

Mathematical modeling of immune response following mRNA- or protein-based vaccine for SARS-CoV-2



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Introduction

Vaccination is the most effective and economical intervention for controlling the spread of epidemics, and various techniques have been employed in the development of SARS-CoV-2 vaccines [1]. S-268019-b is a recombinant protein vaccine comprising a modified recombinant spike protein of SARS-CoV-2 with a squalene-base adjuvant [2]. Although some studies have investigated using mathematical modeling approaches about dynamics of antibodies following mRNA vaccination against SARS-CoV-2 [3, 4], there have been no reports addressing the dynamics of antibodies following vaccination with protein vaccines and dynamics of T cell responses. Those models are expected to contribute to a better understanding of the immunological mechanisms involved in vaccine-induced protection and inform future vaccination strategies.

Objectives

To characterize immune responses following protein- or mRNA-based vaccines of SARS-CoV-2 based on mathematical models for neutralizing antibody titers and T cell responses.

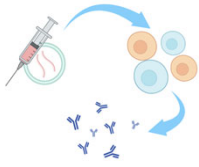
Modeling for Neutralizing Antibody Titers

Clinical Trial Data

- Neutralizing antibody titers in phase 2/3 study of S-268019-b [5] were used for our study.
- The participants who received a single booster vaccination of protein-based vaccine (S-268019-b, N=102) or mRNA-based vaccine (Tozinameran, N=104).

Model and Parameter Estimation

- The model consists of three compartments representing the amount of vaccinated protein or mRNA, the number of antibody-secreting cells, and the neutralizing antibody titer at time t .
- Two key parameters (the maximum rate constant for neutralizing antibody increase $[\gamma]$ and decrease rate constant for the number of antibody-secreting cells $[\delta]$) were estimated.
- Using the non-linear mixed effects model (MONOLIX2023R1)



$$\text{mRNA/Protein } \dot{M}(t) = -dM(t)$$

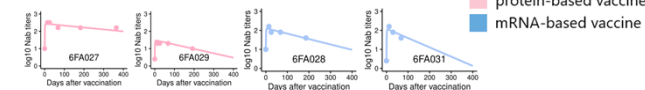
$$\text{B Cells } \dot{B}(t) = rM(t) - \delta B(t)$$

$$\text{Antibody } \dot{A}(t) = pB(t) - cA(t)$$

Quasi-steady state assumption

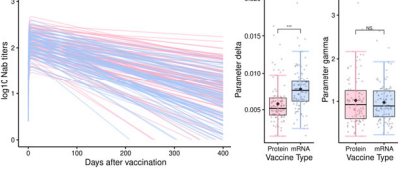
$$\delta \ll c \Rightarrow \begin{cases} \dot{M}(t) = -dM(t) \\ \dot{A}(t) = \gamma M(t) - \delta A(t) \end{cases}$$

- Reconstructed and observed values for each participant (randomly selected results for some participants)

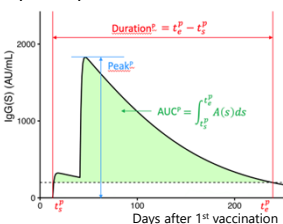


- Our model could well capture the dynamics of neutralizing antibody titer.

- Using the estimated parameter, we reconstructed neutralizing antibody dynamics for each participant.



- Three features of the reconstructed antibody dynamics for each participant were calculated.



	Protein-based vaccine	mRNA-based vaccine
Maximum antibody titer	149 (78.7)	143 (66.8)
Duration* (day)	530 (244)	391 (195)
AUC	32300 (27750)	21350 (14520)

Mean (SD)
*Time to maintain neutralizing antibody titer above of 10

- The mean parameter estimate for duration using the neutralizing antibody titer model was more than 100 days longer for the protein-based vaccine compared to the mRNA-based vaccine.

This result is consistent with previous reports showing that protein-based vaccines more sustained immune responses compared to mRNA-based vaccines [6].

Modeling for T Cell Responses

Clinical Trial Data

- IFN- γ -producing cell count by ELISPOT assay in phase 1/2 [2], 2/3 [5], and 3[7] [8] studies of S-268019-b.
- The participants who received a primary vaccination of protein-based vaccine (N=178) or other vaccines (N=22), and a single booster vaccination of protein-based vaccine (N=30) or mRNA-based vaccine (N=29).

Model and Parameter Estimation

- This model assumes that the response ($\delta(t)$), proliferation or differentiation or disappearance (β_{ET}) of two types of T cells, effector T cells (ET) and memory T cells (MT), to vaccine stimulation changes before and after the time elapsed after vaccination (τ), and RESP, kin, and kout explain $\delta(t)$:

$$\delta(t) = \frac{RESP \cdot kin}{kin - kout} (e^{-kout \cdot t} - e^{-kin \cdot t})$$

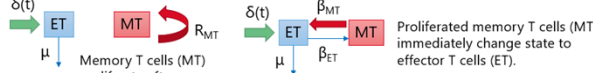
The five parameters (RESP, kin, kout, β_{ET} , τ) were estimated

- Using the non-linear mixed effects model (NONMEM)

(1) primary: vaccination $\sim \tau$ days (2) primary: τ days $\sim$ next vaccination



(3) booster: vaccination $\sim \tau$ days (4) booster: τ days $\sim$ next vaccination



Memory T cells (MT) proliferate after booster vaccinations.

※ (3) and (4) are repeated with each subsequent vaccination.

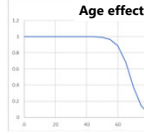
Parameters	Units	Values
$RUVprop$	-	0.417
$RUVadd$	-	9.87
RESP	cells	91.9
kin	day ⁻¹	0.102
kout	day ⁻¹	0.567
β_{ET}	day ⁻¹	0.0546
μ	day ⁻¹	0.2 (fixed)
R_{MT}	day ⁻¹	0.4 (fixed)
β_{MT}	day ⁻¹	10 (fixed)
τ	day	1.45
AGE50	years	68
AGESLP	years ⁻¹	-0.257
INFFLG on RESP	-	2.38

INFFLG on RESP

- RESP (cells): Extent of ET cell response
- kin (day⁻¹): Rate of increase for ET cell response
- kout (day⁻¹): Rate of decrease for ET cell response
- β_{ET} (day⁻¹): ET cell transition rate to MT type
- μ (day⁻¹): ET cell terminal mortality rate (fixed)
- R_{MT} (day⁻¹): Replication of CMT cells in response to revaccination (fixed)
- β_{MT} (day⁻¹): CMT cell transition to ET cell type after replication in response to revaccination (fixed)
- τ (day): Time that CMT cells respond in response to revaccination

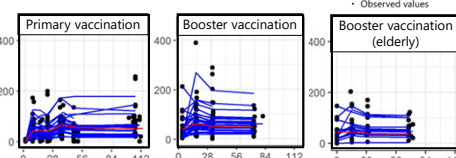
- Using the post-hoc values from the phase 2/3 study, three feature values were calculated using the least squares method (WinNonlin)
- The mean parameter estimate for the maximum number of activated T cells was approximately 1.75 times higher for the protein-based vaccine compared to the mRNA-based vaccine.

$$\text{Age effect} = \frac{1}{1 + \exp[\text{AGESLP} \cdot (\text{AGE} - \text{AGE50})]}$$



The magnitude of the immune response, which declines with age, could be quantitatively evaluated.

- Predicted and observed values for each participant (randomly selected results for some studies)



- Our model could well capture the dynamics of T cell response

	Protein-based vaccine	mRNA-based vaccine
Maximum number of activated T cells (/10 ⁵ cells)	173 (238)	99 (73)
half-life time (day)	8317 (7785)	6654 (5607)
AUC (~day70)	7001 (5929)	4890 (2901)

Mean (SD)

Conclusion

We constructed new models to characterize immune responses following mRNA- or protein-based vaccines of SARS-CoV-2. Those models facilitate more precise interpretation of individual immune response.

In the future, we plan to integrate these models (neutralizing antibody titers and T cell responses) to build a model that can predict the long-term persistence of neutralizing antibody titers from T cell responses.

Reference

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