Long-term Immunogenicity and effectiveness of CD40 targeting vaccination in COVID-19

D-02

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BACKGROUND

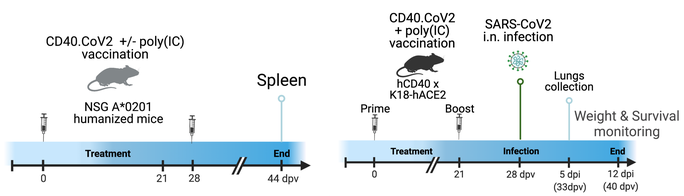
Following natural infection or vaccination, the generation of stem cell-like memory T (Tscm) cells is essential for long-term protective immunity to the virus. Tscm cells have the capacity for self-renewal and multipotency. In SARS-CoV2 infection, the emergence of CD8⁺ Tscm cells is correlated with the number of symptom-free days.

The development of a COVID-19 vaccine able to generate CD8⁺ Tscm cells is of the utmost importance 1) since the emergence of SARS-CoV2 variants of concerns requires maintaining strong and long-lasting immune responses, 2) as an efficient alternative in immunocompromised people who have difficulties raising humoral immune responses.

METHODS

We have developed a new Dendritic Cell-based vaccine composed of a humanized αCD40 monoclonal antibody fused to the RBD protein in its C-terminal Fc-domains and three T cell epitopes spanning sequences from S (S1 and S4 peptides) and N (N peptide) proteins in its light chains (CD40.CoV2). Previous studies have shown that this DC-targeting platform elicited durable and robust T- and B-cell responses and is currently in phase I clinical development in HIV.

We tested the capacity of two injections of the vaccine (10μg, i.p) given with or without poly(IC) (50μg, i.p) at 4 weeks apart to i) elicit human (hu) B-, and huT-cell responses in NSG HIS mice reconstituted with a Human Immune System (HIS mice), ii) protect against SARS-CoV2 infection in the hCD40/K18-hACE2 double transgenic mice.



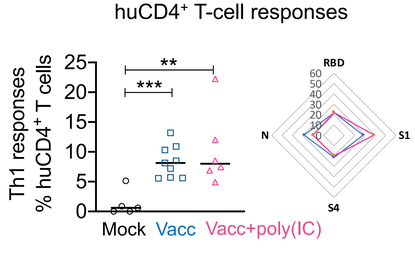
Experimental design for immunogenicity studies

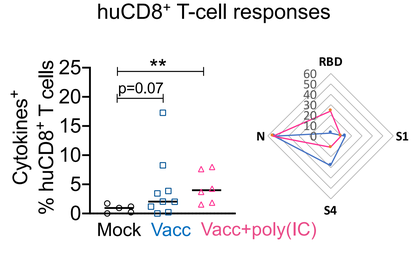
Experimental design for efficacy studies

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RESULTS: Immunogenicity of αCD40.CoV2 vaccine

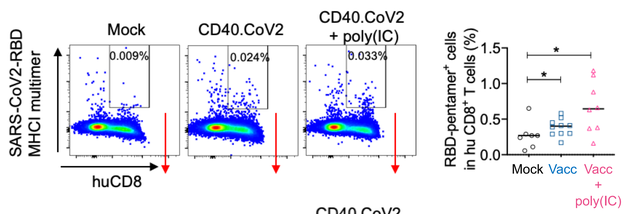
- **Both non-adjuvanted and adjuvanted vaccine induced significant amounts of SARS-CoV2-specific Th1 huCD4⁺ in all vaccinees and cytokines-secreting huCD8⁺ T cells in 67% and 100% of vaccinees.**
- Non-adjuvanted CD40.CoV2 vaccine predominantly induced S1-, S4- and N-specific IFNγ⁺ and/or TNF⁺ CD8⁺ T cells while the adjuvanted formulation mainly raised RBD-, S1- and N-specific cytokines⁺ CD8⁺ T cells



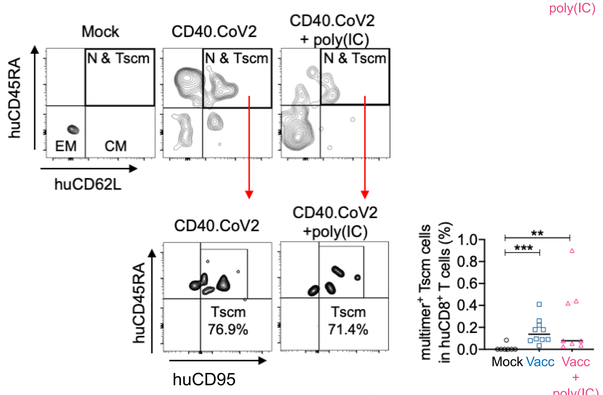


Secretion of IFNγ, TNF and IL-2 by T cells after a 9-day re-stimulation step of spleen cells with overlapping peptide pools spanning the full-length sequence of vaccine antigens. Graphs: sum of the frequency of cytokine-secreting RBD-, S1-, S4- and N-specific CD4⁺ or CD8⁺ T cells. Radar charts: proportion of cytokine-secreting specific CD4⁺ or CD8⁺ T cells for each antigen included in the vaccine.

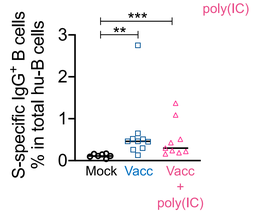
- We confirmed the presence of RBD-specific huCD8⁺ T cells in the spleens of vaccinated animals using RBD-HLA-A*0201 multimer staining



- **A significant proportion of RBD-HLA-A*0201 multimer⁺ huCD8⁺ T cells were Tscm (CD45RA⁺ CD62L⁺ CD95⁺) cells in both vaccinated groups**



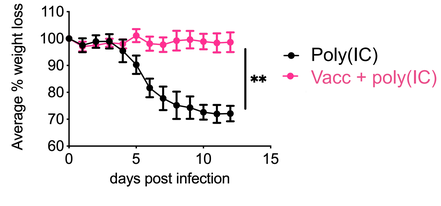
- Significant amounts of spike-IgG⁺ switched huB cells were detected in vaccinated animals using Spike-trimer-PE and flow cytometry



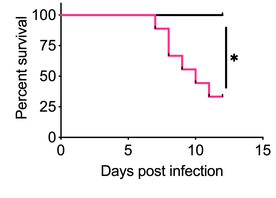
RESULTS: Efficacy of αCD40.CoV2 vaccine

- In contrast to vaccinated animals, controls exhibited a significant weight loss since day 5 post-infection lasting until day 12 post-infection (n=9 animals/group)
- **The CD40.CoV2 vaccine significantly protected animals with a survival rate of 100% (n=6 animals/group)**

Vaccine efficacy evaluated in hCD40/K18-hACE2 double Tg mice

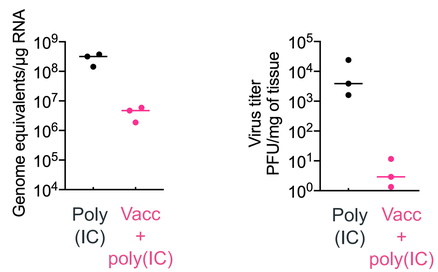


(n=9/group)



*(n=6/group, *p<0.05 Log-rank test)*

- SARS-CoV-2 viral load (genome equivalent/μg RNA) and viral replication (PFU/mg of tissue) measured at day 5 post-infection in the lungs of randomly selected animals were lower or undetectable in vaccinees compared to controls



CONCLUSIONS

We demonstrate that the targeting of SARS-CoV-2 epitopes to CD40 induces significant B and T cells with a long-term memory phenotype in NSG HIS mice and the ability of the vaccine to ensure complete protection against SARS-CoV2 infection

ADDITIONAL KEY INFORMATION

Fundings: Covid-19- ANR-20-COV6-0004 ; ANR Flash Covid-COVI-0066.

Information: The strain BetaCoV/France/IDF0372/2020 was supplied through the European Virus Archive goes Global (Evag) platform.

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