

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

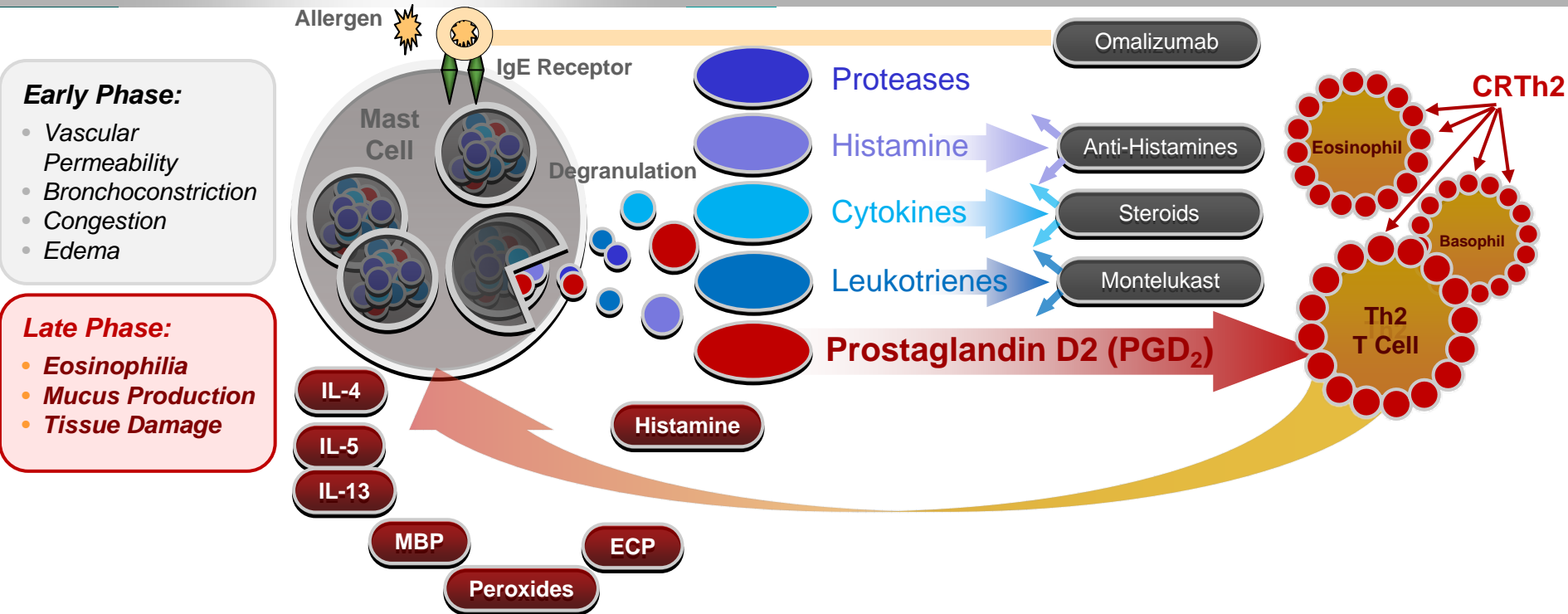
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Abstract 490

Central Role for PGD₂ and CRTh2 in Allergic Inflammation



- PGD₂ is a potent prostanoid released upon mast cell activation
 - Links early & late phase allergen responses
- CRTh2 is the biologically relevant GPC-receptor for PGD₂ & its more stable metabolites
 - Chemoattractant Receptor-homologous molecule expressed on Th2 lymphocytes

CRTh2 Antagonism: Target Validation

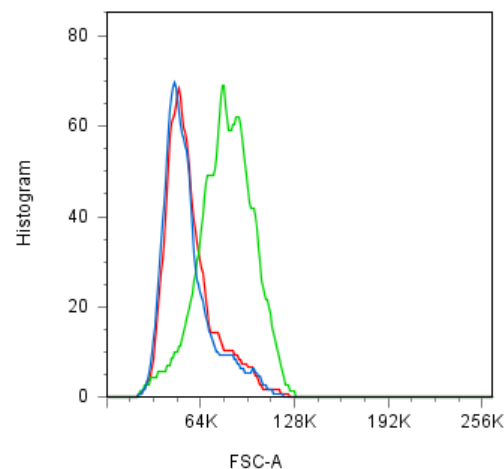
- Selective CRTh2 antagonists have demonstrated preclinical efficacy
 - Significant reduction of eosinophil accumulation in OVA-sensitized mice model of asthma
 - Reduction in pulmonary neutrophilia in a cigarette-smoke mouse model of COPD
- Ramatroban[®], a weak, non-selective CRTh2 antagonist, is approved 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

	ARRY-005	ARRY-006
Human CRTh2 Binding IC ₅₀	1 nM	3 nM
Human CRTh2 Binding IC ₅₀ (4% HSA)	35 nM	107 nM
Selectivity vs. 30 GPCR's, Ion Channels and Transporters	No significant activity @500 nM	No significant activity @500 nM
CRTh2 FLIPR Calcium Mobilization IC ₅₀	5 nM	5 nM
Human Isolated Basophil Chemotaxis IC ₅₀	1 nM	1 nM

- PGD₂ exposed to eosinophils in whole blood results in a shape change
 - Activation of the intracellular motile apparatus
 - Occurs exclusively through CRTh2

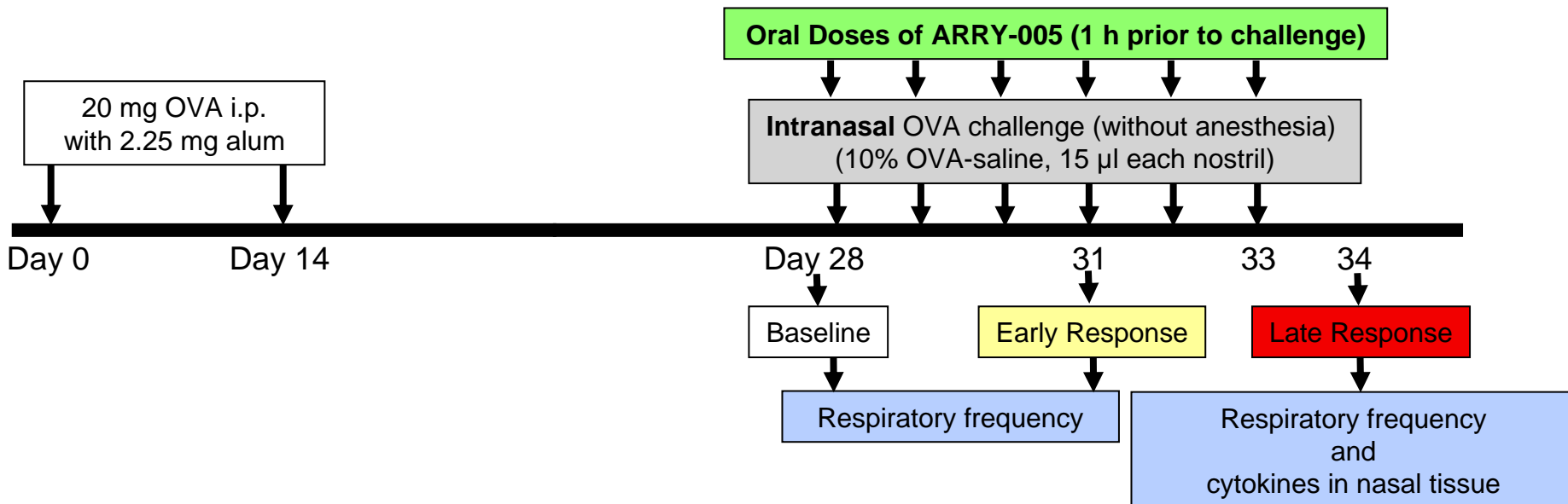
ARRY-005	IC ₅₀
Human Whole Blood Eosinophil Shape Change	33 nM
Human Whole Blood Receptor Internalization	24 nM



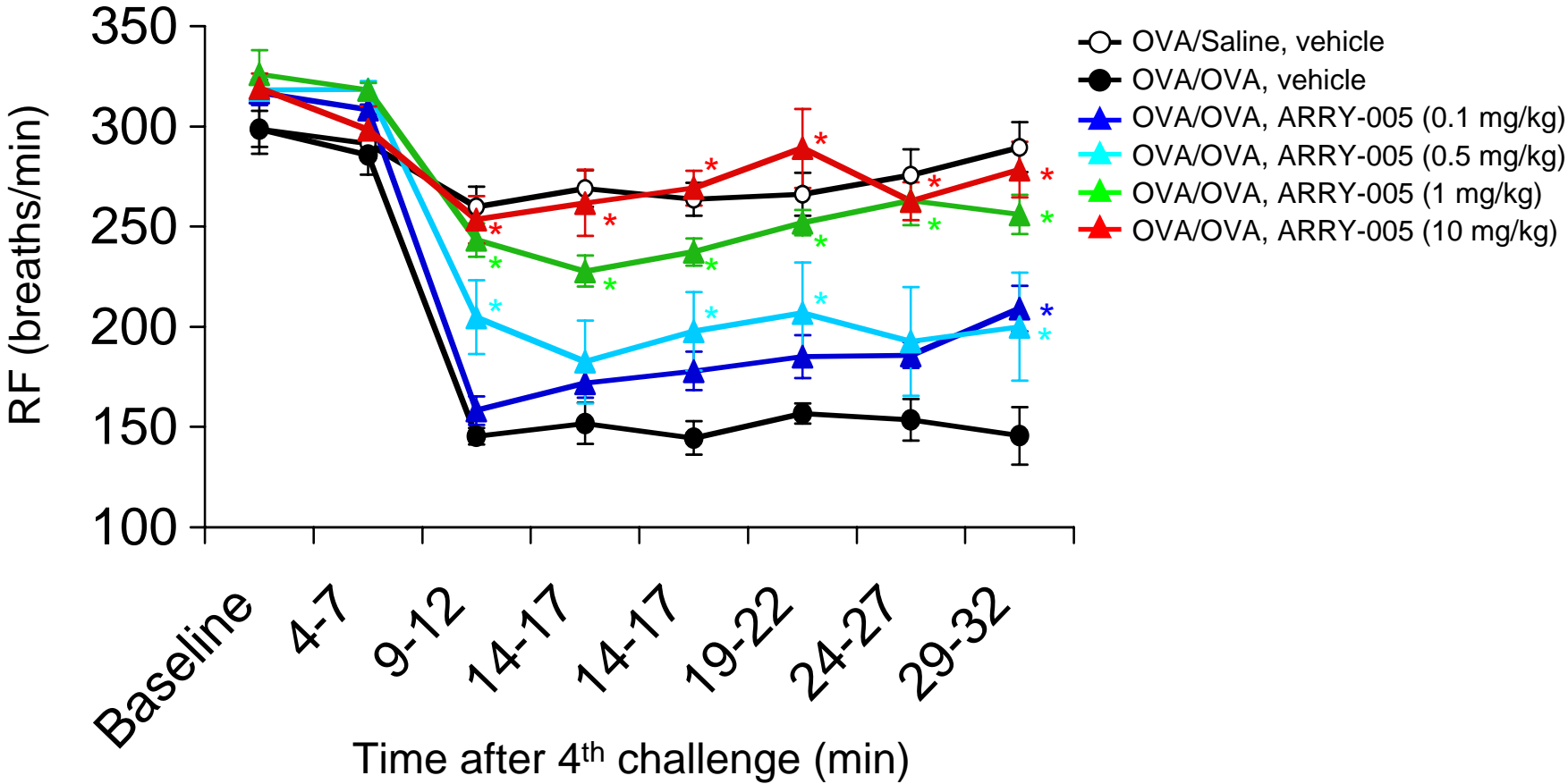
Sample Name
Unstimulated eosinophils.fcs
PGD2 stim eosinophils.fcs
PGD2 stim eos plus ARRY-502.f...

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)**

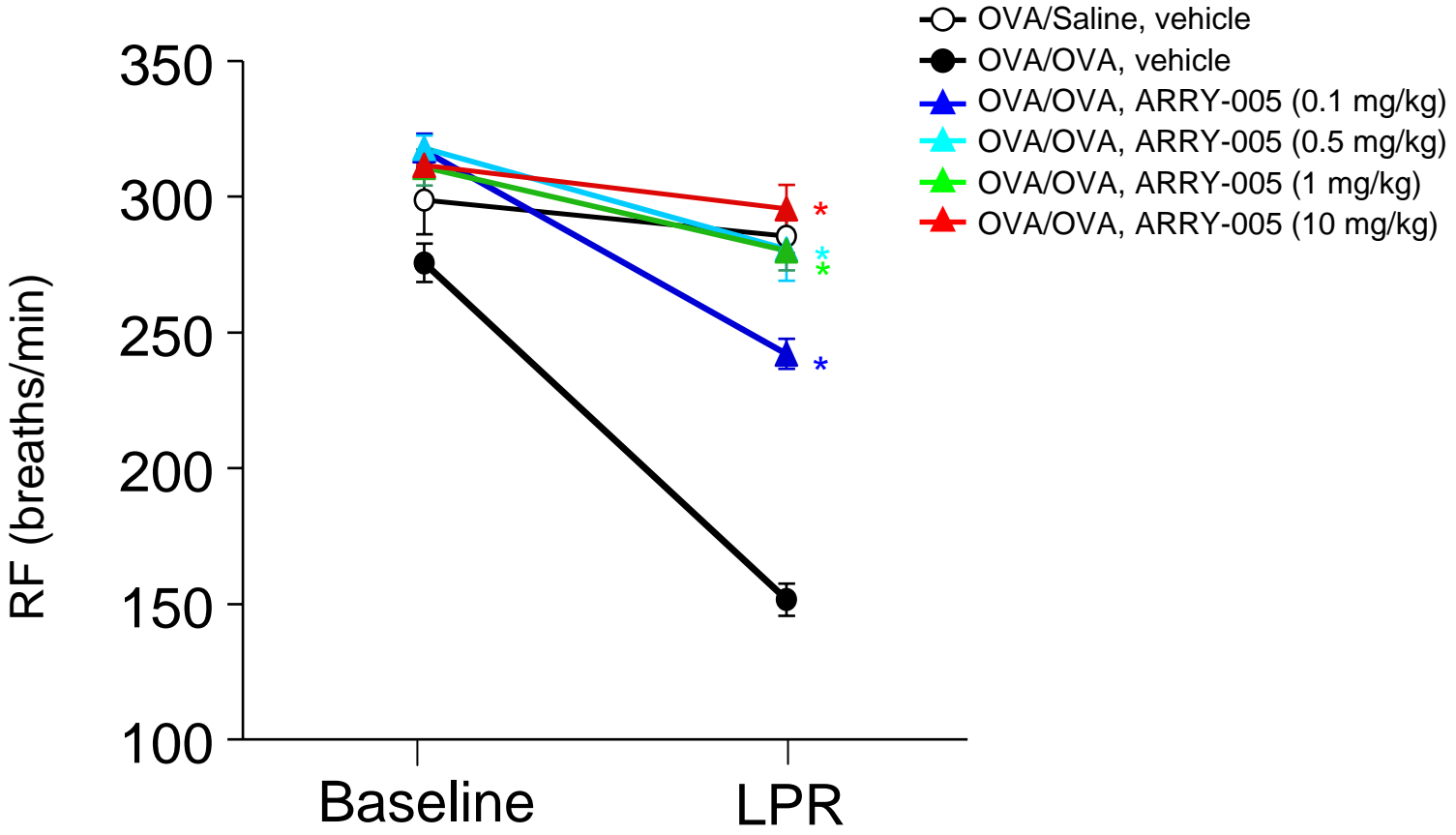


ARRY-005 Exhibits Dose Dependent Inhibition of the Early Phase Response in Allergic Rhinitis Model



*: P < 0.05 vs OVA/OVA, vehicle

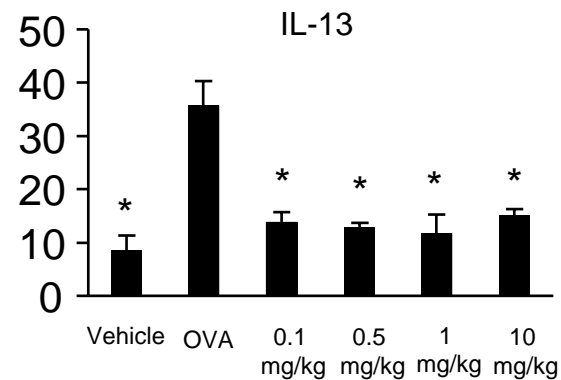
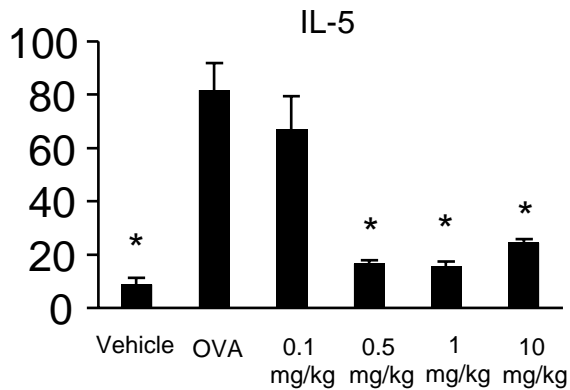
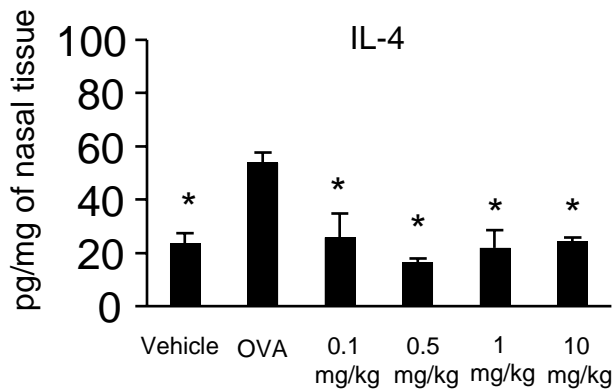
ARRY-005 Exhibits Dose Dependent Inhibition of the Late Phase Response in Allergic Rhinitis Model



*: P < 0.05 vs OVA/OVA, vehicle

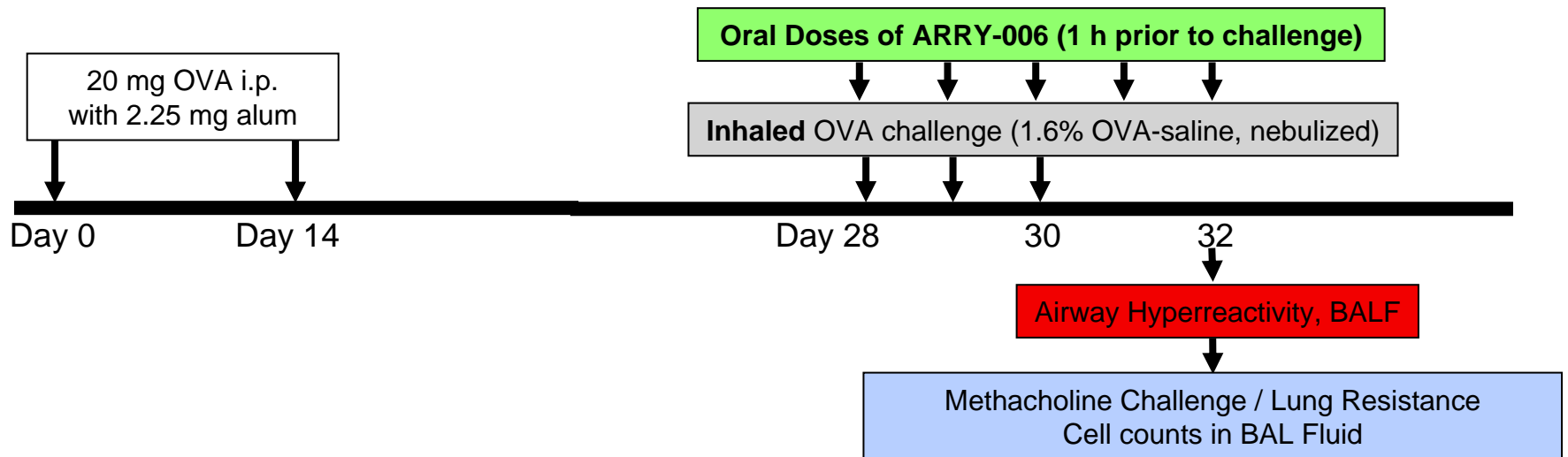
[24 hours after 6th Challenge]

ARRY-005 Reduces Cytokine Levels in the Late Phase of Allergic Rhinitis Model

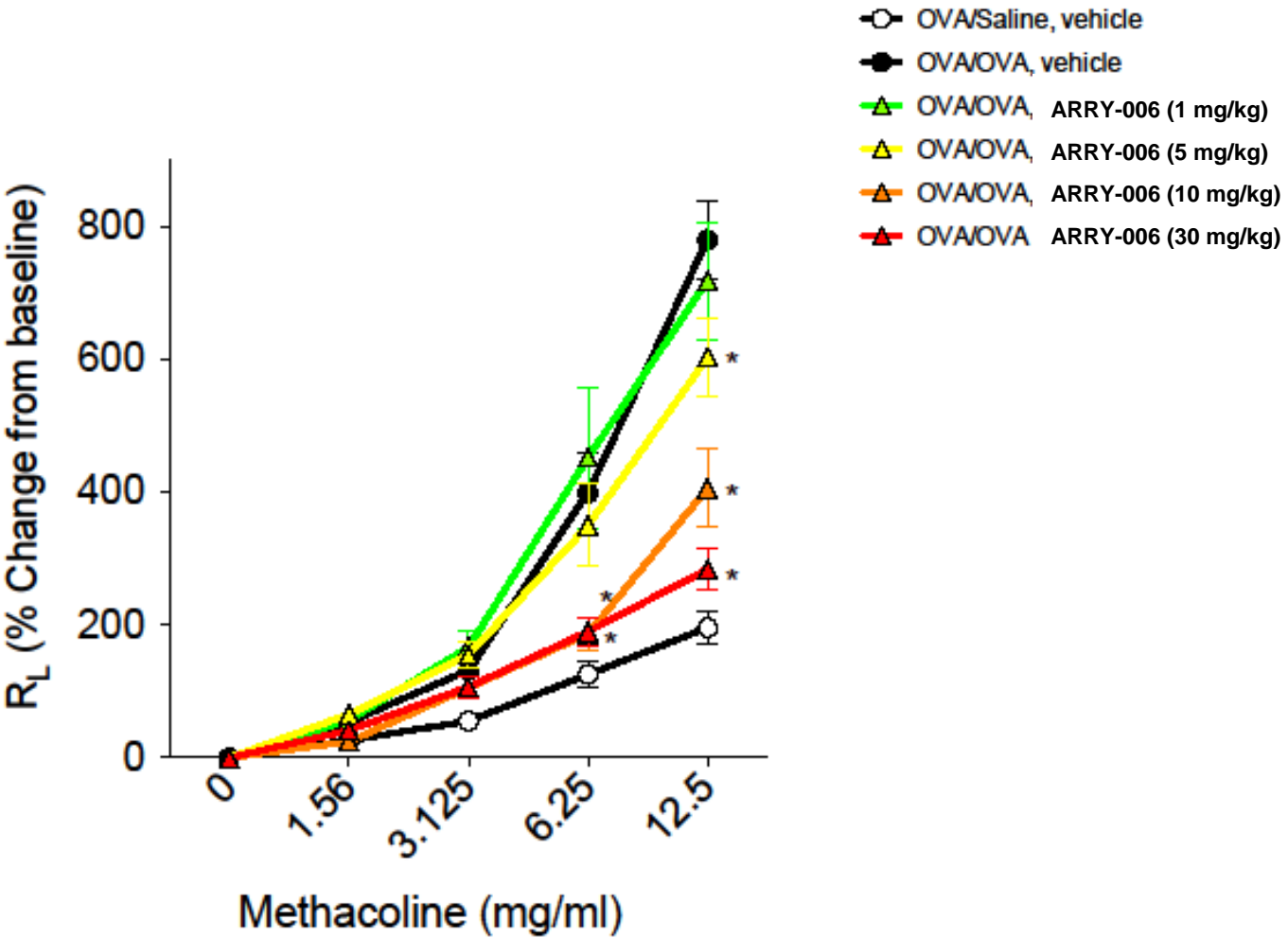


Murine Model of Asthma

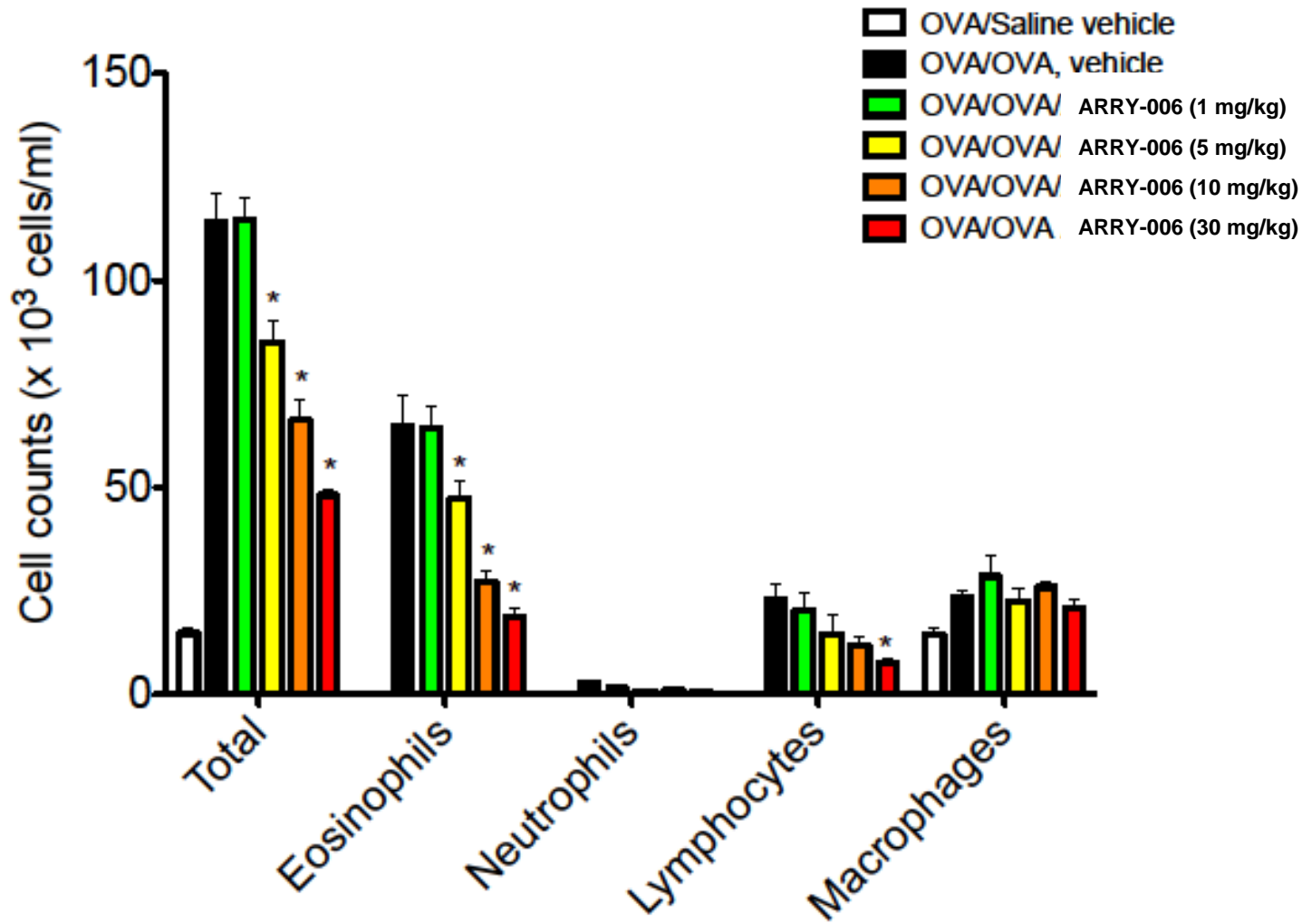
- Mice
 - Female Balb/c mice (6 weeks old)
- Drug treatment
 - Vehicle (0.5% methylcellulose)
 - **ARRY-006 (1, 5, 10, 30 mg/kg, PO)**



ARRY-006 Inhibits Airway Hyperreactivity in Asthma Model

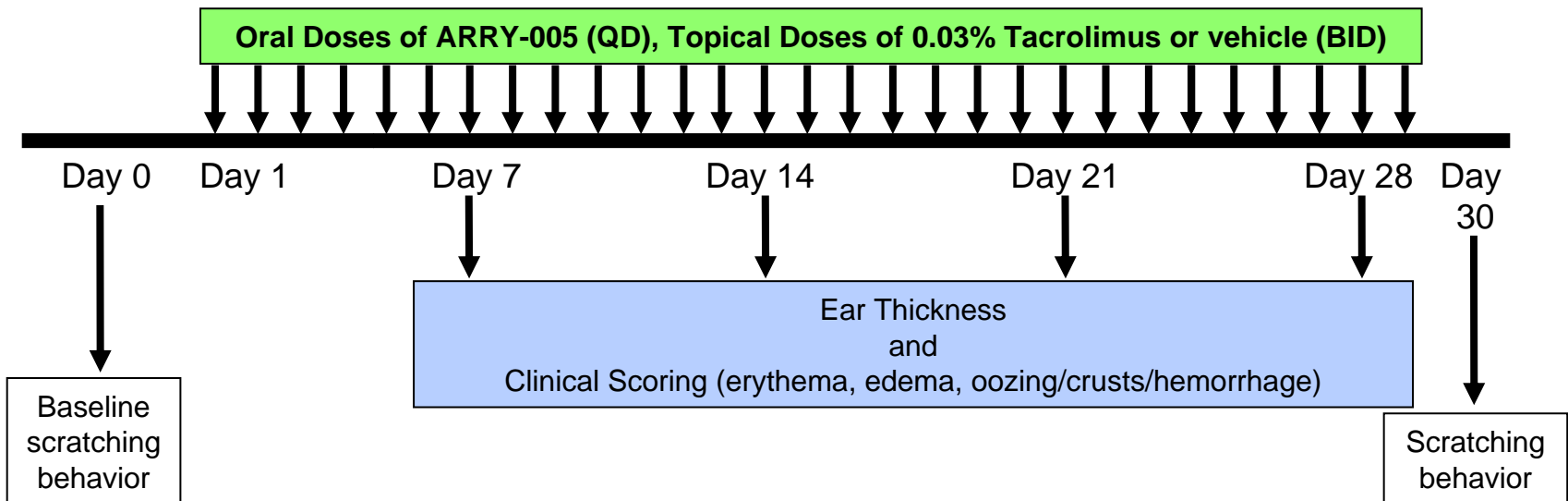


ARRY-006 Inhibits Cell Infiltration in BALF in Asthma Model



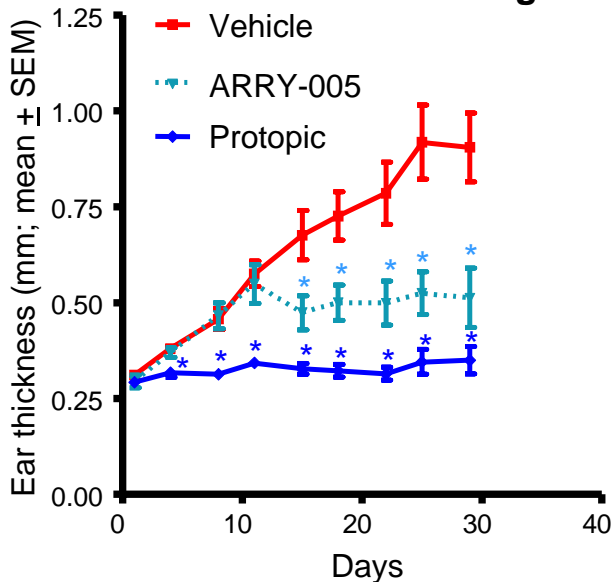
NC/Nga Mouse Model of Atopic Dermatitis

- 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)**

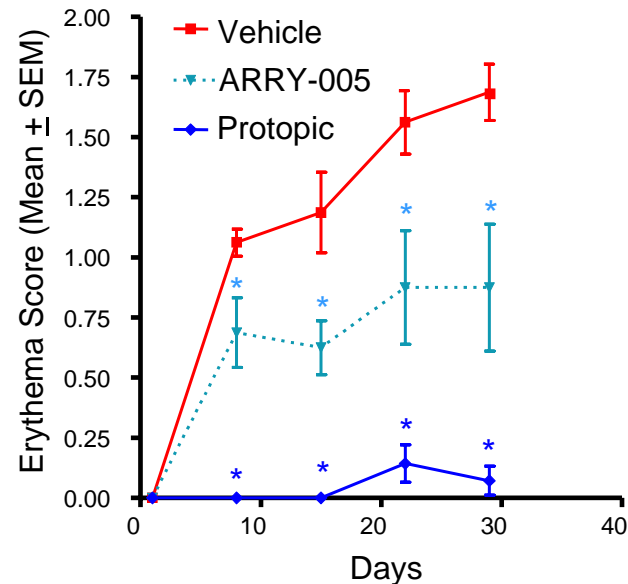


ARRY-005 Inhibits Ear Thickness and Decreases Clinical Scores in Atopic Dermatitis Model

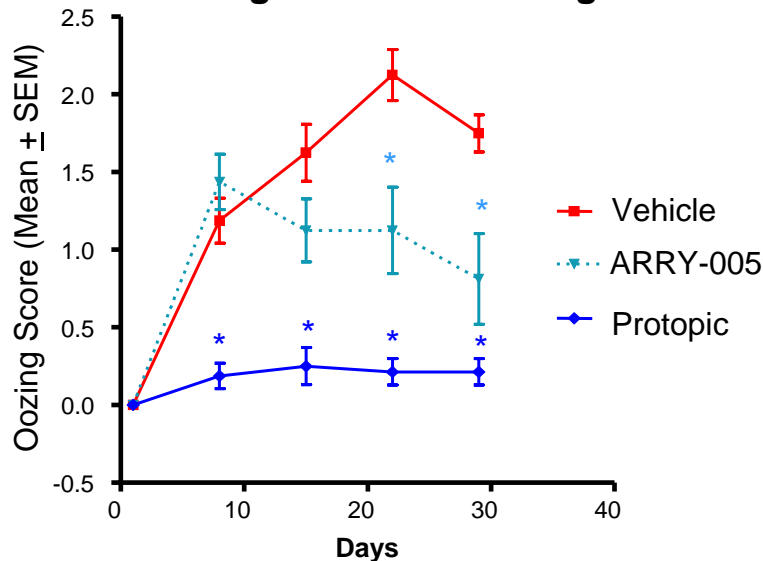
Ear Swelling



Erythema



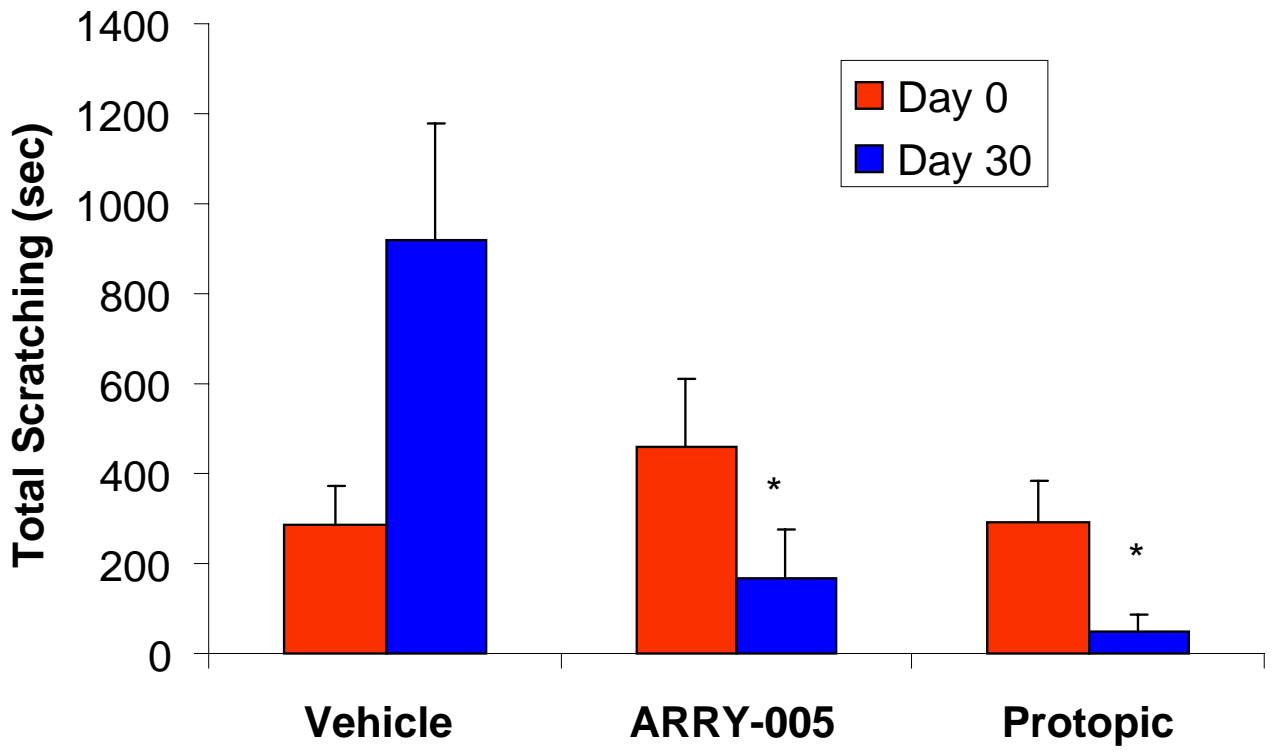
Oozing/crusts/hemorrhage



*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