Potent and Selective CRTh2 Antagonists are Efficacious in Models of Asthma, Allergic Rhinitis and Atopic Dermatitis

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Abstract 490
Central Role for PGD$_2$ and CRTh2 in Allergic Inflammation

- PGD$_2$ is a potent prostanoid released upon mast cell activation
  - Links early & late phase allergen responses
- CRTh2 is the biologically relevant GPC-receptor for PGD$_2$ & its more stable metabolites
  - Chemoattractant Receptor-homologous molecule expressed on Th2 lymphocytes
CRTh2 Antagonism: Target Validation

- Selective CRTh2 antagonists have demonstrated preclinical efficacy
  - Significant reduction of eosinophil accumulation in OVA-sensitized mice model of asthma
  - Reduction in pulmonary neutrophilia in a cigarette-smoke mouse model of COPD

- Ramatroban®, a weak, non-selective CRTh2 antagonist, is approved for allergic rhinitis (Japan)
  - Improved the symptoms, nasal obstruction & daily discomfort compared to terfenadine in a Phase 3 study

- OC000459, a selective CRTh2 antagonist, improved lung function in mild to moderate asthmatics in a Phase 2a study
  - FEV1 increased over baseline by 9.2% (treatment) vs. 1.8% (placebo)
  - FEV1 did not plateau – still improving at week 4
  - Significant improvement in peak expiratory flow
  - Significant decreases in serum IgE & sputum eosinophil counts
  - No serious AE’s
### ARRY-005, ARRY-006: *In Vitro* Potency, Selectivity and Functional Activity

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<thead>
<tr>
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<th>ARRY-005</th>
<th>ARRY-006</th>
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<tbody>
<tr>
<td>Human CRTh2 Binding</td>
<td>IC$_{50}$</td>
<td>1 nM</td>
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<tr>
<td>Human CRTh2 Binding</td>
<td>IC$_{50}$ (4% HSA)</td>
<td>35 nM</td>
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<tr>
<td>Selectivity vs. 30 GPCR’s, Ion Channels and Transporters</td>
<td>No significant activity @500 nM</td>
<td>No significant activity @500 nM</td>
</tr>
<tr>
<td>CRTh2 FLIPR Calcium Mobilization IC$_{50}$</td>
<td>5 nM</td>
<td>5 nM</td>
</tr>
<tr>
<td>Human Isolated Basophil Chemotaxis IC$_{50}$</td>
<td>1 nM</td>
<td>1 nM</td>
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- PGD$_2$ exposed to eosinophils in whole blood results in a shape change
  - Activation of the intracellular motile apparatus
  - Occurs exclusively through CRTh2

**Table:**

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<th>ARRY-005</th>
<th>IC$_{50}$</th>
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<tr>
<td>Human Whole Blood Eosinophil Shape Change</td>
<td>33 nM</td>
<td></td>
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<tr>
<td>Human Whole Blood Receptor Internalization</td>
<td>24 nM</td>
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Murine Model of Allergic Rhinitis

- **Mice**
  - Female Balb/c mice (6 weeks old)

- **Drug treatment**
  - Vehicle (0.5% methylcellulose)
  - **ARRY-005** (0.1, 0.5, 1, 10 mg/kg, PO)

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**Intranasal OVA challenge (without anesthesia)**
- 10% OVA-saline, 15 µl each nostril

**Oral Doses of ARRY-005 (1 h prior to challenge)**

- 20 mg OVA i.p. with 2.25 mg alum

**Baseline**
- Respiratory frequency

**Early Response**
- Respiratory frequency and cytokines in nasal tissue

**Late Response**
ARRY-005 Exhibits Dose Dependent Inhibition of the Early Phase Response in Allergic Rhinitis Model

![Graph showing dose response](image)

- **OVA/Saline, vehicle**
- **OVA/OVA, vehicle**
- **OVA/OVA, ARRY-005 (0.1 mg/kg)**
- **OVA/OVA, ARRY-005 (0.5 mg/kg)**
- **OVA/OVA, ARRY-005 (1 mg/kg)**
- **OVA/OVA, ARRY-005 (10 mg/kg)**

**Time after 4th challenge (min):**
- Baseline
- 4-7
- 9-12
- 14-17
- 19-22
- 24-27
- 29-32

**RF (breaths/min):**
- 100
- 150
- 200
- 250
- 300
- 350

*: P < 0.05 vs OVA/OVA, vehicle
ARRY-005 Exhibits Dose Dependent Inhibition of the Late Phase Response in Allergic Rhinitis Model

**RF (breaths/min)**

- OVA/Saline, vehicle
- OVA/OVA, vehicle
- OVA/OVA, ARRY-005 (0.1 mg/kg)
- OVA/OVA, ARRY-005 (0.5 mg/kg)
- OVA/OVA, ARRY-005 (1 mg/kg)
- OVA/OVA, ARRY-005 (10 mg/kg)

*: P < 0.05 vs OVA/OVA, vehicle

[24 hours after 6th Challenge]
ARRAY-005 Reduces Cytokine Levels in the Late Phase of Allergic Rhinitis Model
Murine Model of Asthma

- **Mice**
  - Female Balb/c mice (6 weeks old)

- **Drug treatment**
  - Vehicle (0.5% methylcellulose)
  - **ARRY-006 (1, 5, 10, 30 mg/kg, PO)**

 timelines:

- Day 0: 20 mg OVA i.p. with 2.25 mg alum
- Day 14: Oral Doses of ARRY-006 (1 h prior to challenge)
- Day 28: \textbf{Inhaled} OVA challenge (1.6% OVA-saline, nebulized)
- Day 30: Airway Hyperreactivity, BALF
- Day 32: Methacholine Challenge / Lung Resistance
  Cell counts in BAL Fluid
ARRY-006 Inhibits Airway Hyperreactivity in Asthma Model

![Graph showing the effect of ARRY-006 on airway hyperreactivity in asthma model.]
ARRY-006 Inhibits Cell Infiltration in BALF in Asthma Model
NC/Nga Mouse Model of Atopic Dermatitis

- **Mice**
  - Male NC/Nga mice (8 weeks old)

- **Drug treatment**
  - Vehicle
  - **ARRY-005** (30 mg/kg, QD, PO)
  - **Protopic Cream** (0.25 mg/kg, BID, Topical)

**Diagram:**
- Oral Doses of ARRY-005 (QD), Topical Doses of 0.03% Tacrolimus or vehicle (BID)
- Ear Thickness and Clinical Scoring (erythema, edema, oozing/crusts/hemorrhage)
- Baseline scratching behavior
- Scratching behavior
ARRY-005 Inhibits Ear Thickness and Decreases Clinical Scores in Atopic Dermatitis Model

**Ear Swelling**

- Vehicle
- ARRY-005
- Protopic

**Erythema**

- Vehicle
- ARRY-005
- Protopic

**Oozing/crusts/hemorrhage**

- Vehicle
- ARRY-005
- Protopic

*p*<0.05 compared to vehicle
ARRY-005 Inhibits Scratching Behavior in Atopic Dermatitis Model

Total Scratching: Day 0 and Day 30

* p<0.05 compared to respective vehicle
Summary

- CRTh2 is an important target in allergic disease

- ARRY-005 and ARRY-006 are potent, selective CRTh2 antagonists that demonstrate functional activity

- ARRY-005 and ARRY-006 demonstrate efficacy in murine models of allergic disease upon oral dosing
  - Control of early and late nasal reactivity
  - Control of airway hyperreactivity and cellular influx in the lung
  - Control of ear swelling, skin inflammation and pruritus