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Using vaccine Immunostimulation/Immunodynamic modelling methods to inform vaccine dose decision-making

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Immunostimulation/ Immunodynamic (IS/ID) modelling:

Proposed new field to address the lack of quant models used to develop vaccines

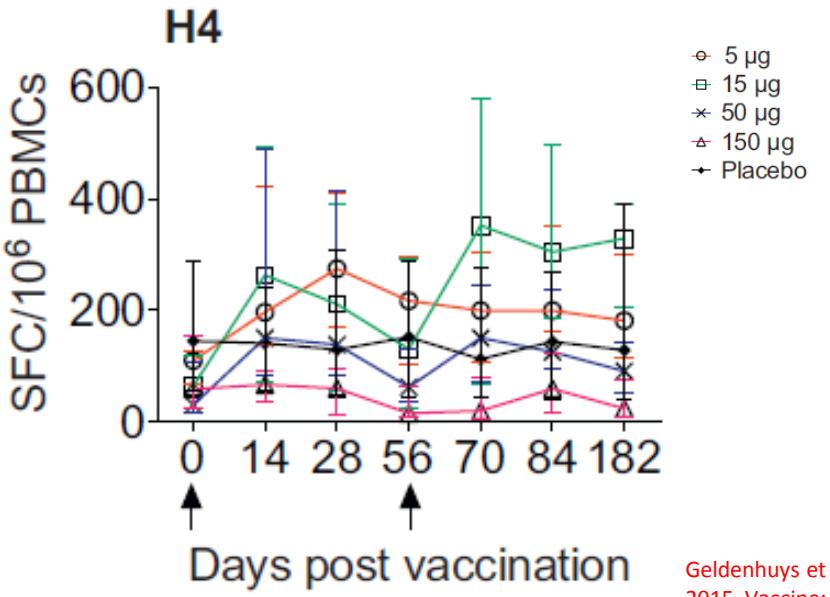
IS = the immune response stimulation following vaccination, ID= the measured immune response dynamics

["dose" = antigen dose amount]

TB vaccine dosing

- Dose response data in humans for novel TB vaccine H4 +IC31 have shown a non-saturating pattern (Not a unique phenomenon – seen in other diseases (Malaria, flu…)
  - At day 56, 5 and 15 μg doses are superior to 50 and 150 μg of vaccine antigen (adjuvant constant)
  - yet 50 μg chosen for a safety study of an immunologic effect
- Choice of dose to study have been too high? Should we go even lower than 5ug?

- Which doses should we focus on in humans to find the "optimal" dose?
- Can we use animal data and mathematical modelling to predict the range in which we think the optimal dose would be?



Geldenhuys et al. 2015, Vaccine: H4 in South African Adults

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Aim

Use IS/ID modelling calibrated to mouse multi-dose response data from the novel TB vaccine H56 to predict human dose-dependent response dynamics

Stage 1. Generate longitudinal H56 dose response data in mice and analyse the H56 dose response curve (at fixed time intervals)

Stage 2. Translate the H56 longitudinal dose-dependent responses from mouse to human

Stage 1

Use IS/ID modelling calibrated to mouse multi-dose response data from the novel TB vaccine H56 to predict human dose-dependent response dynamics

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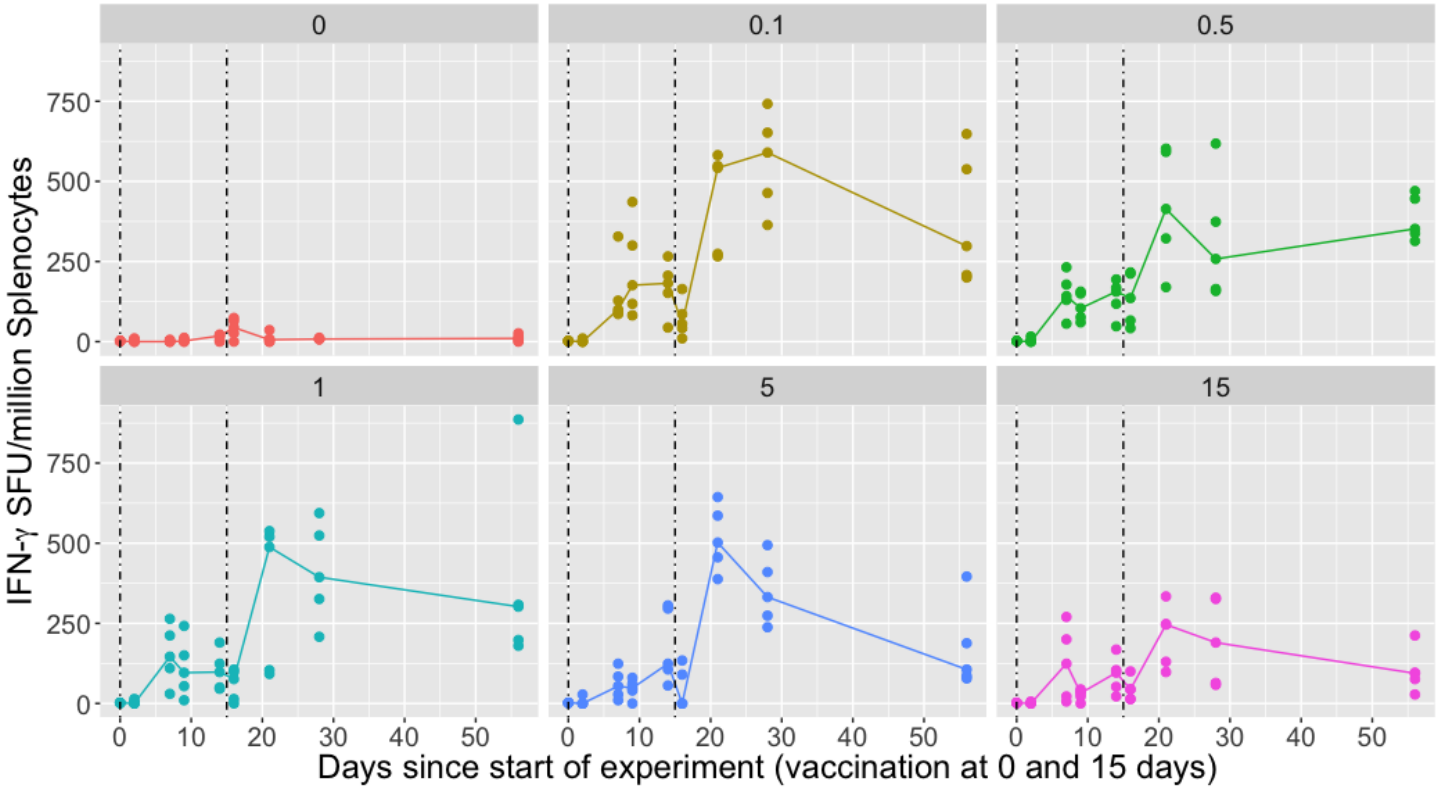
Stage 2. Translate the H56 longitudinal dose-dependent responses from mouse to human

Mouse H56+IC31 dose data

We conducted multi-dose, multi-time point experiment of TB vaccine H56 +IC31 in F1 mice

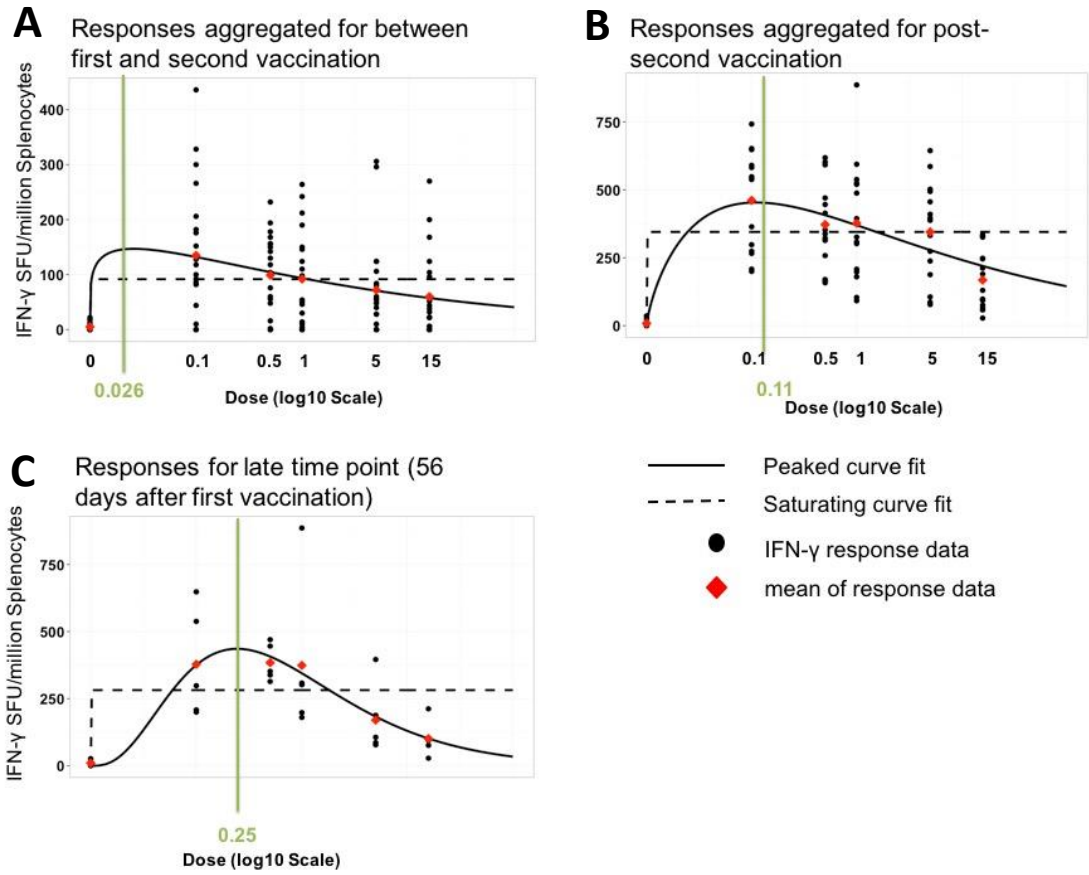
- Six doses: 0.1 to 15 µg H56 + control
- Two vaccinations at day 0 and 15.
- 8 time points sampled over 56 days
- 5 mice per time point (per dose)



Mouse dose response curve analysis

Same data as previous slide, but dose vs response with panels as time ranges

- Peaked (gamma pdf function) curve better fit to the data for all time ranges than saturating curve.
- Peaked curve predicts “most immunogenic dose” at lower value than has been used historically.



$$\textbf{\textit{Saturating curve}}:\ Response = Baseline + \frac{Rmax * Dose^{p}}{R50 + Dose^{p}}$$

$$\textbf{\textit{Peaked curve}}:\ Response = Baseline + \left(S * \frac{rate^{shape}}{\Gamma(shape)} * Dose^{(shape-1)} * e^{-rate*Dose}\right)$$

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Stage 2

Use IS/ID modelling calibrated to mouse multi-dose response data from the novel TB vaccine H56 to predict human dose-dependent response dynamics

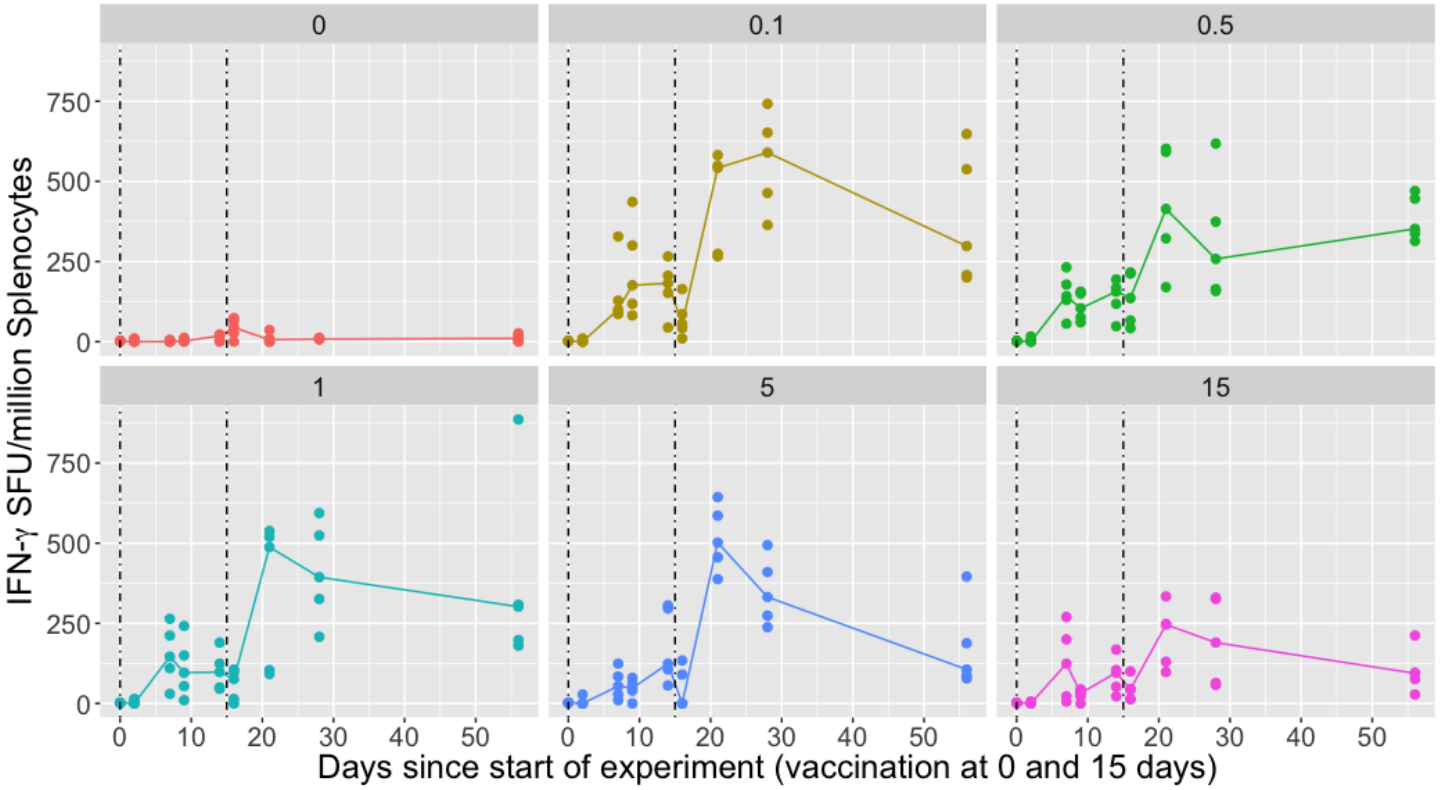
Stage 1. Generate longitudinal H56 dose response data in mice and analyse the H56 dose response curve (at fixed time intervals)

Stage 2. Translate the H56 longitudinal dose-dependent responses from mouse to human

Mouse H56+IC31 dose data

Mouse doses

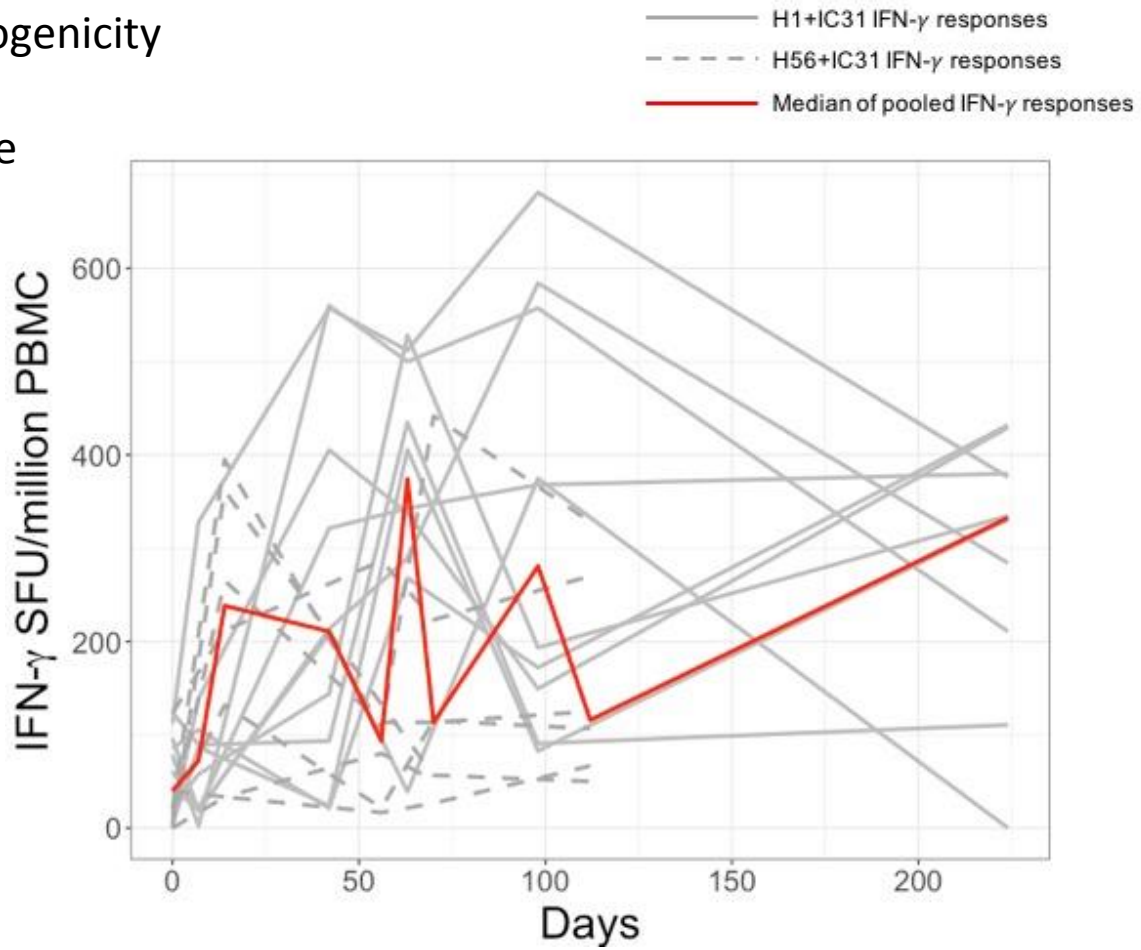
- Three dose groups:
  - low (0.1-1 µg H56+100nmol IC31)(N=15)
  - middle (5 µg H56+100nmol IC31)(N=5)
  - high (15 µg H56+100nmol IC31)(N=5)



Human H56/H1+IC31 dose data

Human

- Data from a phase 2a immunogenicity trial in South Africa
- South African, HIV-ve, LTBI –ve participants (N= 16)
- 50µg H56 + 500nmol IC31



Allometric dose mapping – Linking mouse to human response

Mouse doses

- Three dose groups:
  - low (0.1-1 µg H56+100nmol IC31)(N=15)
  - middle (5 µg H56+100nmol IC31)(N=5)
  - high (15 µg H56+100nmol IC31)(N=5)

Human dose

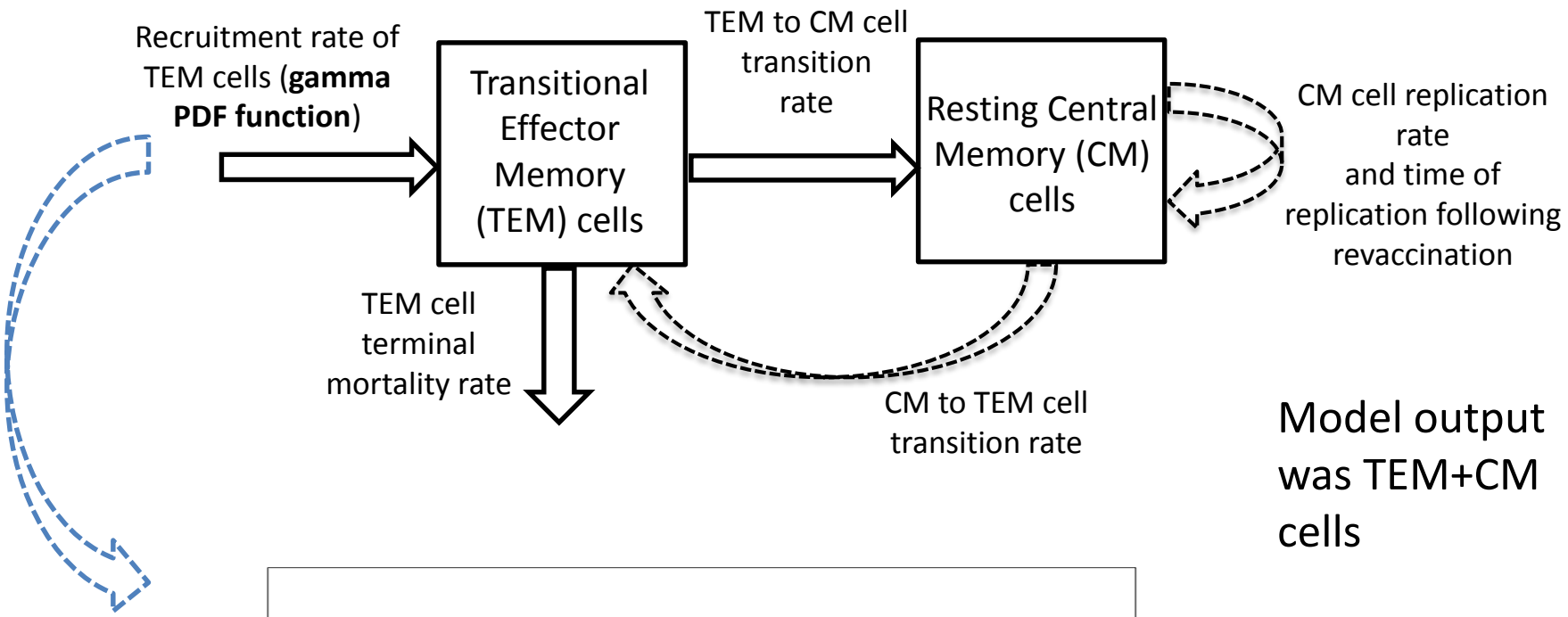
- **1-10 µg H56 + 500nmol IC31 (predicted)**
- 50µg H56 + 500nmol IC31 (empirical)
- **150 µg H56 + 500nmol IC31 (predicted)**

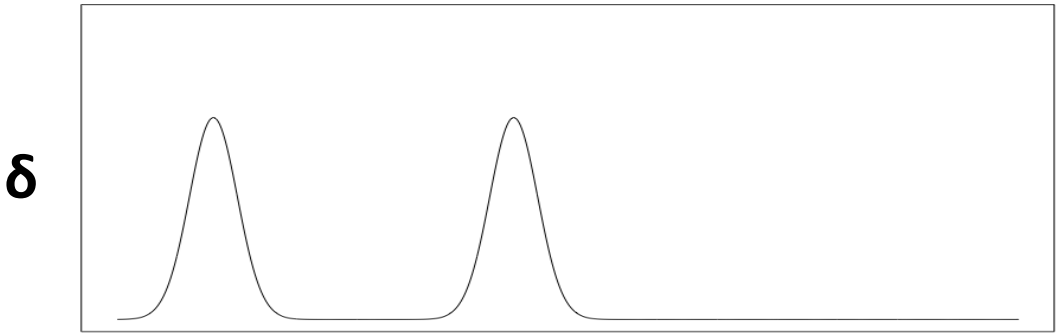
Assumed dose allometric scaling factor of **10** *(current (published) assumption for H-series)*:

i.e. dose **50 µg** + IC31 H56 in **humans** = **5 µg** H56+ IC31 in **mice (middle dose group)**
(adjuvant dose kept constant)

Therefore aim to use empirical mouse data to predict human **low** and **high** dose groups based on mouse dose groups **1-10** and **150** µg H56+IC31, respectively

IS/ID IFN- γ secreting CD4+ T cell Model





Model output was TEM+CM cells

The model was calibrated to the data using SAEM in Monolix software

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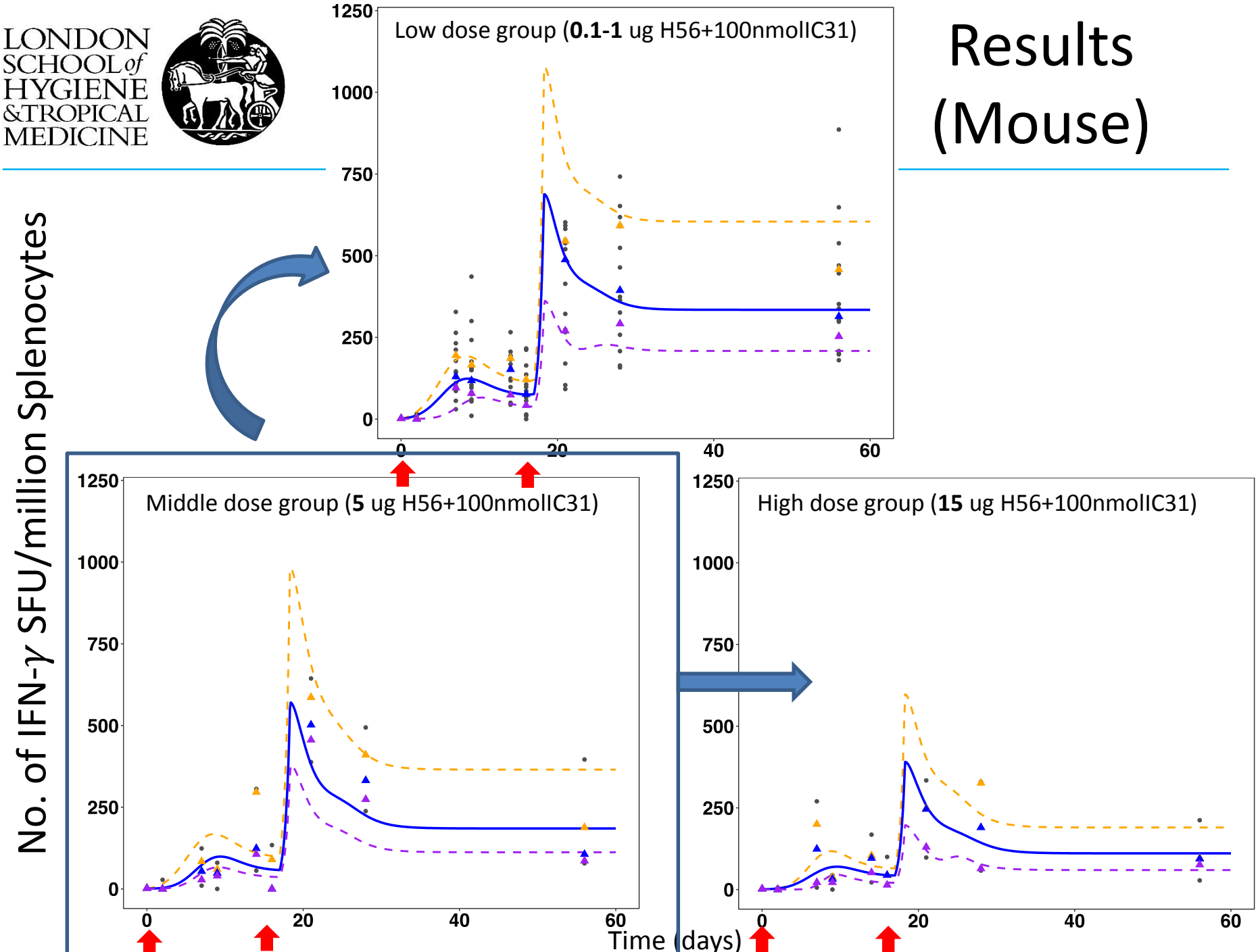
Results (Mouse)



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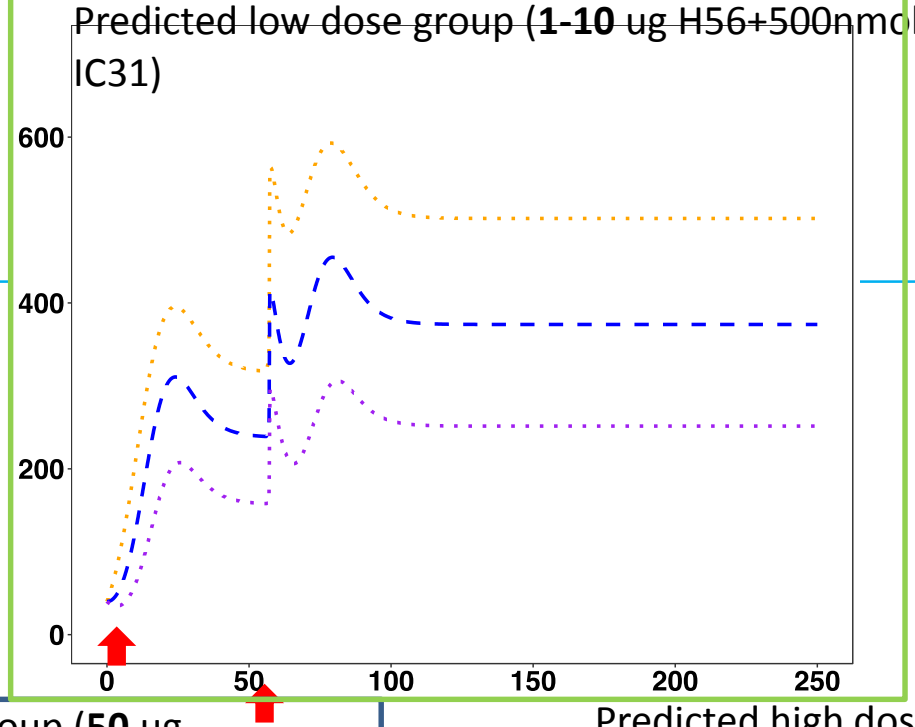
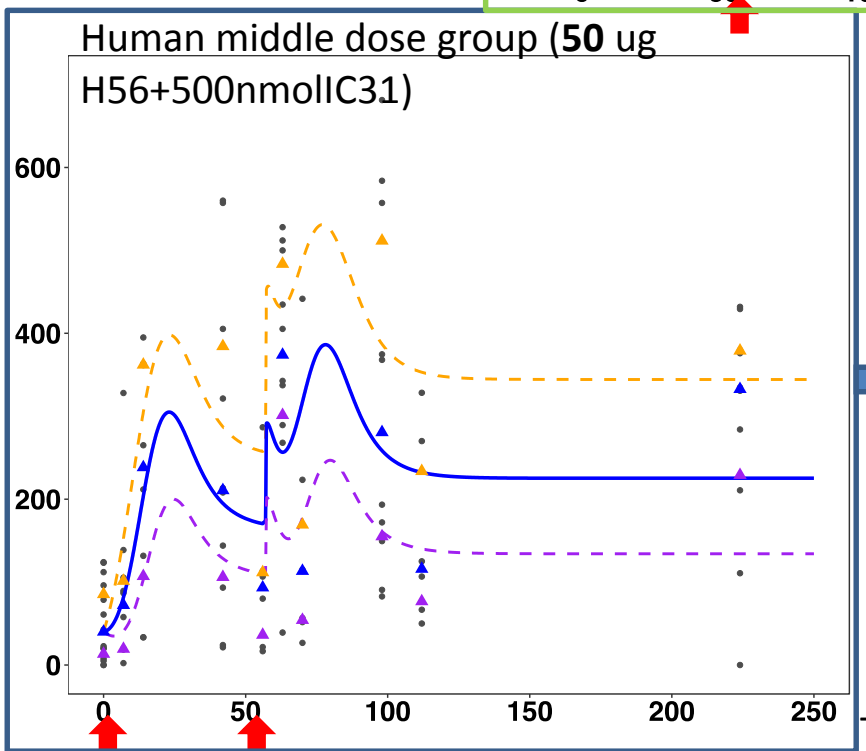
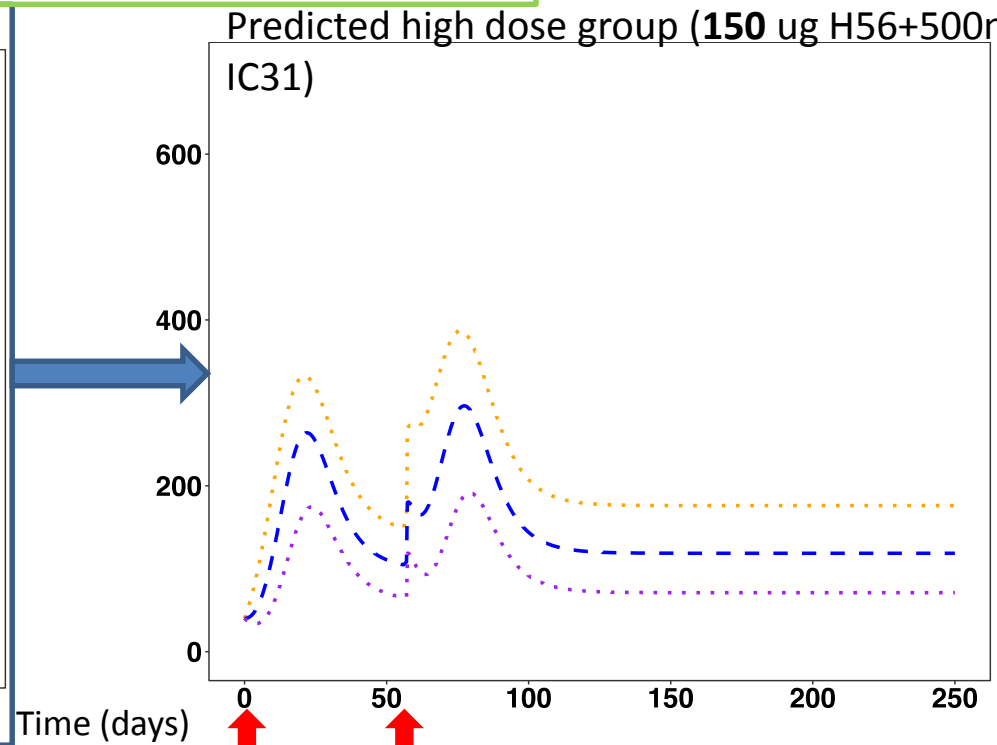
Results (Human)







No. of IFN-γ SFU/million PBMC

Time (days)

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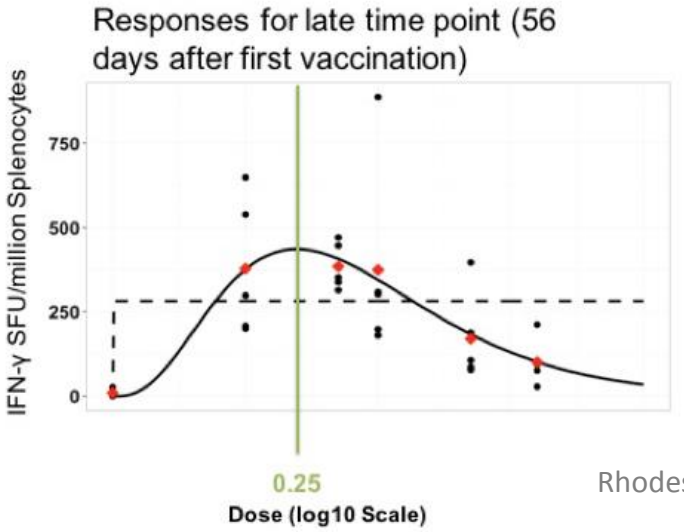
Discussion/conclusion

- Modelling predicts lower (1-10ug H56+IC31) doses maybe more immunogenic in humans based on mouse data
- Model predictions validated by recent empirical dose ranging study: H56+IC31 in humans has shown a low dose (within 1-10ug) has been shown to be as immunogenic as higher doses

Future work – Stage 3

Stage 3: Modelling to design next best H56 mouse experiment



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Based on TB vaccine, H56+IC31 mouse dose response curve at late time point, can modelling (stats and maths) tell us which experiment to conduct next to increase of confidence in best dose (green line), using a limited amount of mice?

Eventually use method to design clinical trials (i.e. Modelling to tell us minimum amount of subjects at most to gain most dose response information?)

Future work – Stage 4

Stage 4: Further develop and evaluate quantitative methods to optimize vaccine dose for other vaccines (antibody based)

1. Similar to the TB work, use animal dose response data to predict human dose for using published data on Ebola and Dengue vaccines.
2. Use published vaccine dose response data for Dengue, Japanese Encephalitis and West Nile disease to parameterise mechanistic models and predict vaccine dose response curve for emerging related disease, Zika.
3. Use statistical methods to predict best dose for a multi-dimensional tetravalent Dengue vaccine dose response curve

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