An Oral Synthetic Biology Platform for Host-Directed Protection Against Respiratory Viral Infection

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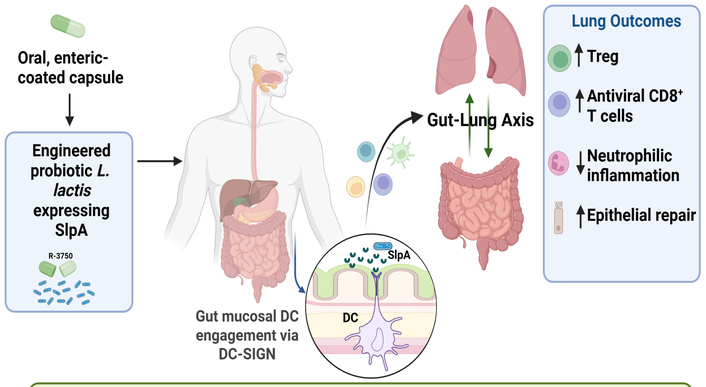
1. BACKGROUND / OBJECTIVES

- Respiratory viral infections remain a major threat to military readiness and global health
- Current countermeasures are often pathogen-specific and may depend on cold-chain distribution and clinical infrastructure
- Host-directed platforms that broadly enhance immune readiness across viral families represent a strategic need

- **<u>Objective:</u> Development of an oral, capsule-based immunoprotectant to prevent viral infection**

2. R-3750 PLATFORM

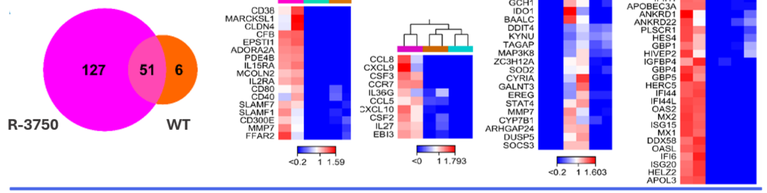


- ✓ GRAS-designated
- ✓ GI-localized
- ✓ Stable at room temperature
- ✓ Scalable manufacturing / low cost of good

3. METHODS

- Human dendritic cell stimulation and transcriptomic profiling
- Murine influenza challenge models
- Sequential heterologous influenza rechallenge model
- Immune phenotyping, cytokine analysis, lung histopathology, and lung transcriptomics
- Phase 1 clinical safety and immune biomarker assessment

4. HUMAN DC ANTIVIRAL REPROGRAMMING



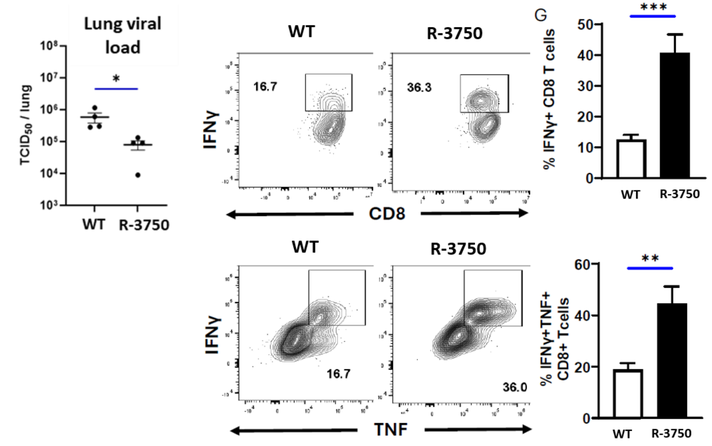
Pathway	Representative Genes
Antiviral ISGs	IFIT1, MX1, OAS2, RSAD2, DDX58, ISG15
Antigen Presentation / APC Activation	CD80, CD40, SLAMF7
Chemokine / IL-27 Axis	CXCL10, CXCL9, CCL5, IL27
Barrier / Epithelial Defense	AGER, CLDN4, EPSTI1, MCOLN2
Inflammation / Neutrophil Drivers	CSF3, IL36G
Stress / Metabolic Regulation	IDO1, SOCS3, DDIT4

R-3750 programs human DCs to induce antiviral and lung-protective pathways

5. ORAL R-3750 PROTECS AGAINST INFLUENZA-INDUCED LUNG INJURY

- ✓ Reduced influenza-associated weight loss
- ✓ Improved lung histology and lower histopath score
- ✓ Reduced neutrophil infiltration
- ✓ Increased regulatory T cells

6. ORAL R-3750 PRIME LUNG-RESIDENT T CELLS



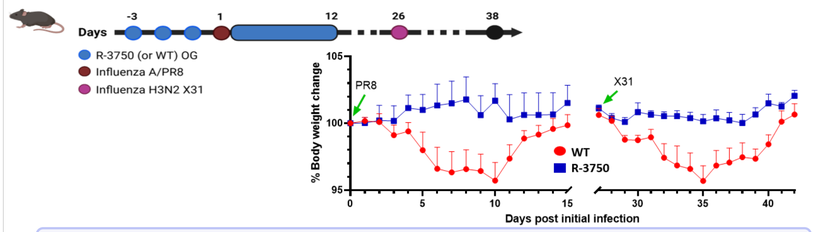
R-3750 enhances antiviral CD8+ T cell response in influenza A-infected mice

7. LUNG TRANSCRIPTOME REMODELLLING

Pathway / Biological Process	Suppressed by R-3750 (vs. WT)
Chemokines & inflammatory recruitment	↓ Chemokines, IL-1 family, IL-6, NLRP12
Stress / acute phase / danger signals	↓ Hpx, Hspa11, Ptk2, Gpsm1
Tissue destruction & matrix remodeling	↓ Mmp3, Mmp9, Mmp19, Adamts family
Fibrosis & aberrant repair	↓ Collagens, ECM genes, Lox, Fn1, Crtap
Immune modulators / transcriptional regulators	↓ Bach2, Bcl6b, Arpp21, Fzd1, Marcks

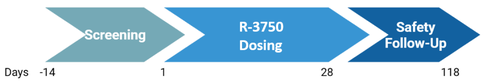
R-3750 shifts the influenza-driven lung transcriptome toward a less inflammatory, less destructive, and more lung-protective state.

8. CROSS STRAIN PROTECTION



Protection persists and supports cross-strain resilience without additional dosing

9. IMPECCABLE HUMAN SAFETY



Dose	n	Drug-related AEs	SAEs
9E9 CFU	3	0	0
3E10 CFU	3	0	0
9E10 CFU	15	0	0

Key Findings

- No SAEs reported and no clinical lab changes.
- No systemic R-3750 dissemination observed.
- Blood immune analyses showed increases in Tregs and activation of antiviral gene programs consistent with mucosal immune training.

MILITARY RELEVANCE

Oral capsule administration | Room-temperature stability | Scalable manufacturing | Rapid deployment potential for military and pandemic settings

Arming personnel to protect against viral infection

RISE THERAPEUTICS