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

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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, 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).

ChAd/samRNA vaccine drives potent CD8+ T cell responses

- Increase in T cell response with a samRNA boost at a 30 µg dose
- Long intervals (>2mo) between samRNA doses reveal highly durable responses
- T cell response increased with lower doses of samRNA

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

Mice treated with anti-interferon alpha/beta receptor (aIFNAR1) mAb at 24 h lead to increased CD8+ T cell response 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

Neutalizing Antibodies

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 reduced in number of patients to 30µg (from 300µg) and adjustment of samRNA dosing intervals to 8 weeks in the Phase 2 portion of these clinical studies.