# Lower doses of self-amplifying mRNA drive superior neoantigen-specific CD8⁺ T cell responses in cancer patients versus high doses

#4159

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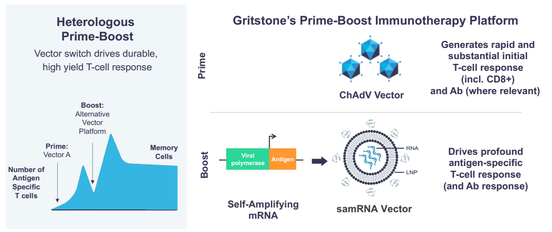
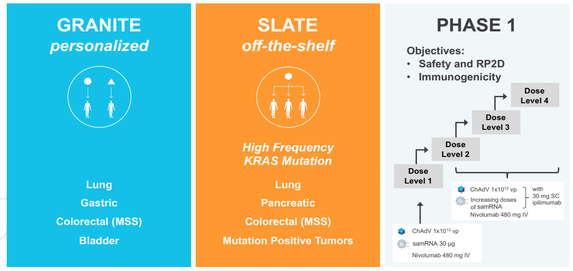
## Background

The immunogenicity and efficacy of RNA-based vaccine platforms has been shown through their application in prophylactic SARS-CoV-2 vaccines. In contrast to mRNA based vectors, self amplifying mRNA platforms may offer a dose-sparing opportunity with superior induction of T cell responses, and may also trigger distinct innate immune pathways, which may exert adjuvanting or inhibitory effects on vaccine-induced immunity.

Gritstone bio, Inc., has developed a heterologous prime/boost vaccination approach consisting of a Chimp Adenovirus (ChAd) prime and repeated self-amplifying mRNA (samRNA) boosts in order to drive strong CD8+ T cell responses to personalized neoantigens in cancer patients.



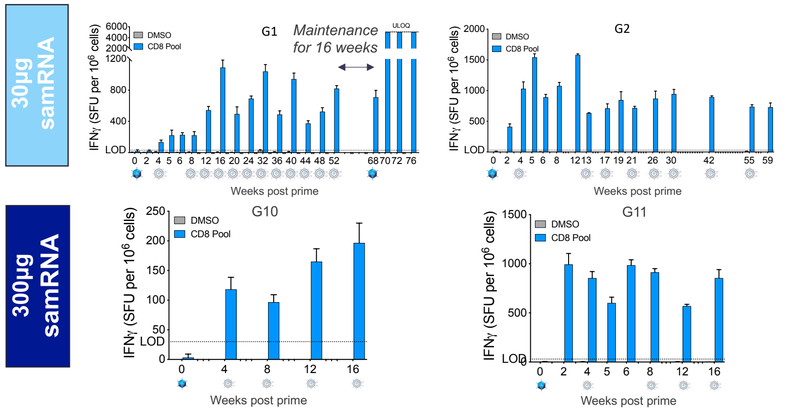

Optimal dosing for samRNA boosts was evaluated in two first-in-human phase 1/2 clinical trials assessing personalized neoantigen vaccines in patients with advanced stage metastatic cancer (NCT03639714, NCT03953235).




Dose dependent effects on activation of innate immune pathways as well as CD8 T cell response were investigated in patients, as well as non-human primates (NHP). The latter using various model antigens.

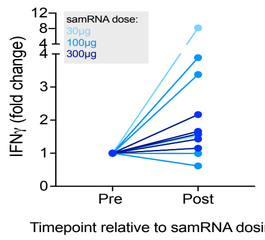
## ChAd/samRNA vaccine drives potent CD8⁺ T cell responses

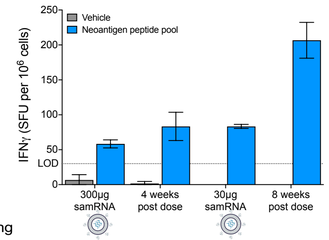
- *Increase in T cell response with a samRNA boost at a 30 µg dose*
  - *not observed at 300 µg dose*
- *Long intervals (> 2mo) between samRNA doses reveal highly durable responses*




- *T cell response increased with lower doses of samRNA*

*Ex-vivo IFNγ ELISpot following overnight stimulation with patient-specific peptide pool of predicted CD8 epitopes. PBMCs assessed at peak timepoint post samRNA administration in each patient*

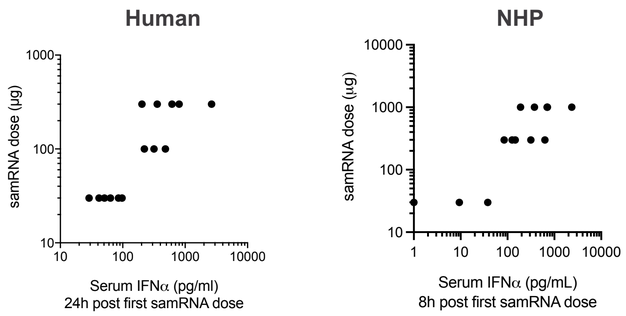



Patient received 300µg doses until protocol change to 30µg dose

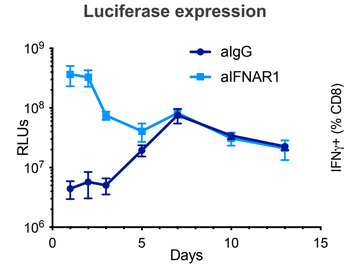
## Dose-dependent induction of IFNα following samRNA immunization in patients and non-human primates

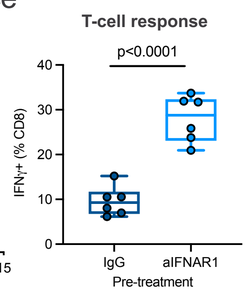
*Serum IFNa2a levels assessed by ELISA at specified timepoint post first SAM immunization in humans (ChAd prime followed by SAM boost at week 4) or rhesus macaques (SAM prime).*



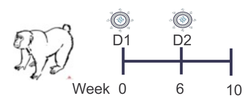

## Inhibition of type I IFN activation increases samRNA expression and immunogenicity in mice

*Mice treated with anti-interferon alpha/beta receptor (aIFNAR1) mAb (2mg, IP) 24 hours prior to samRNA (10 ug, IM) vaccination. (Left) C57BL/6 mice imaged at various timepoints following immunization with samRNA encoding luciferase reporter, mean+-SE, n=5. (Right) Balb/c mice. AH1-specific CD8+IFNg+ T cell response assessed by intracellular cytokine staining two weeks following immunization with samRNA encoding model antigen cassette. Median, IQR, range.*

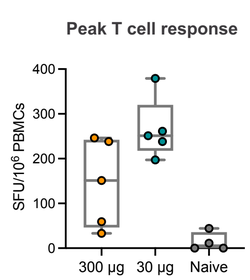


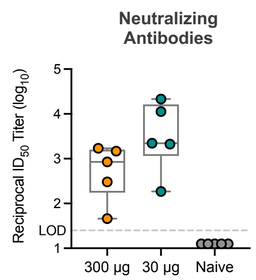




## Higher T cell and antibody response to SARS-CoV-2 Spike antigen with 10-fold lower samRNA dose in NHP

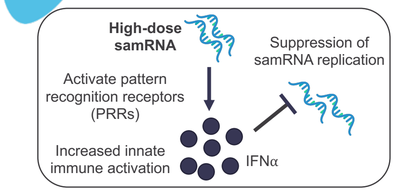


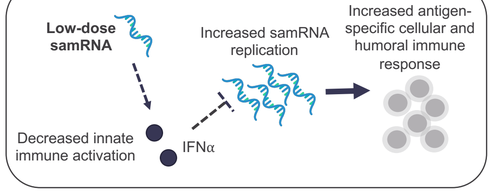

*Rhesus macaques immunized twice with SAM encoding SARS-CoV-2 Spike antigen at specified dose.*
*PBMCs assessed by ex-vivo IFNγ ELISpot following overnight stimulation with Spike-specific overlapping peptide pool. Neutralizing antibodies measured in serum at study week 8 by pseudovirus neutralization assay.*




## Conclusions




- 30 µg samRNA boost increases T cell responses following ChAd prime in humans, while higher doses of samRNA lead to maintenance of response but no clear boost.
- Dose dependent induction of IFNα in both cancer patients and NHP suggest inhibitory impact of early innate immune activation on samRNA amplification or expression, which may result in blunted T cell response with higher doses of samRNA. Suppression of IFNα induction leads to increased samRNA expression and T cell response in mice.
- samRNA dose response was evaluated in NHP and higher cellular and humoral immune response was observed with a 10-fold lower samRNA dose.
- These data resulted in reduction of the samRNA dose to 30µg (from 300µg) and adjustment of samRNA dosing intervals to 8 weeks in the Phase 2 portion of these clinical studies.

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