and *in vitro*
- 3-HKA inhibits the IFN-γ mediated STAT1/NF-κB pathway in dendritic cells, reducing the release of pro-inflammatory chemokines and cytokines
- The inventors have generated 12 novel analogs for 3-HKA with a variety of chemotypes through an *in silico* screening platform
- **PoC Data:** 3-HKA has demonstrated efficacy in reducing disease hallmarks in mouse models of psoriasis, lupus nephritis, and Crohn's disease
- Analogs of 3-HKA appear to have similar anti-inflammatory properties as 3-HKA and significantly reduced IL-1b and TNF-α production in a model of lupus

Inventors:
Laura Santambrogio

Patents:
Provisional Filed

Publications:
Clement et al. *Nature Communications*. 2021.

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Technology Applications

- 3-HKA analogs as potential treatments of autoimmune disease, including psoriasis, Chron's disease, and lupus
- Antagonism of 3-HKA for other therapeutic applications, including cancer immunotherapy

Technology Advantages

- Demonstrated efficacy across multiple indications (psoriasis, nephrotoxic lupus, and Chron's disease)
- Variety of chemotypes identified with different properties suitable for medicinal chemistry

Supporting Data / Figures

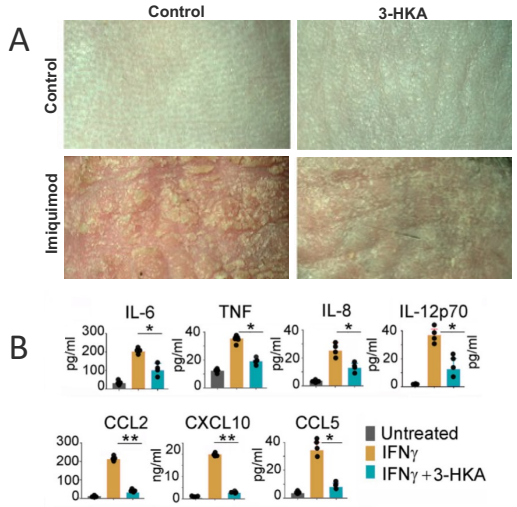

Figure 1: A: 3-HKA treatment ameliorates psoriasis plaques in the imiquimod mouse model. **B:** 3-HKA decreases pro-inflammatory chemokines and cytokines in human dendritic cells, which are activated in psoriasis.

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Supporting Data / Figures

3-HKA as a Treatment for Nephrotoxic Nephritis

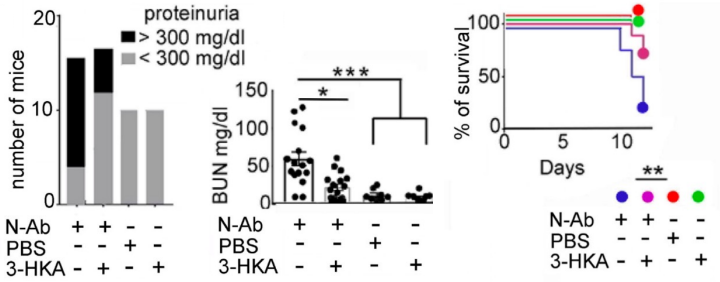

Figure 2: 3-HKA treatment decreases nephrotoxic nephritis in mice. Mice were administered either nephrotoxic serum (N-Ab) or control (PBS). Mice treated with the 3-HKA showed lower levels of proteinuria and decreased increased serum urea nitrogen, which show reversal of renal dysfunction. The treatment also significantly improved the survival of mice given nephrotoxic serum.

3-HKA Analogs Reduce IL-1β and TNF-α Levels

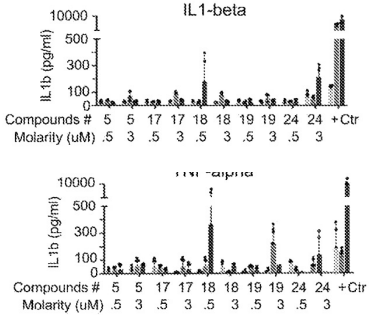

Figure 3: 3-HKA analogs decrease inflammation IL-1b and TNFa levels in a human lupus model. Healthy human polymorphonucleated cells (PBMC) were incubated with sera from patients with active systemic lupus erythematosus (SLE) with or without 3-HKA analogs. The tested compounds significantly reduced IL-1b and TNF-α production.

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