Intricate PK and PD for the novel immunocytokine CEA-IL2v and their pre-clinical to clinical translation

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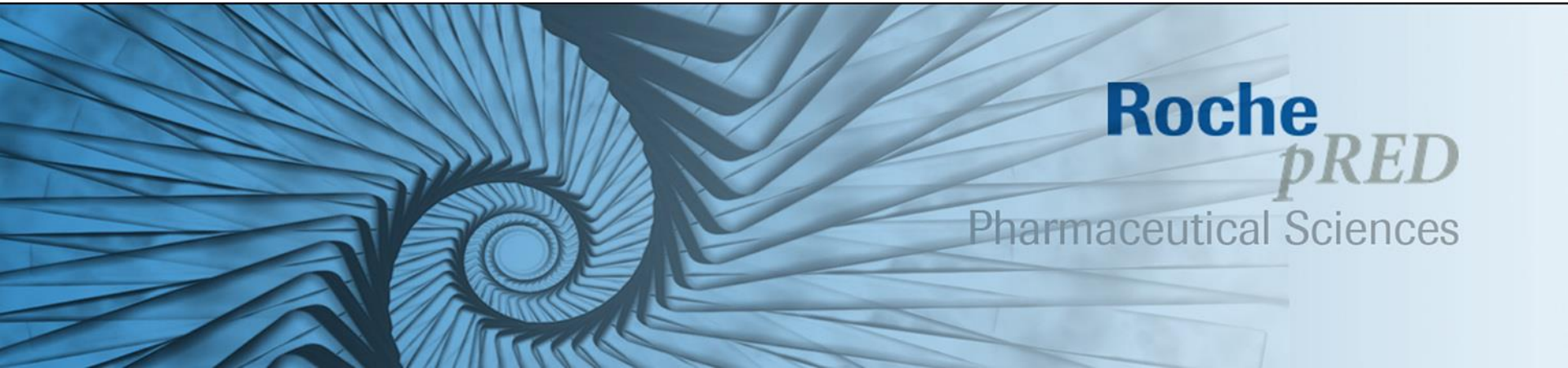
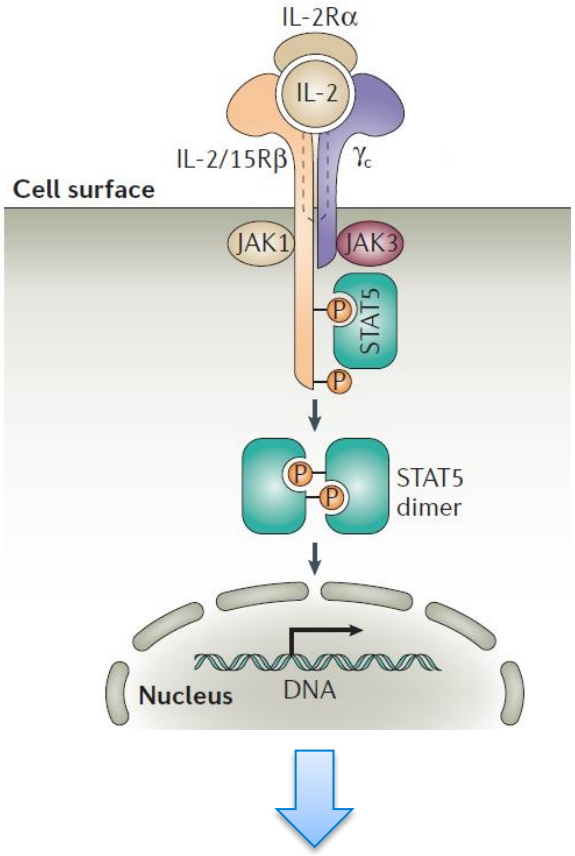


Interleukin 2 (IL-2) pharmacology

Can produce durable remissions in some types of cancer – strong need for improved safety profile



activation & proliferation of T-cells

PROLEUKIN® (aldesleukin)

for injection, for intravenous infusion

Rx Only

WARNINGS

Therapy with Proleukin® (aldesleukin) should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.

Proleukin should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

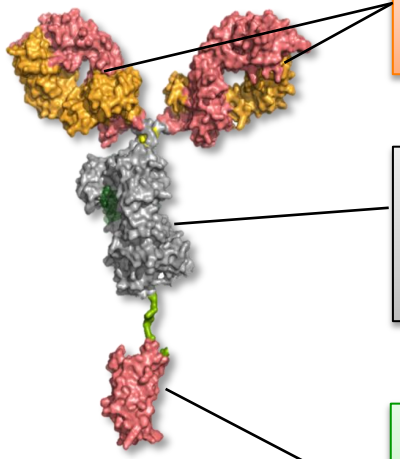
Proleukin administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

Proleukin administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

Novel CEA-targeted immunocytokine

For combination with immunomodulators and ADCC-competent MAbs



Cergutuzumab Amunaleukin

- High affinity for tumor antigen CEA
- Dead Fc part with proprietary P329G LALA mutation
- Monomeric human IL2v(ariant) with abolished CD25 binding

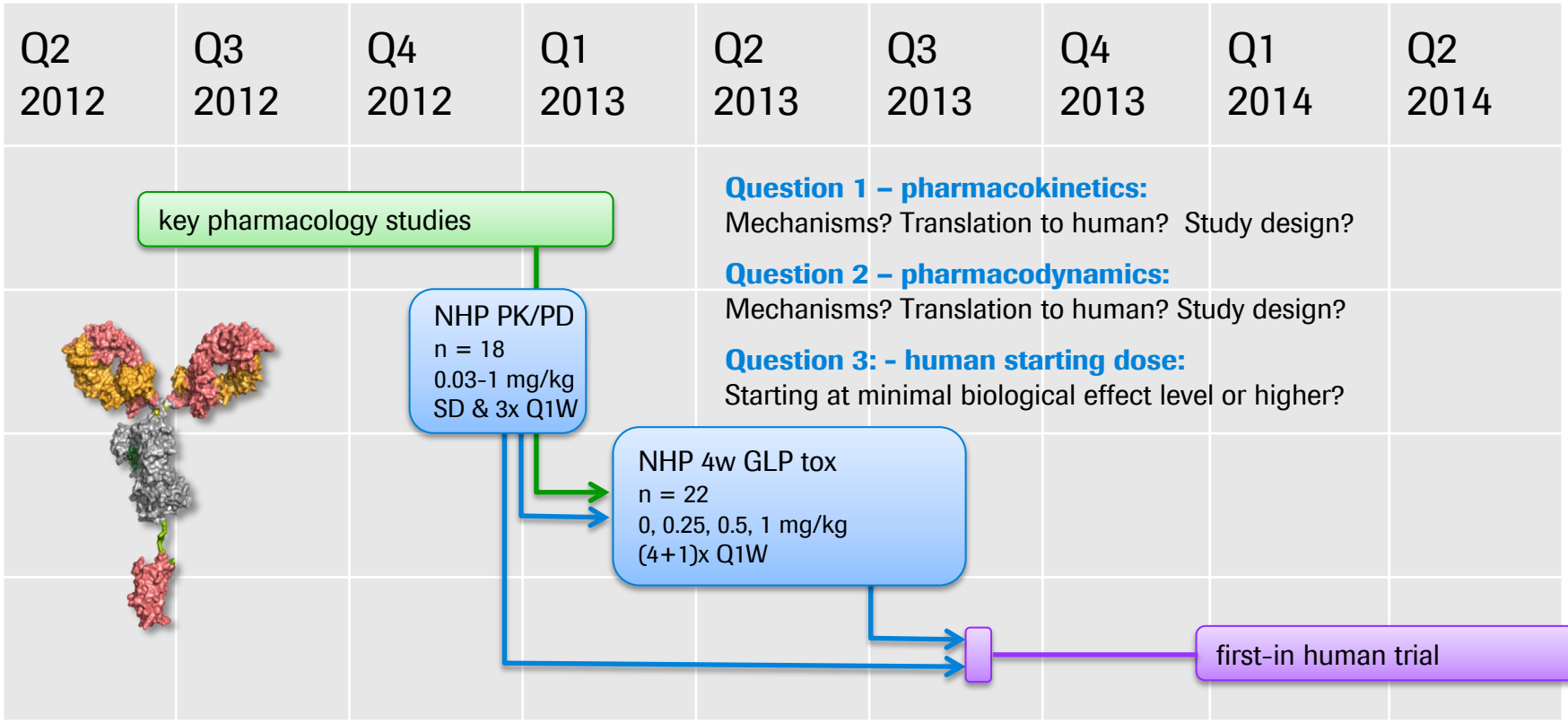
Expected advantages over rhuIL-2:

- tumor targeting
- extended exposure
- reduced toxicity
- reduced Treg activation

CEA = Carcino Embryonic Antigen

How to best support Phase I design?

Leverage non-clinical multi-scale data

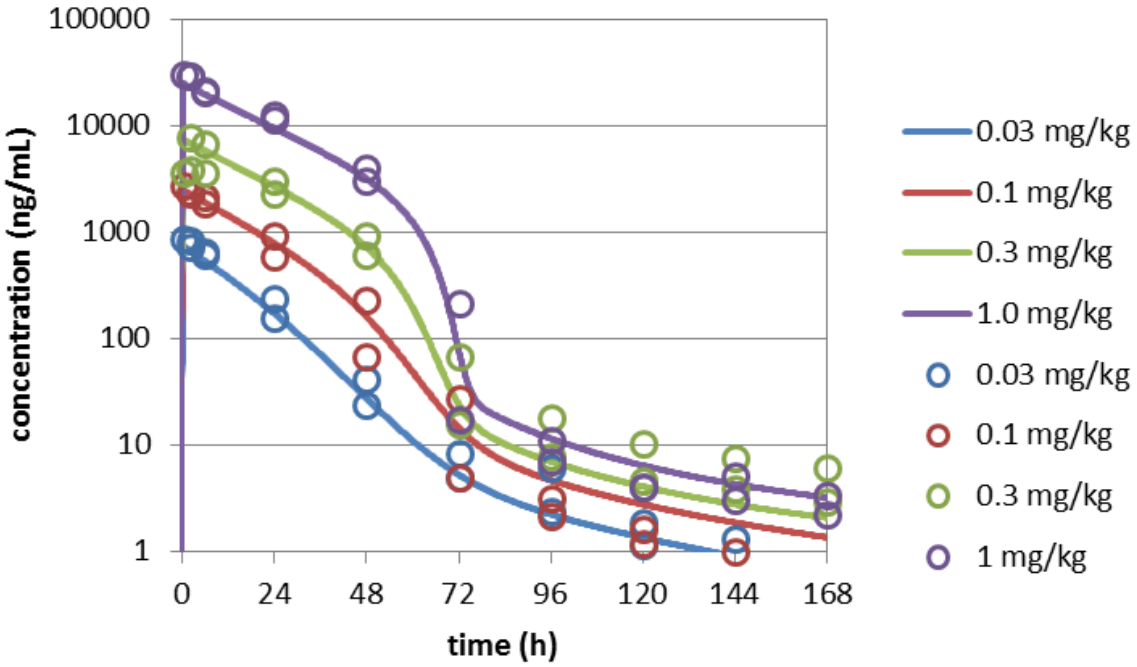


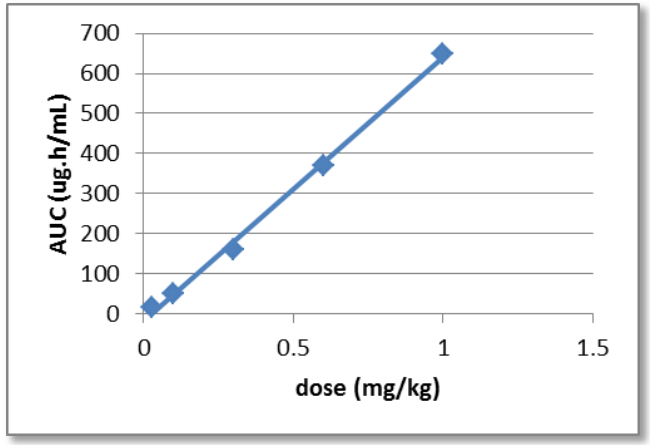
Questions need to be answered quickly – modeling done on the fly.

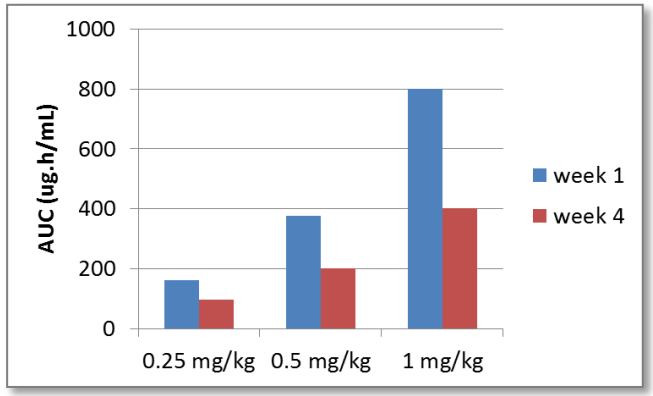
Intricate pharmacokinetics

Data from PKPD and GLP tox studies in NHP

Selected PK data from PKPD and GLP tox (dots) overlay with tentative model simulations (lines):





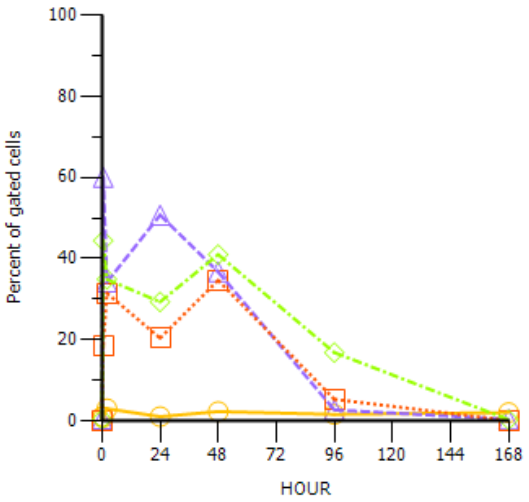


Some hints of strong TMDD, however AUC seems almost linear with dose.

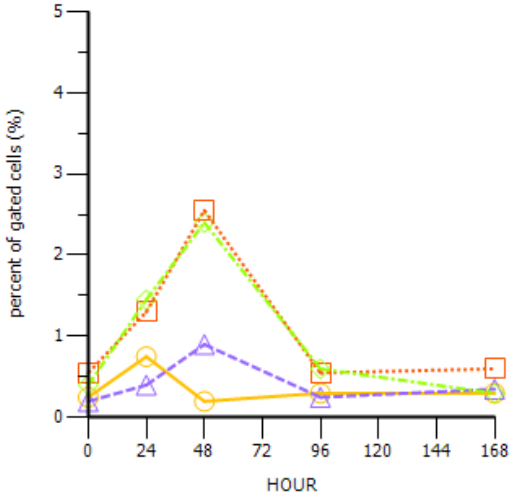
Multi-scale pharmacodynamics

Activation cascade witnessed by flow cytometry

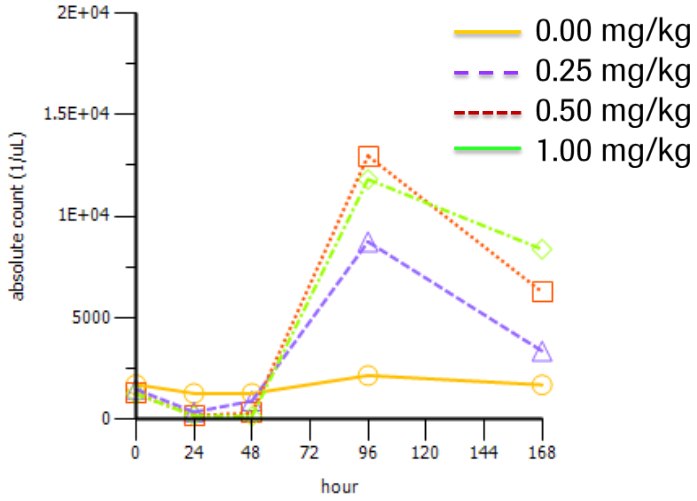
Early sign of activation:
phosphorylation of STAT5



Late signs of activation:
up-regulation of CD25, CD69, Ki67



Cell count dynamics:



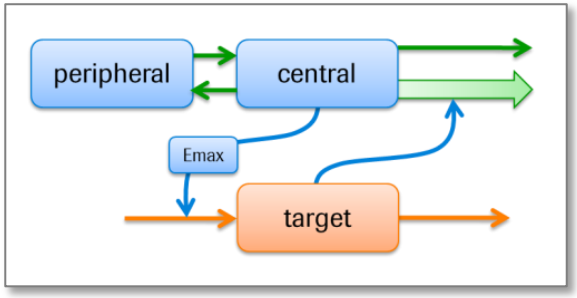
All data available for CD4+ and CD8+ T-cells, Tregs, NK cells.

Exposure leads to activation, activation leads to expansion ...

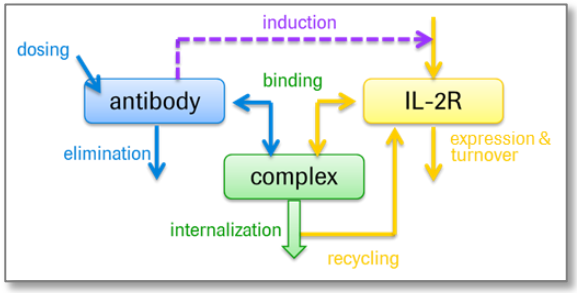
… expansion leads to increased TMDD!

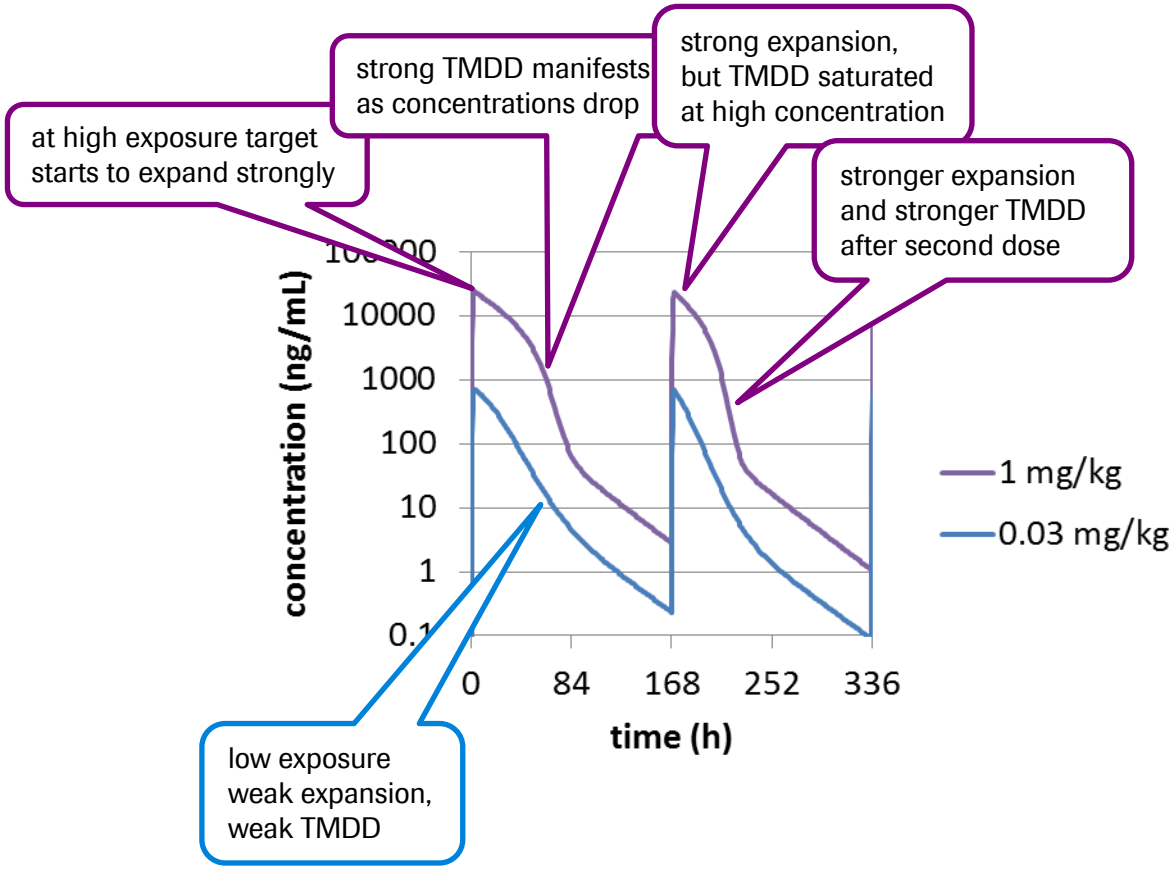
A coherent explanation of the PK features

1st generation model (Vmax-KM)



2nd generation model (full TMDD)

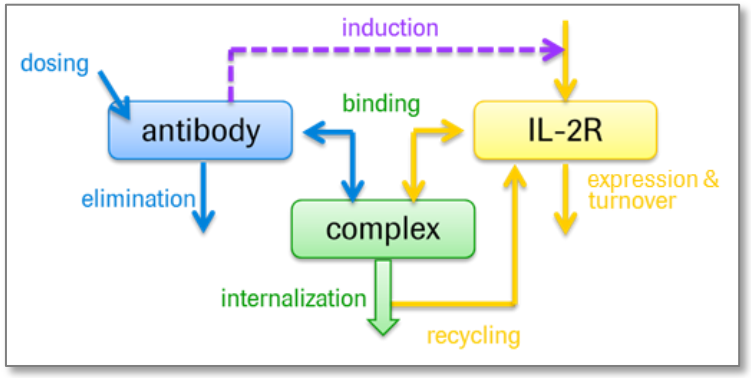




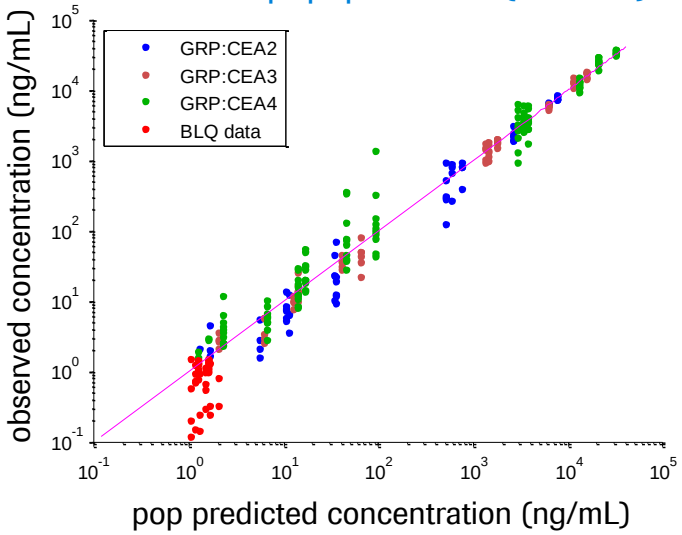
CEA-IL2v induces its own target-mediated drug disposition!

The best PK model so far ...

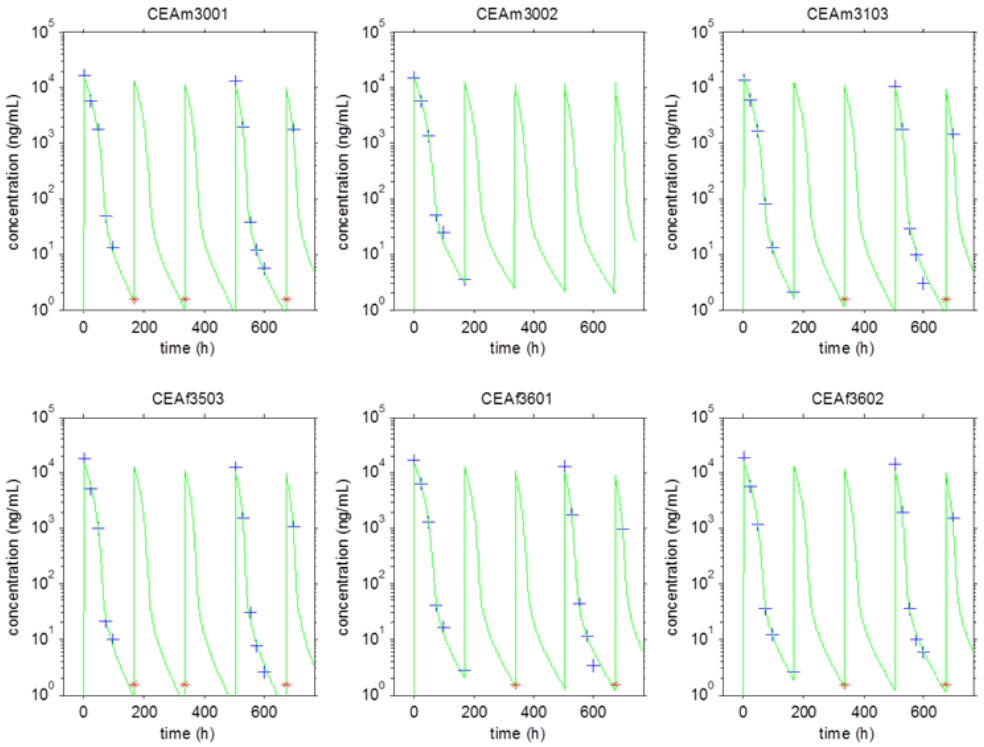
Plausible values for parameters



observed vs pop. predicted (GLP tox):

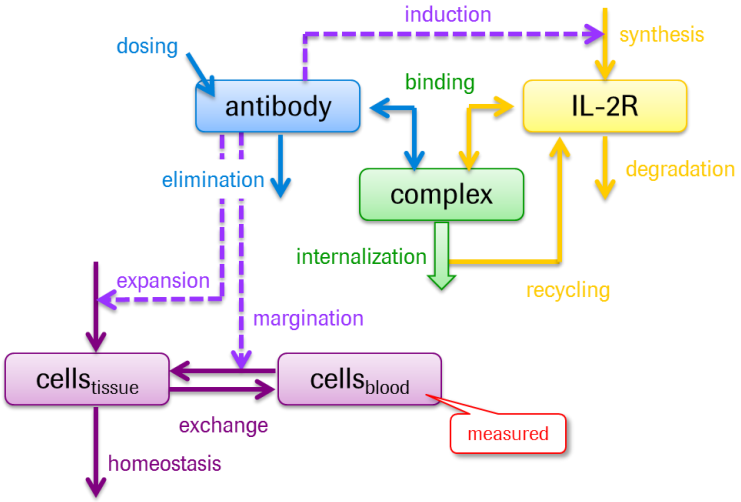


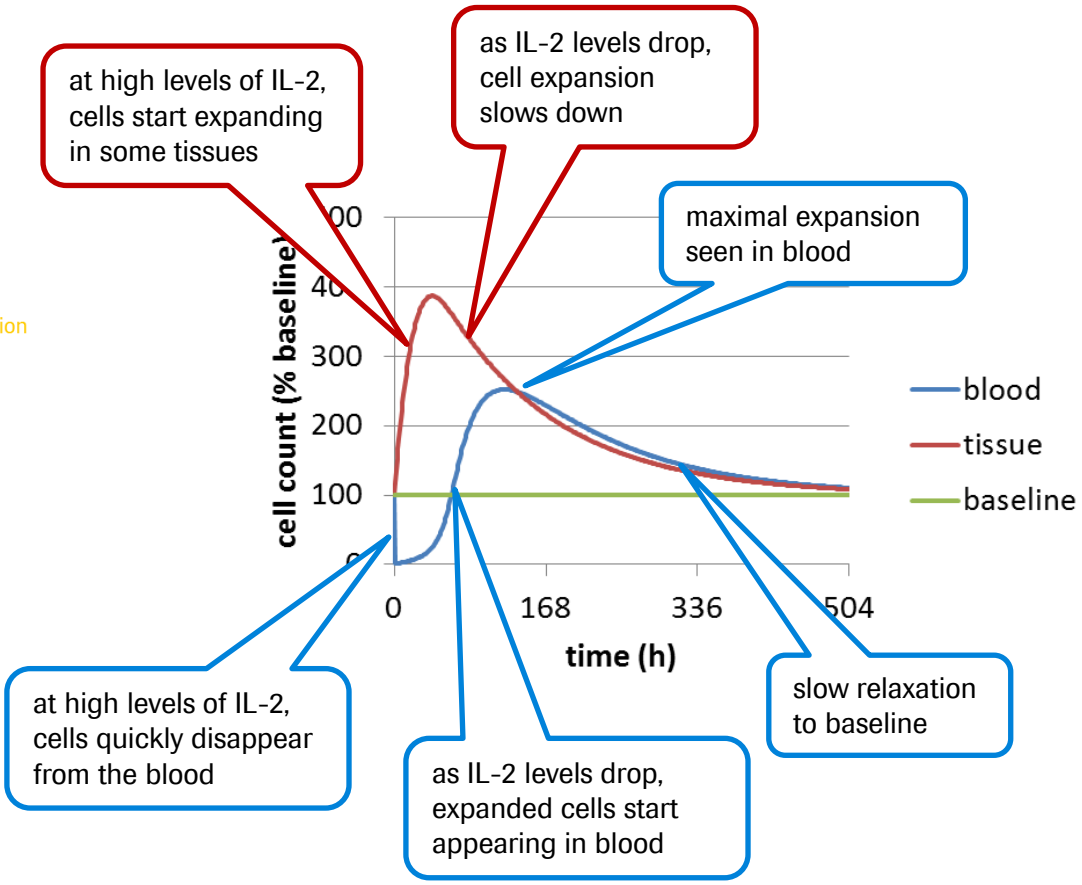
Individual fits from GLP tox at 0.5 mg/kg:



PKPD: IL-2 induced lymphocyte dynamics

Early depletion – expansion - relaxation

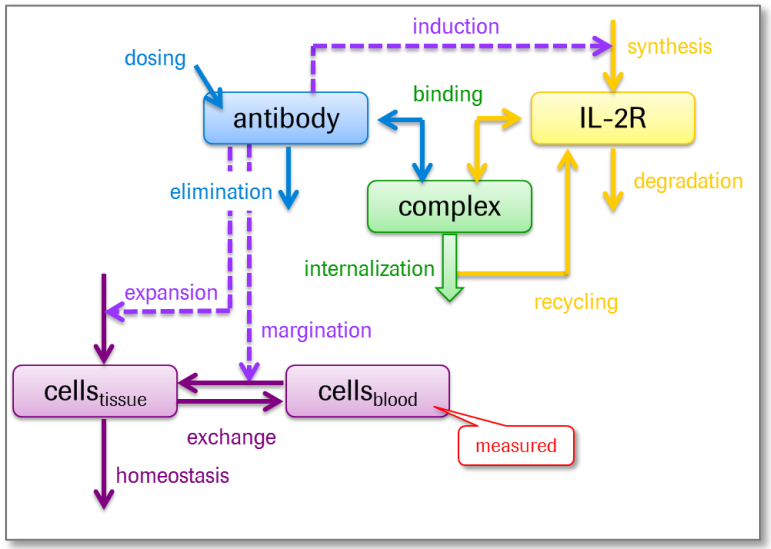




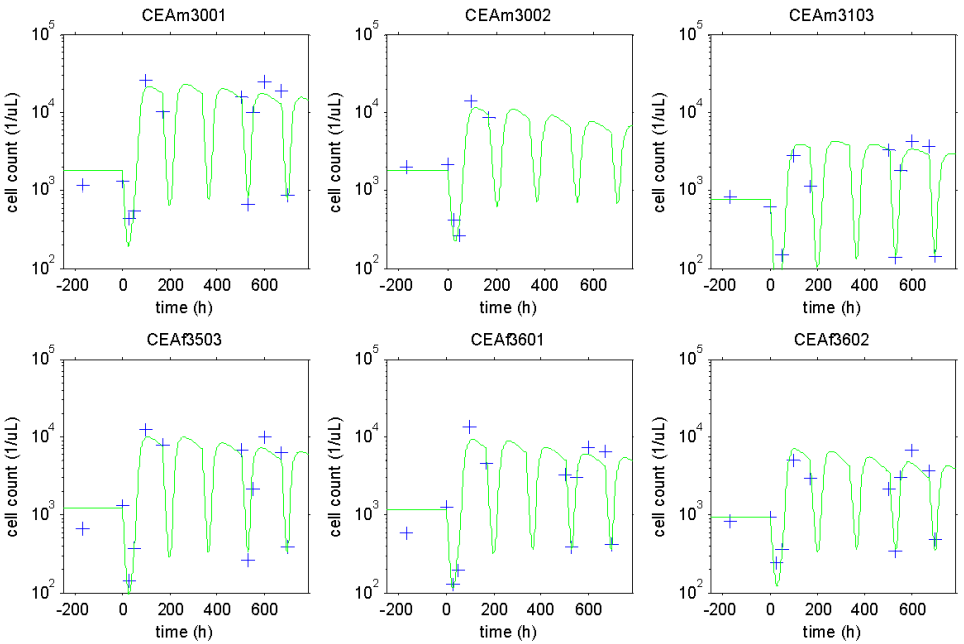
Similarity (*not equality*) of cell number and receptor dynamics.

Lymphocyte dynamics model (example CD8+)

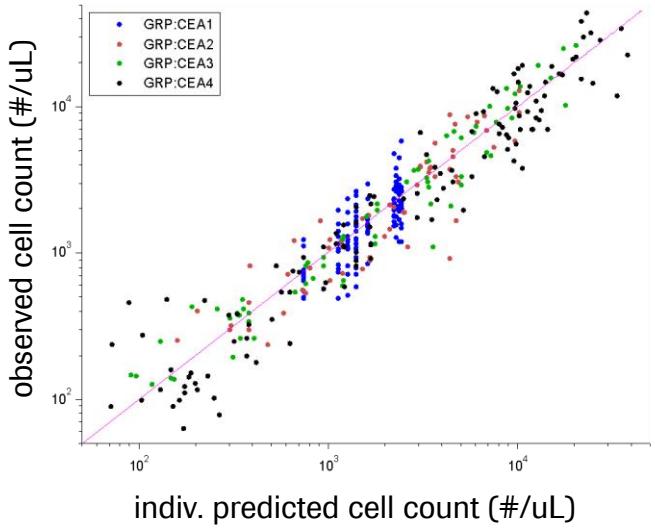
Allows quantitative comparisons



Individual fits from GLP tox at 0.5 mg/kg:



Observed vs indiv. predicted (GLP tox):



Starting dose discussion

Assembly of information put into context of anticipated Cmax

proliferation of pre-activated PBMC (CD8+)

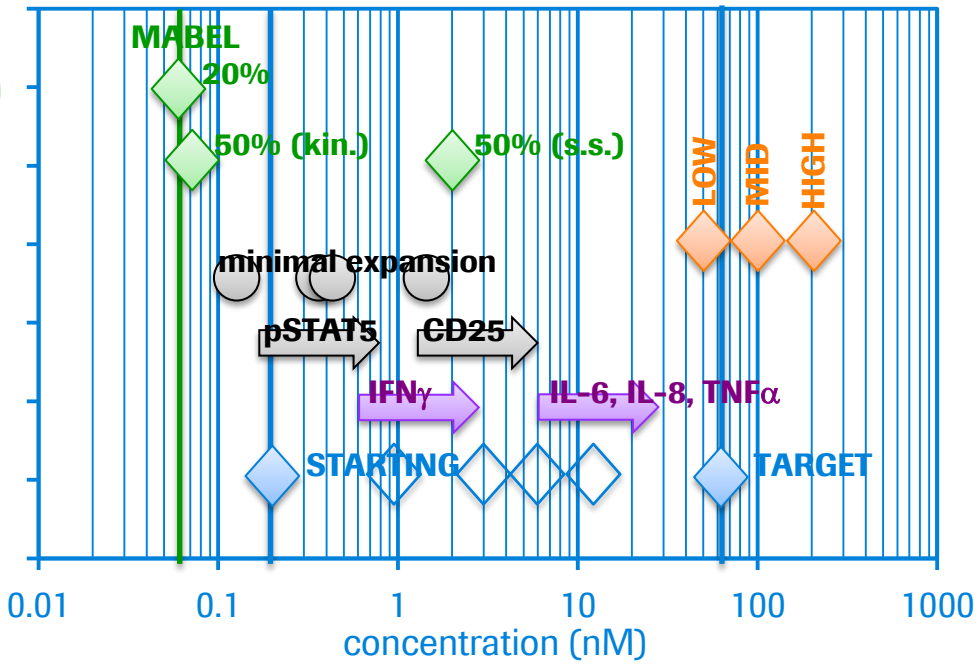
binding to pre-formed hulL-2Rβγ (SPR)

Cmax in GLP tox study (day 1)

PD biomarkers in GLP tox (model derived)

Human whole blood assay *in vitro*

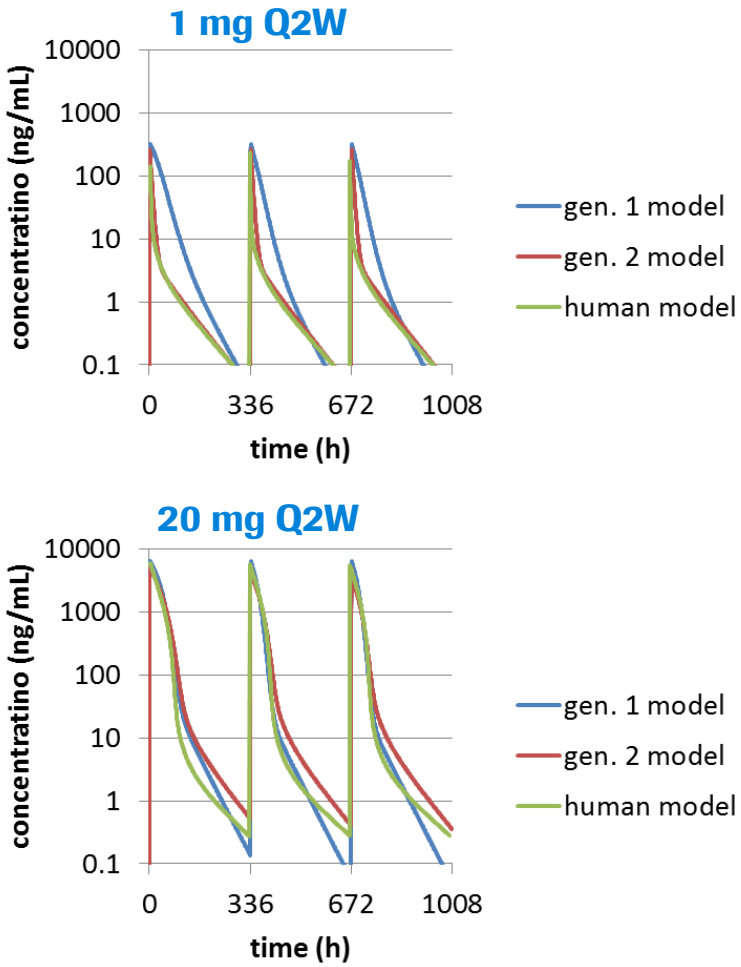
proposed starting dose (100 ug) and rough estimate of target dose (30 mg)



Approval of 100 ug starting dose with rapid escalation in first part of Phase I.

Human PK by allometric scaling of TMDD model

Comparison to model based on clinical data



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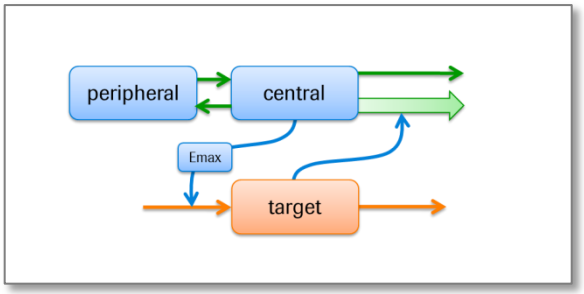

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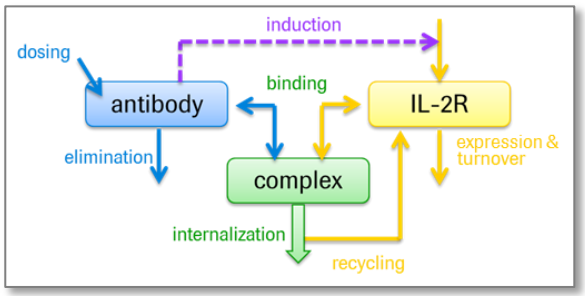

Good human projection with full TMDD model – helpful for robust study design.

Conclusions

Thorough analysis of non-clinical PK and PD data supporting the first-in human trial

- providing explanations to complex PK behavior
- confirming the relative potency on lymphocyte subpopulations
- providing a thorough evaluation of PD and safety markers
- guiding dose selection and schedule of the assessments in the FIH study
- prototyping PK and PKPD models that are now employed with human data

Doing now what patients need next