

# Silencing RAGE Expression with an Epithelial-Targeted RNAi Trigger Conjugate Suppresses Pulmonary Allergic Inflammation

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**Arrowhead Pharmaceuticals**

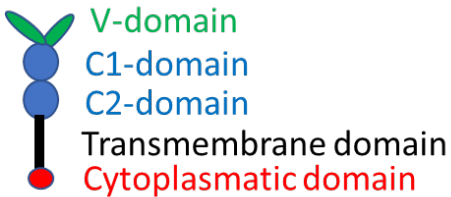


# Disclosure of Conflict of Interest

- The presenter and all co-authors are current or former employees of Arrowhead Pharmaceuticals, and have, had or may have ownership of shares or vested exercisable share options or ownership of restricted stocks
- Arrowhead Pharmaceuticals plans to initiate a Phase 1/2a clinical trial to evaluate ARO-RAGE. No commercial product(s) from Arrowhead Pharmaceuticals are currently marketed
- No current, past, or future relationships exist or are planned with tobacco, cannabis, or vape Industries by the presenter, co-authors, or Arrowhead Pharmaceuticals

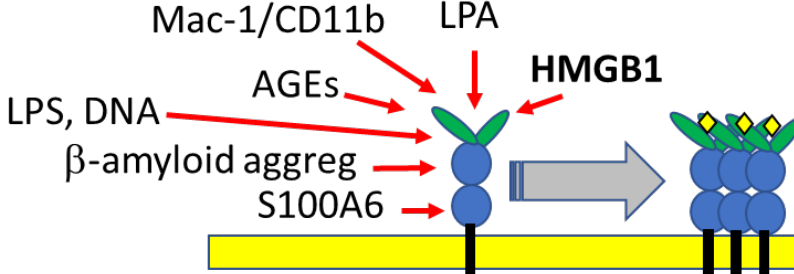
# RAGE: Receptor for Advanced Glycation End products

**Ab-like structure**



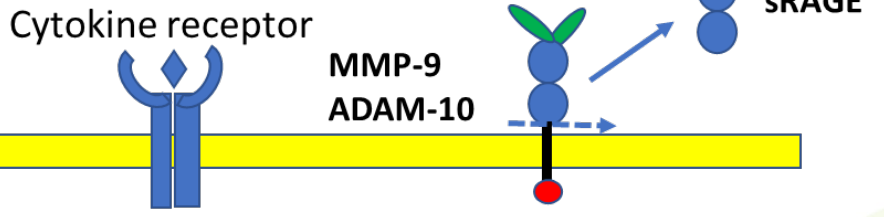
RAGE

**Multiple ligands**

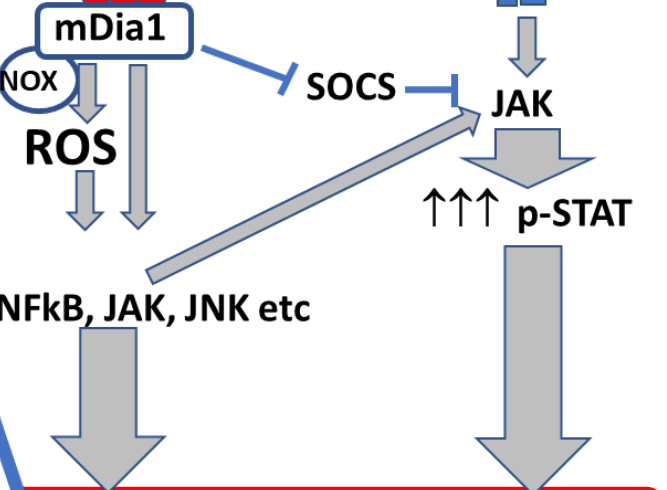


**Amplification Signaling**

**Circulating biomarker**



**Multiple Pathways**

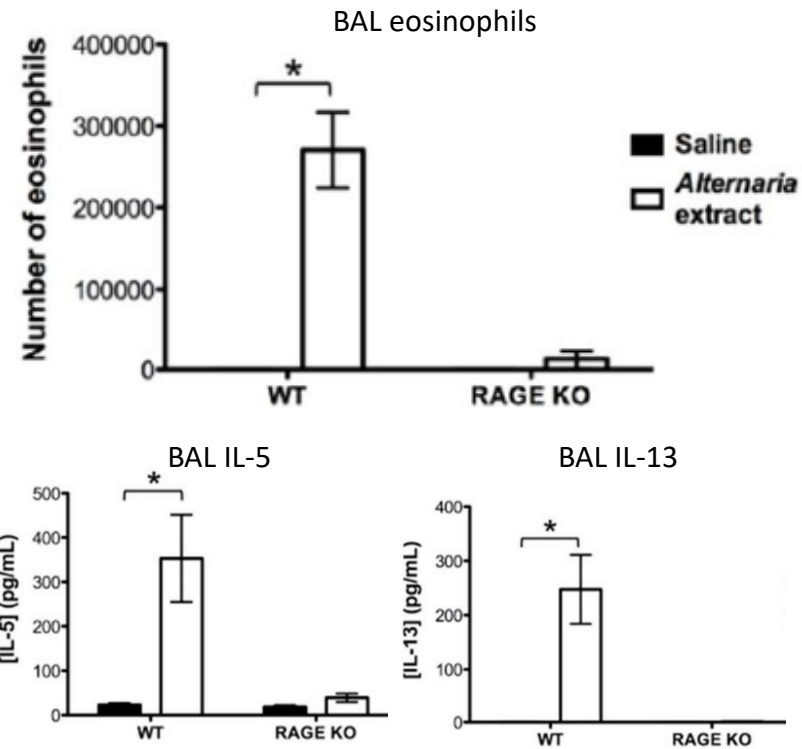


**Activation of Transcription**

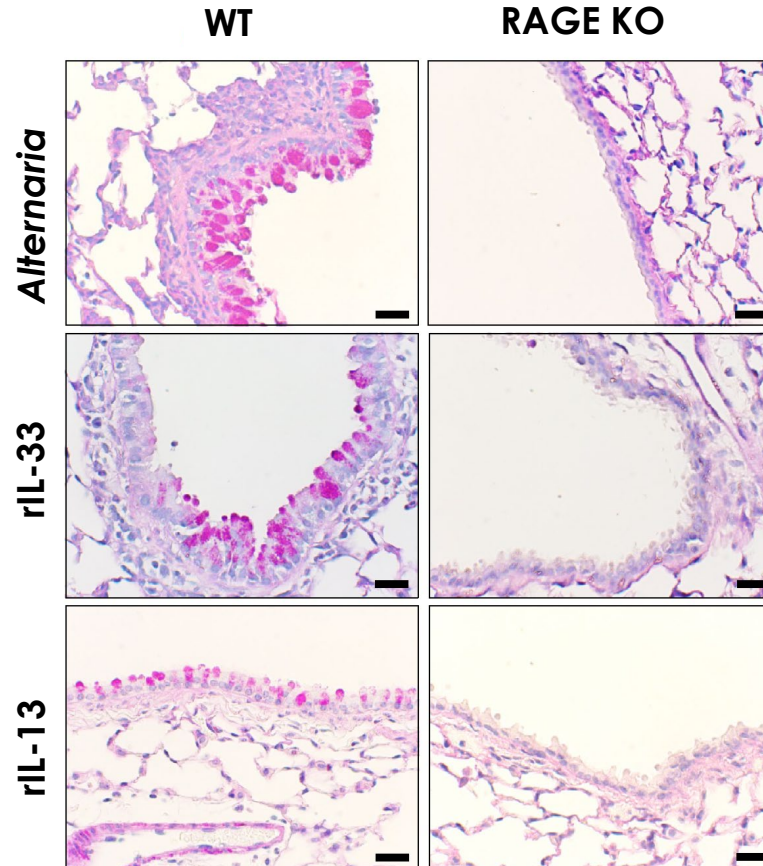
Mod. from Oczipok et al, Paediatr Respir Rev, 2017

# RAGE knockout mice are protected from allergic inflammation

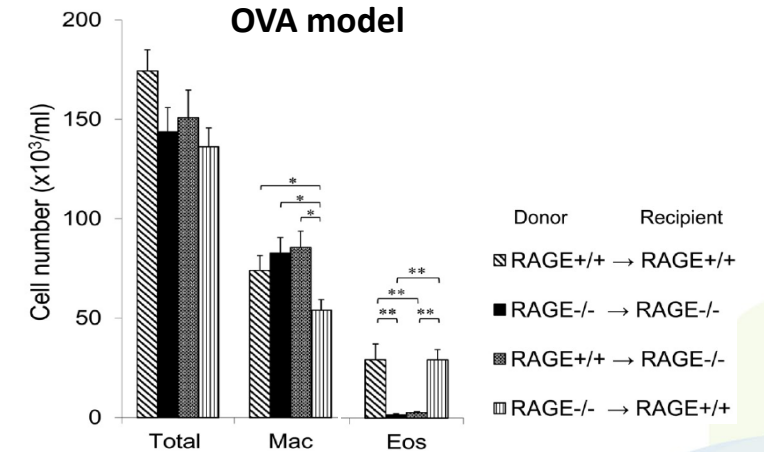
## Limited inflammatory cell infiltration and cytokine expression



## Reduced MUC5AC expression



## Pro-inflammatory RAGE is from lung structural cells



Does silencing pulmonary RAGE with inhaled siRNA phenocopy genetic deficiency?

Allergy 2020  
JACI, 2019  
JACI, 2015  
AJP Lung, 2015  
Clin Exp Allergy, 2012

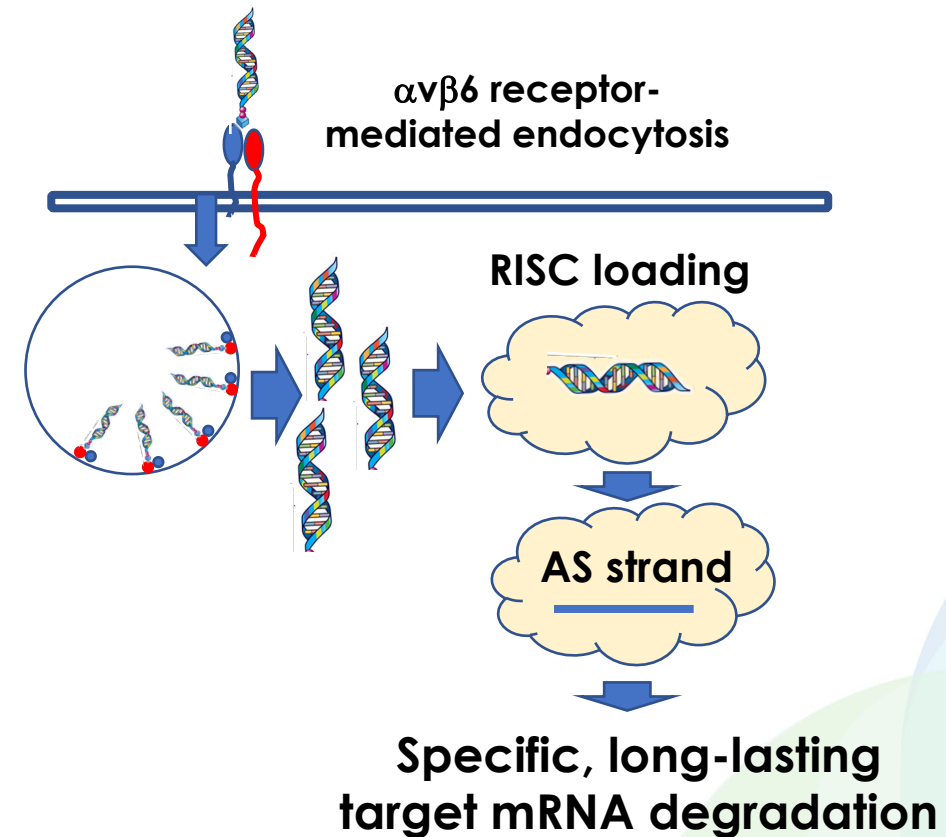
# Silencing RAGE expression with an epithelium-targeted inhaled RNAi trigger conjugate

## TRiM™ platform



- siRNA trigger sequence optimized to specifically silence RAGE expression while avoiding off-target genes
- Modifying chemistries maximize potency and stability
- Epithelial targeting moiety

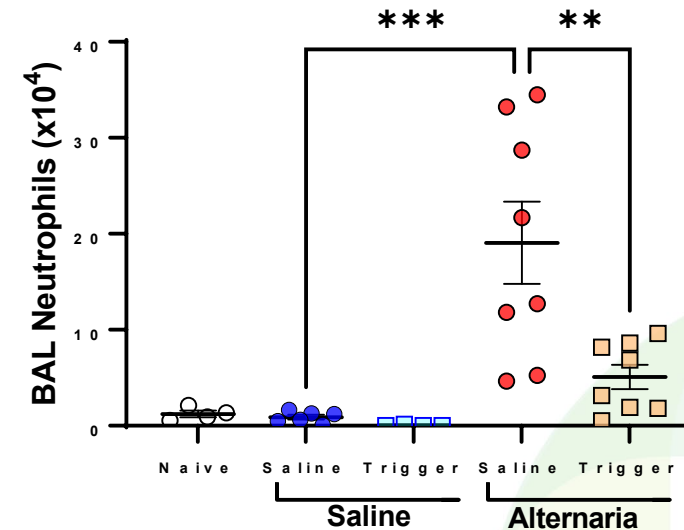
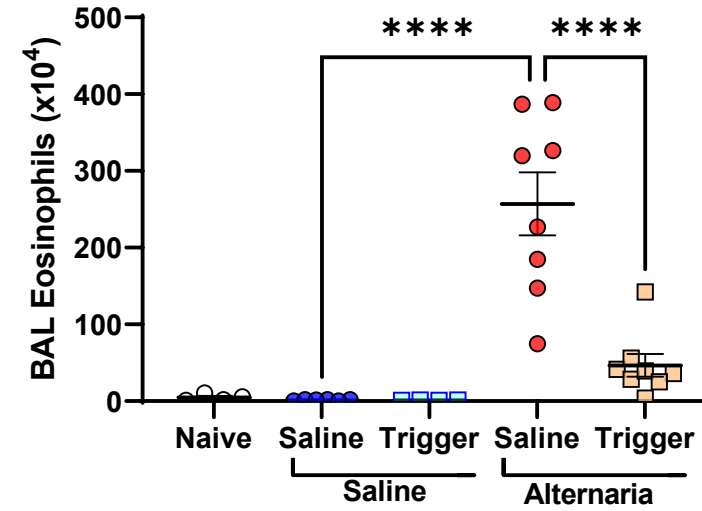
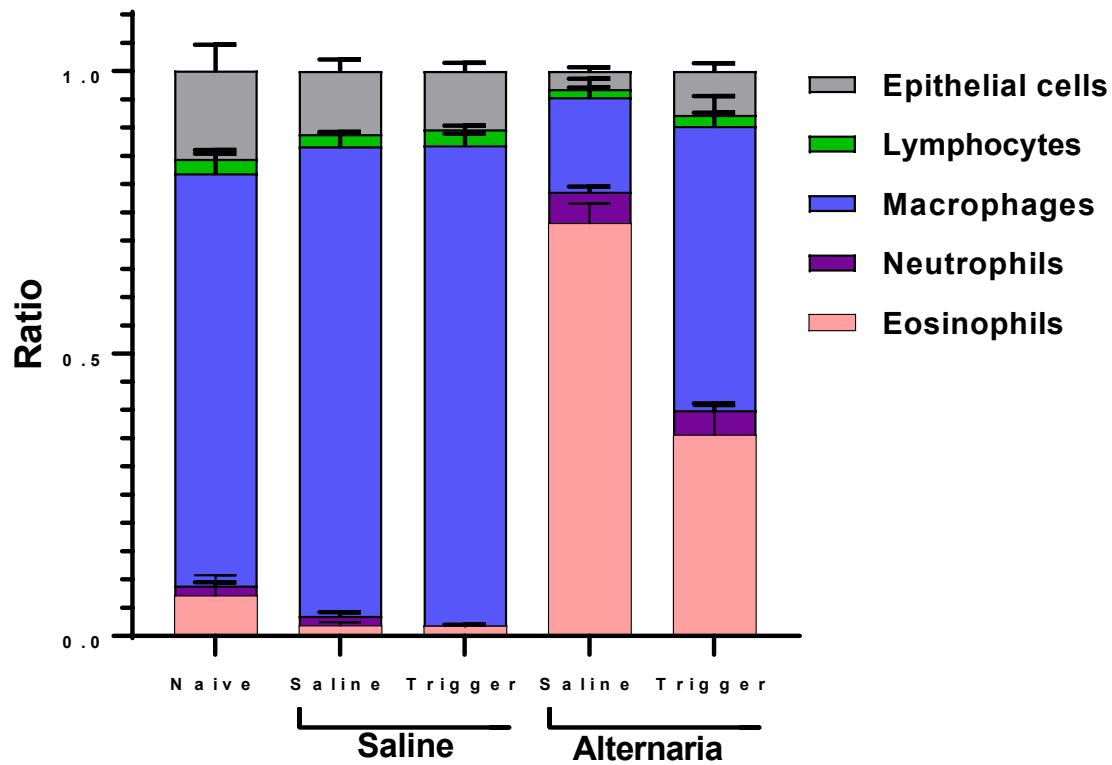
## Mechanism of action





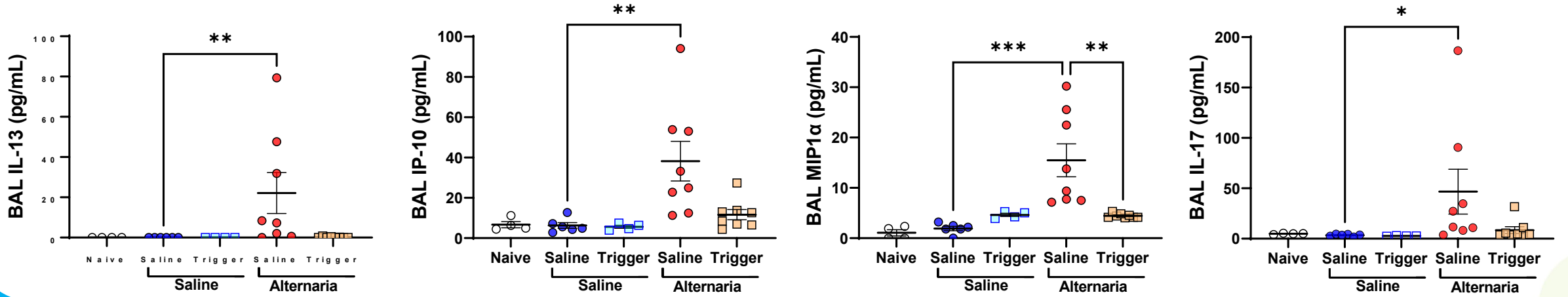
# RAGE silencing limits inflammatory cell recruitment

## BAL differential cell counts

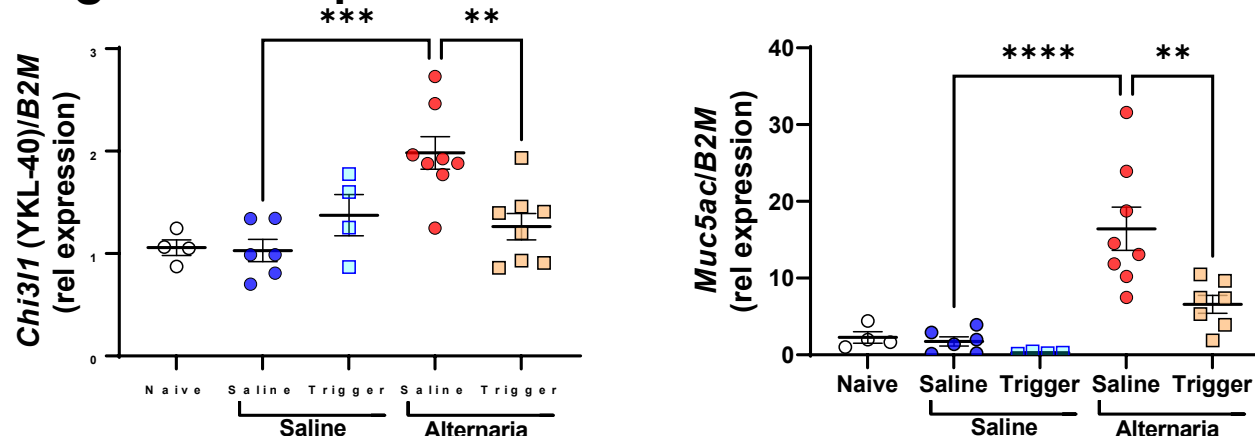


# RAGE silencing limits pro-inflammatory BAL cytokines and gene expression

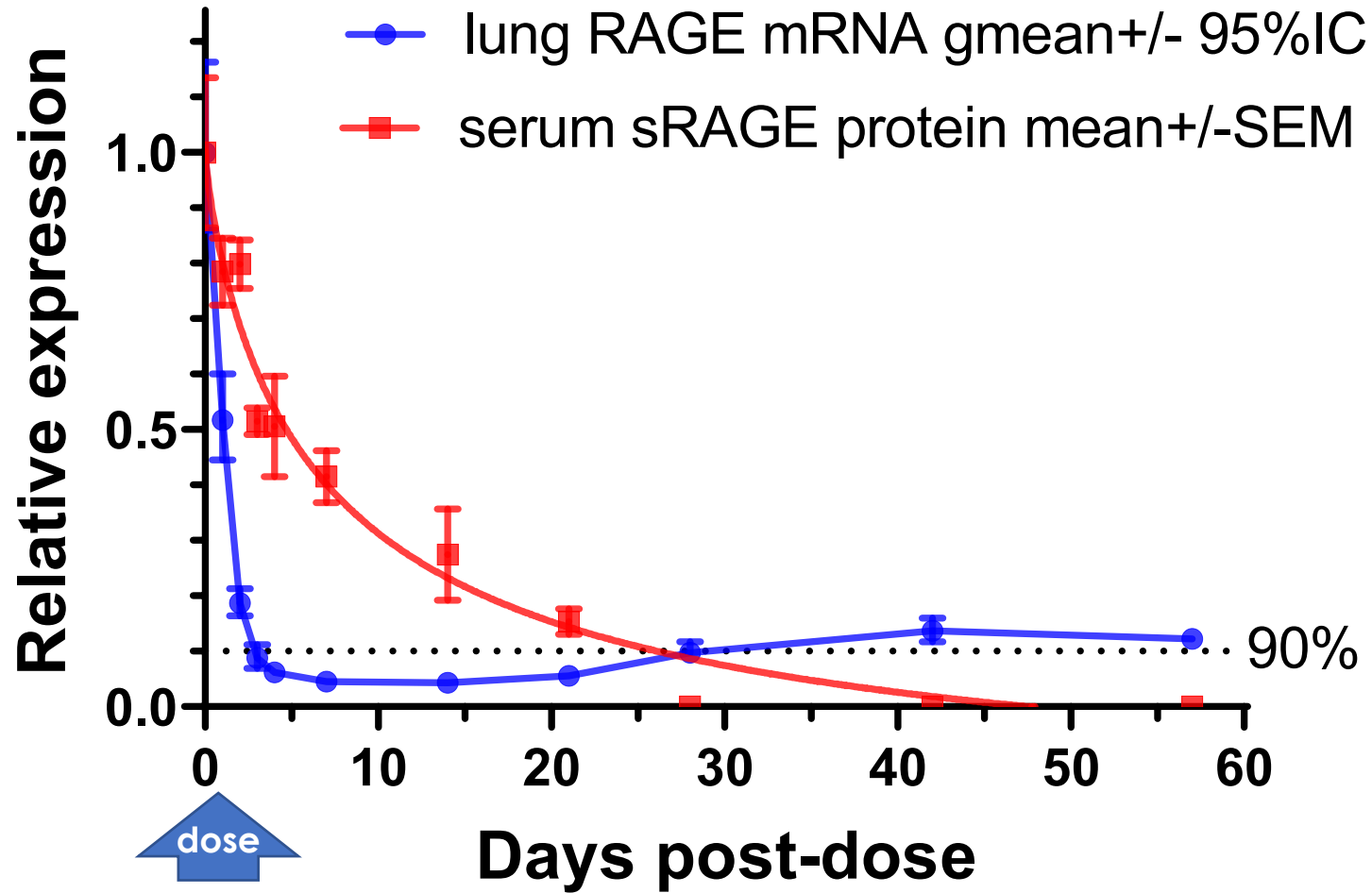
## BAL cytokine/chemokine



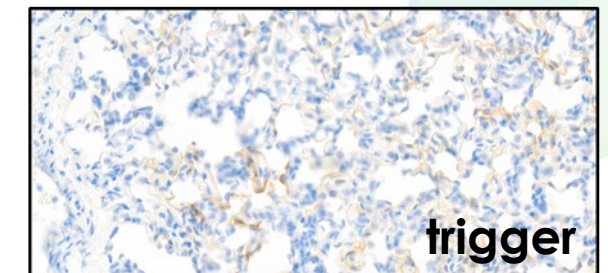
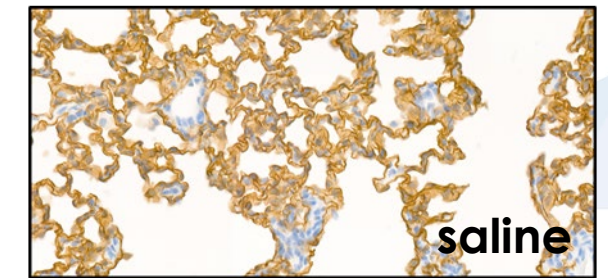
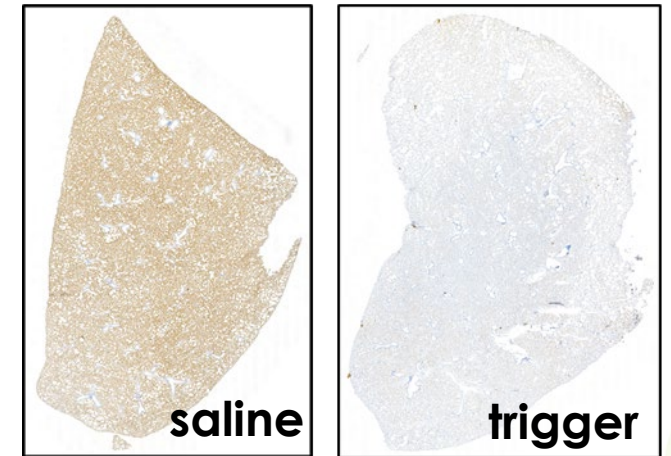
## Lung mRNA expression



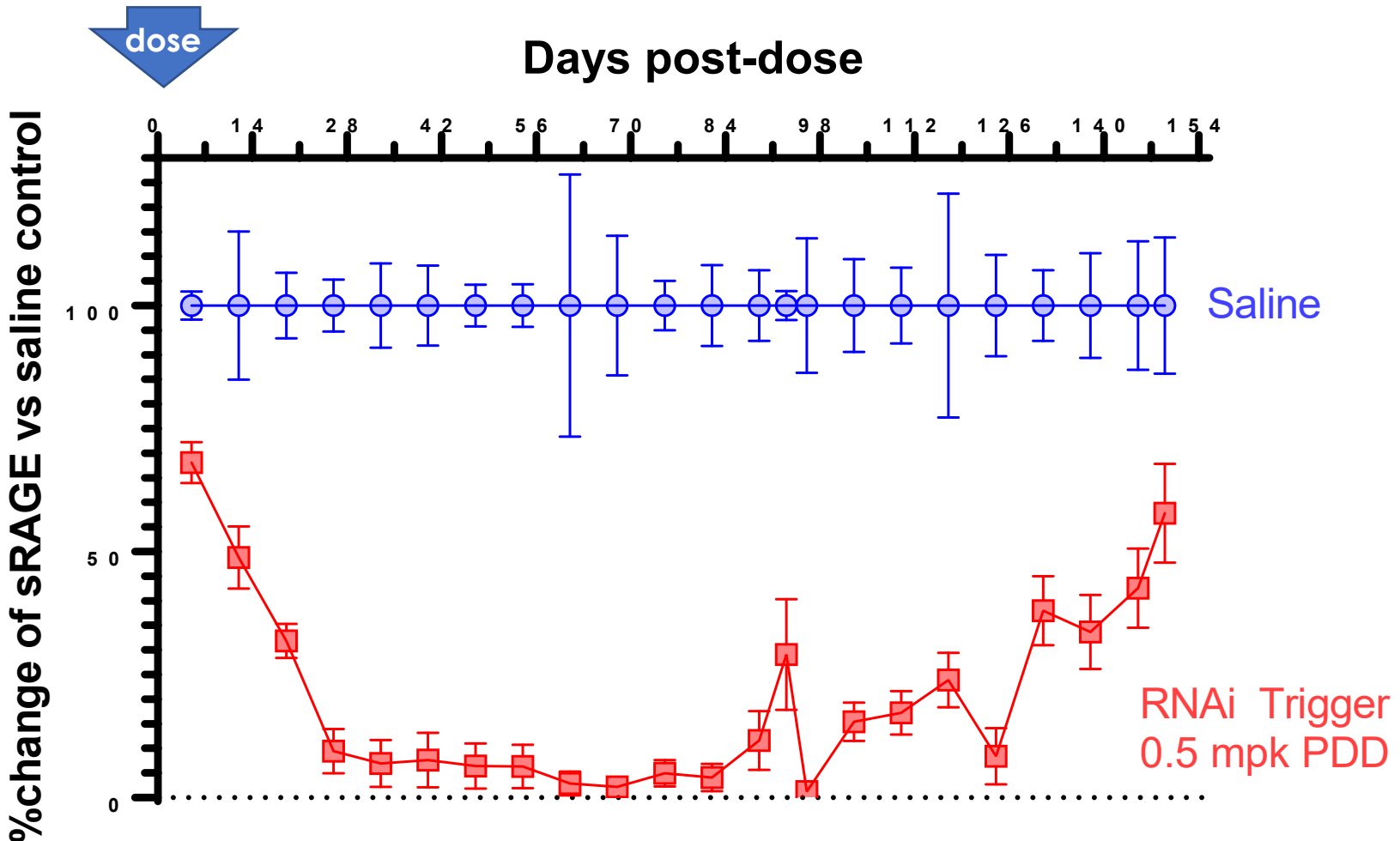
# Deep and sustained lung RAGE mRNA and protein silencing after single inhaled 0.5 mg/kg RNAi trigger conjugate in rats



## Day 36 RAGE protein IHC

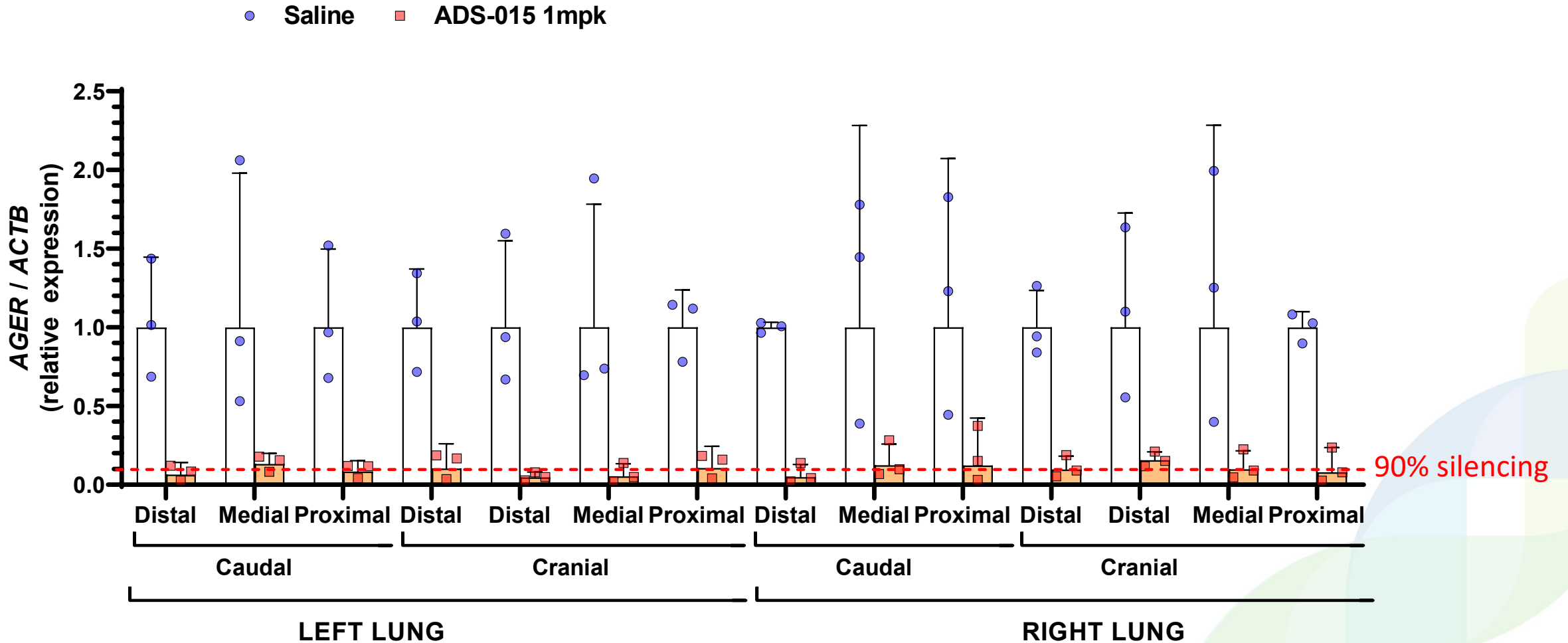


# sRAGE target engagement biomarker kinetics in rat support bimonthly or quarterly dosing



- Slow recovery of serum sRAGE 3-5 months post-dose of RNAi trigger conjugate
- Q70 day dosing interval maintains serum sRAGE near limit of detection
- A 6-month, Q70 day dosing regimen was well tolerated with no adverse histopathological findings

# A single inhaled dose of ARO-RAGE (ADS-015) silences >90% of pulmonary RAGE expression in cynomolgus monkeys



# Summary & Conclusion

- ✓ The TRiM™ RNAi trigger delivery platform offers an important therapeutic alternative for traditionally difficult-to-drug targets like RAGE
- ✓ Epithelium-targeted RNAi trigger conjugates effectively and durably silence pulmonary RAGE expression and significantly reduce allergic inflammation in rats
- ✓ Serum sRAGE can be easily monitored as a target engagement biomarker
- ✓ Inhaled ARO-RAGE effectively silences RAGE expression in cynomolgus monkeys
- ✓ Arrowhead plans to initiate a Phase 1 / 2a clinical trial to evaluate ARO-RAGE as a potential treatment for asthma and other inflammatory lung diseases

