

Integrated *In Vitro/In Silico* Systems Immunology Model to Quantify Drug-Induced Changes in the Immune Response after Influenza A Virus Infection

A Blueprint for the Preclinical Assessment and Clinical Translation of Infection Risks for Biologics

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Background

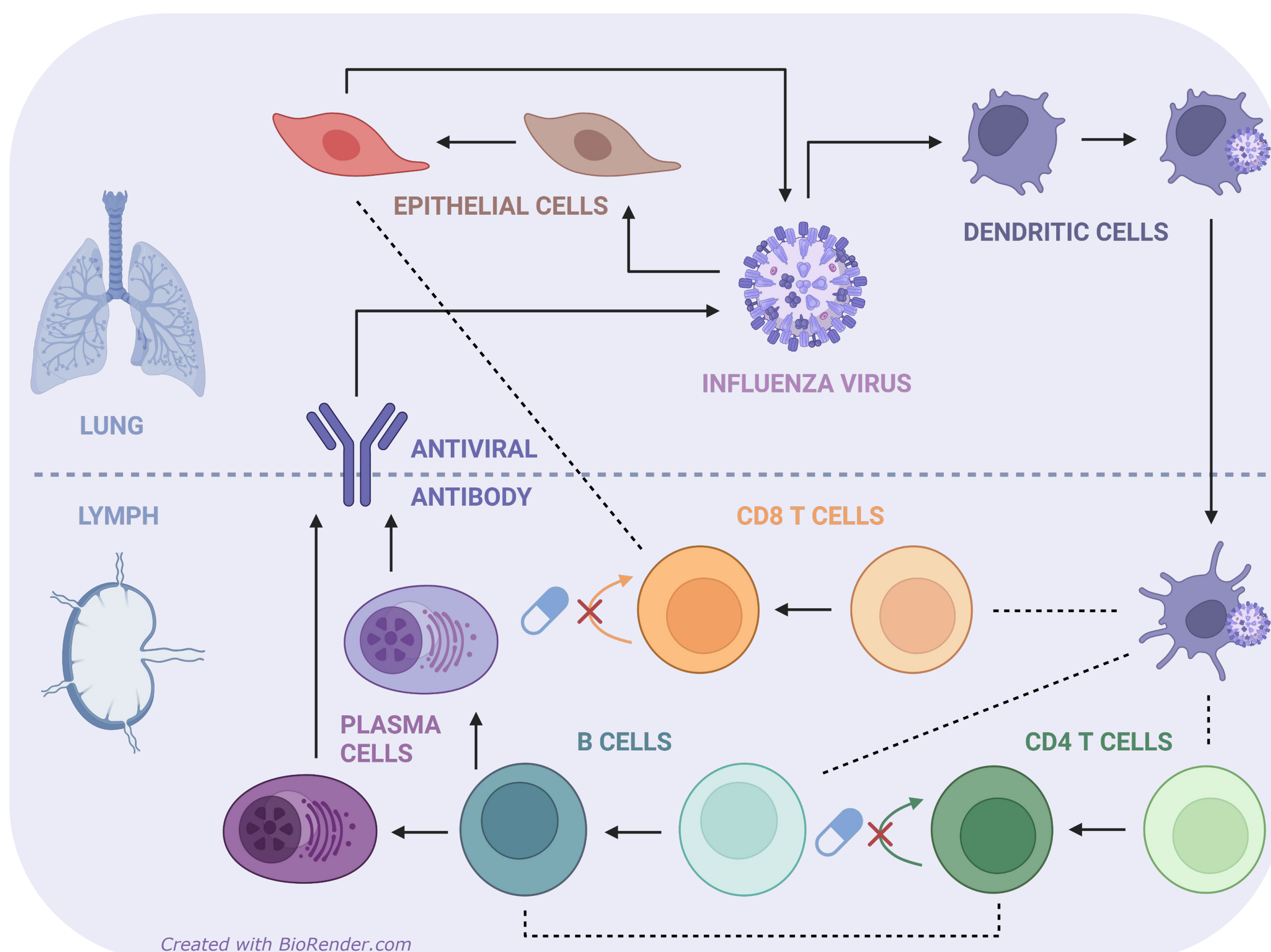
- Biological modalities, such as antibody- or Nanobody®-based biologics, have revolutionized the treatment of many neoplastic and inflammatory diseases. The immunosuppressive modulation of targeted immune system components might also give rise to compromised infection response to pathogens in patients.
- Balancing effectiveness against increased rates of infections by various pathogens are thus a key safety consideration for biological modalities.
- A quantitative mechanistic model of human infection response is crucial to assess and predict potential risks of therapeutic biologics.

In Silico Assessment of the Immune Response to Infections

- The immune response to infections is a complex biological process involving multiple cell types, pathways and anatomical compartments, and it is difficult to interpret solely at the level of *in vitro* assays.
- Mathematical models and computer simulations have been widely used to study the dynamics of the immune responses to infections, including the Influenza A Virus (IAV) and reactivation of Tuberculosis (TB). These models integrate mechanistic knowledge and quantitative understanding of biological processes across multiple biological levels using mathematical equations.
- Linking such systems immunology models with drug-related, experimentally accessible parameters permits exposure-related predictions and simulations of the modulated immune response to infections.

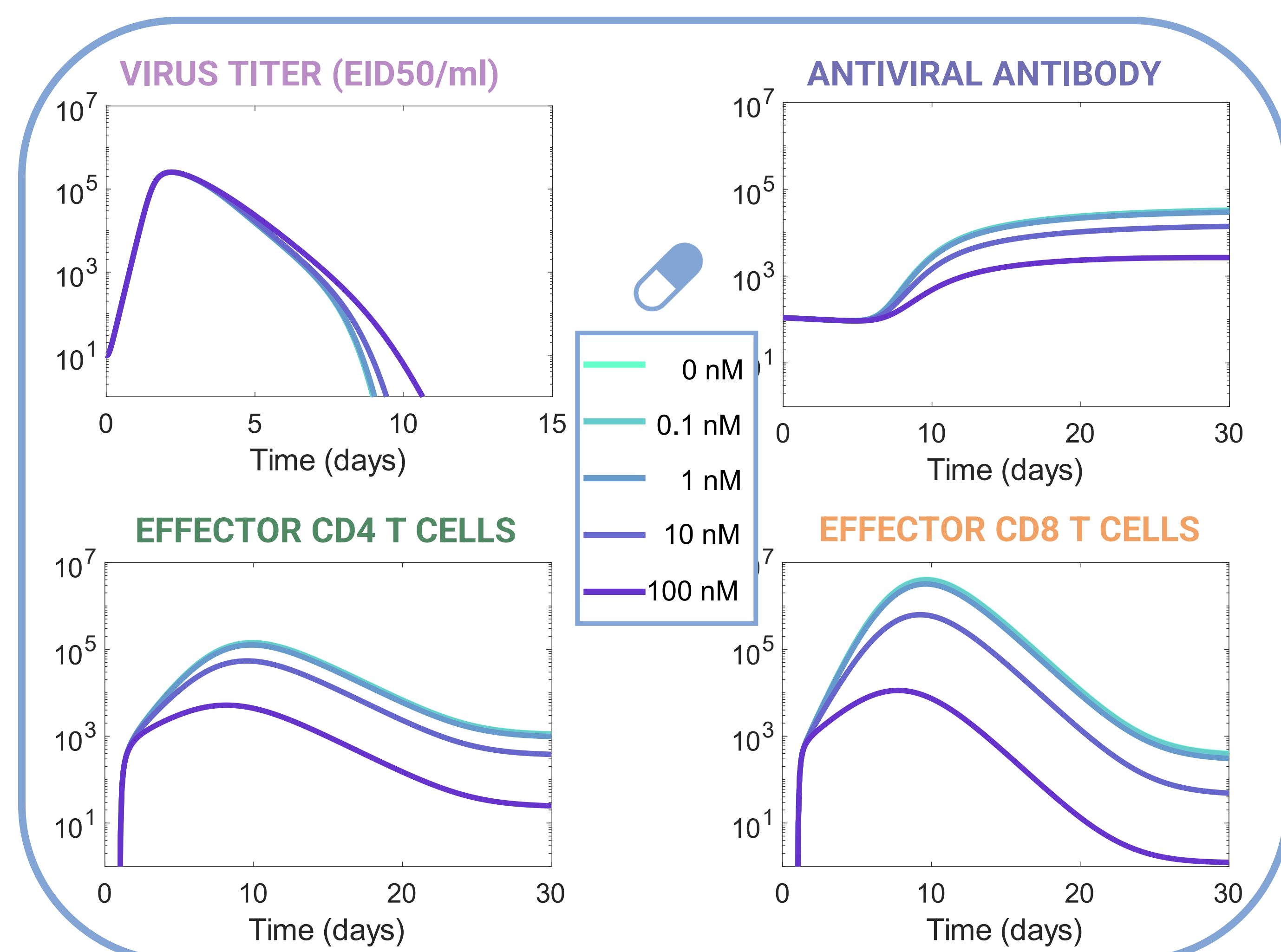
Immune Response to Influenza A Virus Infection – A Comparative Study to Derisk a Preclinical Molecule

Systems Immunology Model

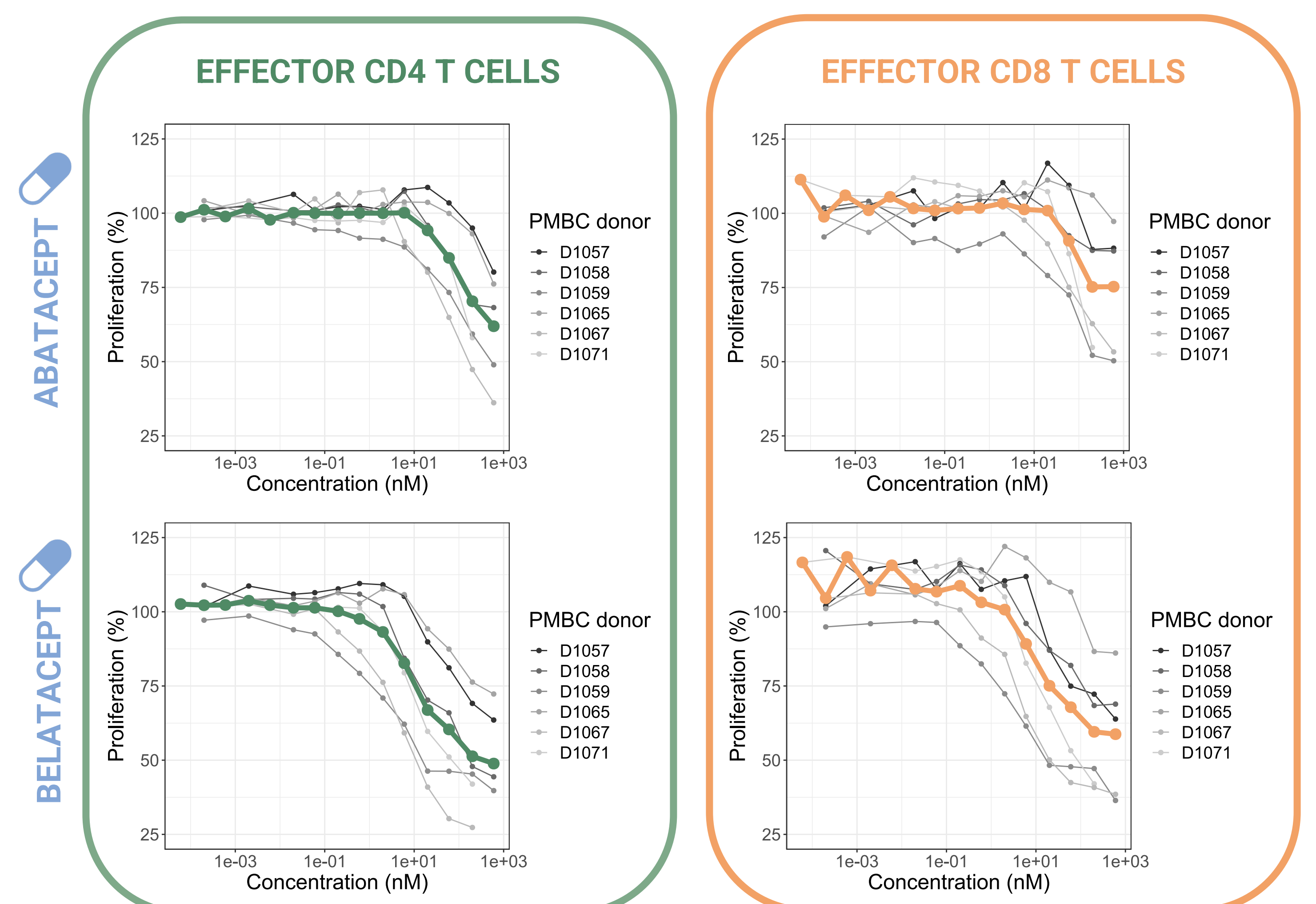


Visualization of the mathematical model for the immune response of IAV in mice (Lee et al. J Virol 2009).

Predicted Immune Response after Primary IAV Infection during Treatment with the Proprietary Preclinical Molecule



In Vitro Data on Proliferation Inhibition



Data from mixed lymphocyte reaction assays performed at Sanofi (preclinical molecule not shown)

Comparative Study of the Predicted Immune Responses after Primary IAV Infection

	Days to viral clearance			Antibodies after 30 days		
	ABATACEPT	Preclinical Molecule	BELATACEPT	ABATACEPT	Preclinical Molecule	BELATACEPT
0 nM	Δ (%)	Δ (%)	Δ (%)	Δ (%)	Δ (%)	Δ (%)
0.1 nM	+0	+0	+<1	>-1	-1	-3
1 nM	+<1	+<1	+2	-4	-11	-24
10 nM	+2	+5	+9	-31	-58	-79
100 nM	+11	+19	+18	-82	-92	-93

- Immune responses to IAV infection are concentration-dependent for a preclinical candidate molecule and its comparators.
- Drug-induced changes in days to viral clearance and the antibody level of the preclinical molecule can be ranked between those of Abatacept and Belatacept.
- Drug-dependent modulation of the immune response to IAV infection is consistent for primary and secondary infection (*not shown*).

Interpretation: No burden of an increased infection risk associated with the preclinical molecule at the anticipated effective doses in comparison to competitors with known clinical safety profile.

Conclusions

1. An *in silico* systems immunology approach can be used to quantify the risk of delayed immune response due to specific immunosuppressive therapies.
2. The *in vitro* informed mechanistic model is not tailored to a specific modality and can cover potentially adverse effects of different targeted receptors.
3. The study serves as blueprint for the quantitative assessment of various common infections and their associated clinical risks, including reactivation of TB.



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