Intranasal administration of a novel synthetic TLR4 agonist suppresses allergen-specific Th2 responses in mice

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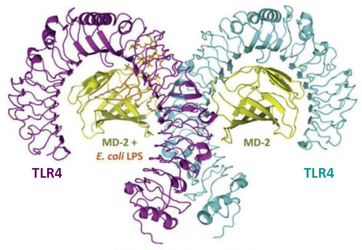
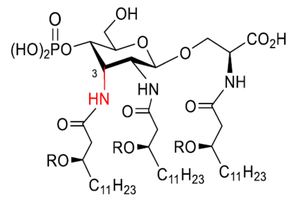
ABSTRACT

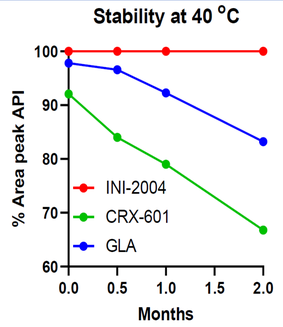
Allergen-agnostic immunotherapies to treat seasonal allergic rhinitis are not currently available. Antihistamines are the most common form of seasonal allergic rhinitis treatment – minimizing symptoms instead of addressing underlying immune dysfunction. Allergen specific immunotherapies (AIT) are also available for seasonal allergic rhinitis but require a known allergen and long-term treatment regiments that can be costly and take several years to complete. Here we report a novel synthetic TLR4 agonist that prevented Th2 allergic responses in an OVA-sensitized mouse model. Our novel synthetic TLR4 agonist that has improved stability compared to other TLR4 agonists used as vaccine adjuvants or immunotherapeutics. After sensitizing Balb/c mice to OVA using IP injections of OVA + alum, intranasal treatment with the novel TLR4 agonist at one, three, or seven days prior to intranasal OVA challenge reduced or ameliorated OVA-specific Th2 allergic responses. Specifically, intranasal INI2004 treatment reduced OVA-induced airway hypersensitivity, eosinophil influx, and Th2 T cell cytokine secretion – hallmarks of Th2 allergic immune responses. These data suggest this novel synthetic TLR4 agonist can potentially treat the underlying immune dysfunction associated with allergic responses for a durable cure of seasonal allergic rhinitis.

Figure 1: INI-2004 is a stable, potent TLR4 agonist



Protein Data Bank ID 3FXI





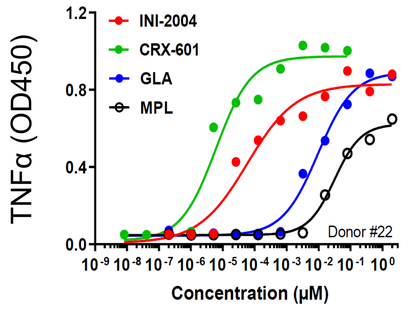
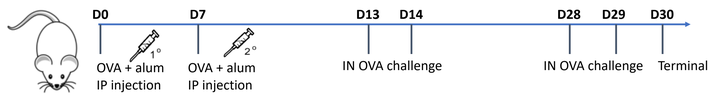
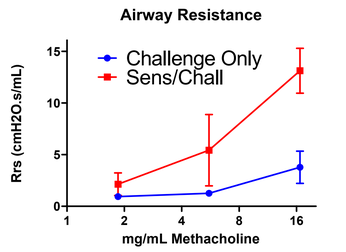
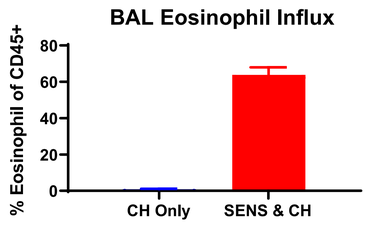


Figure 2: OVA-sensitized mouse model







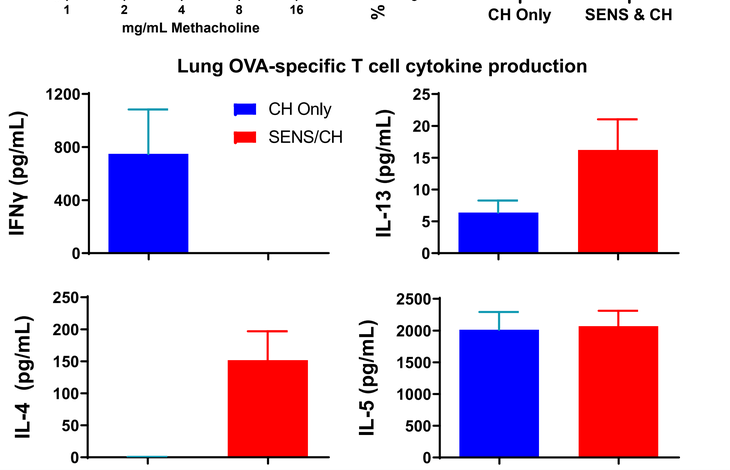
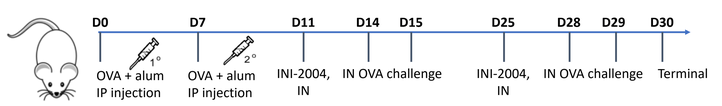
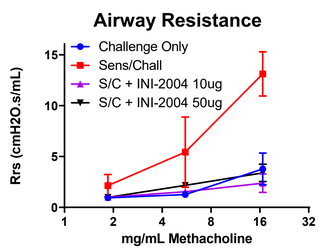
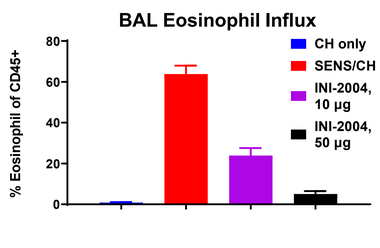


Figure 3: Intranasal administration of INI-2004 suppresses OVA-specific allergic responses







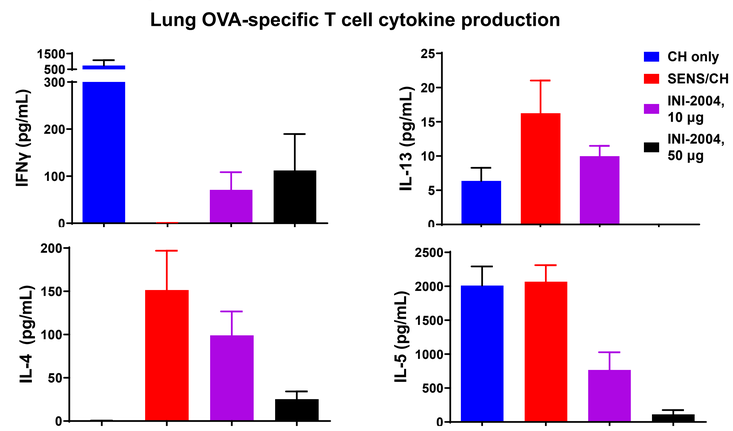
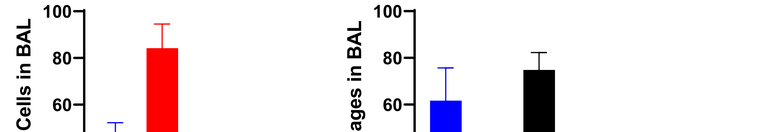
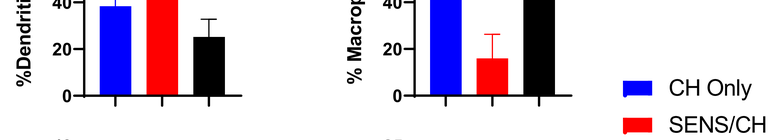


Figure 4: 50 μg INI-2004 suppresses OVA-specific allergic responses over a 7-day window





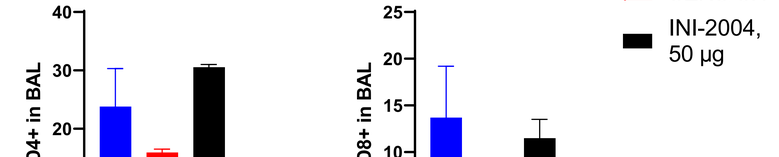


Figure 5: INI-2004 increases macrophage and T cell infiltration in BAL

Conclusions & Future Directions

- INI-2004 administered IN is an effective therapeutic for allergic rhinitis when given up to 7 days before allergen exposure
- The mechanism of action in the mouse model is strong suppression of eosinophil influx along with suppression of OVA-specific Th2 responses
- While the frequency of T cells in BAL increase post-treatment, these T cells are not OVA-specific
- INI-2004 is advancing to Phase I clinical trial for seasonal allergic rhinitis in late 2023

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