New Results

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Towards pharmacokinetic profile predictions for monoclonal antibodies using sequence based machine learning derived parameters and compartmental modeling

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doi: https://doi.org/10.1101/2025.05.22.655474

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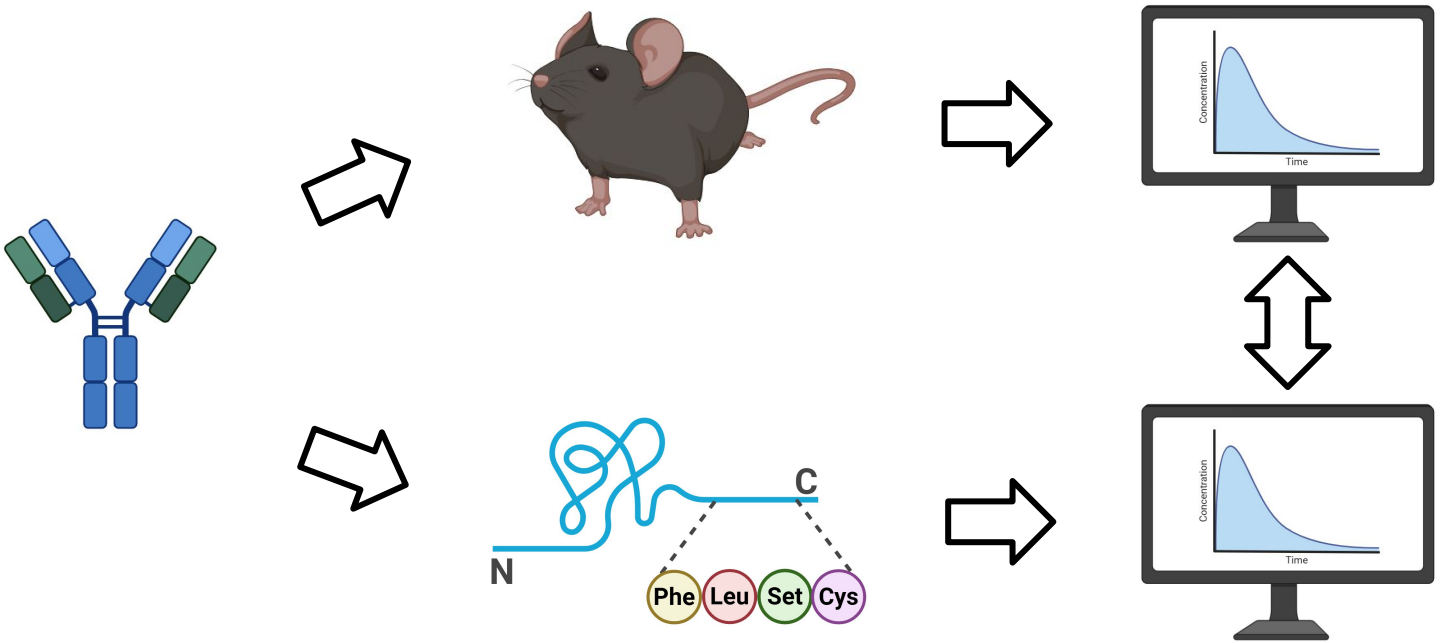
Peer Review on AI in Biology
May 21, 2026

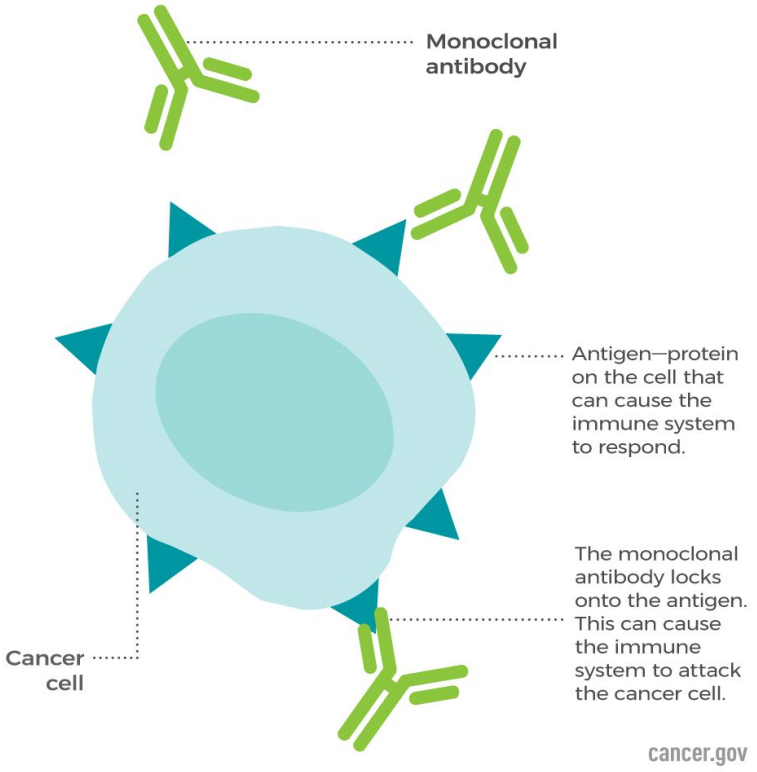
Main Claim and Goal of the Paper

“This study presents a novel approach for predicting complete pharmacokinetic (PK) profiles of monoclonal antibodies (mAbs) ***based solely on their amino acid sequences****, addressing a critical gap in early-stage therapeutic antibody development.”*

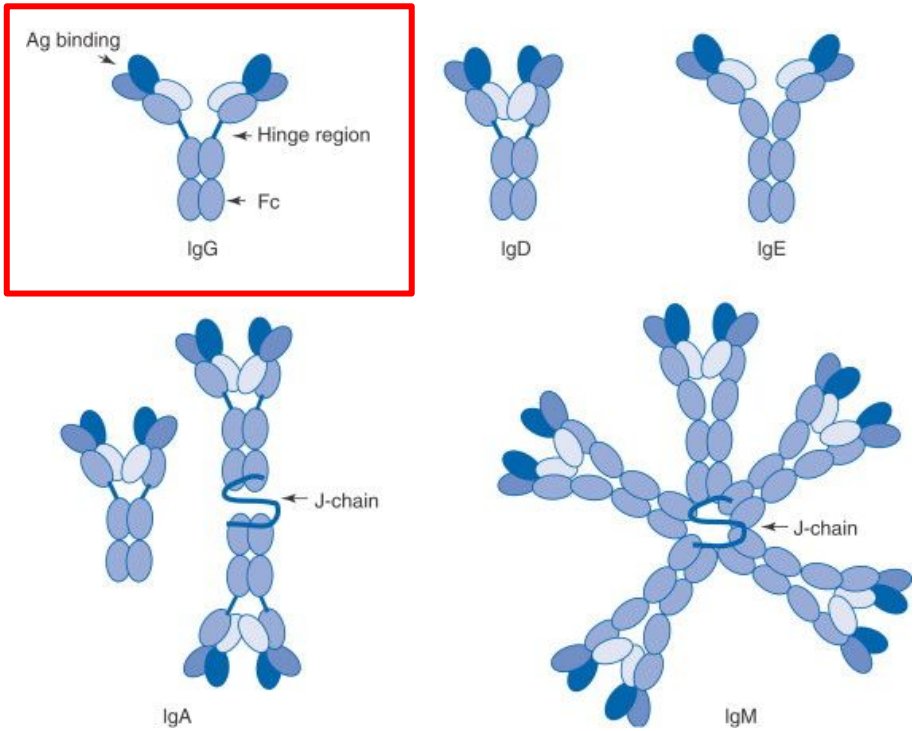


Monoclonal antibodies (mAb)

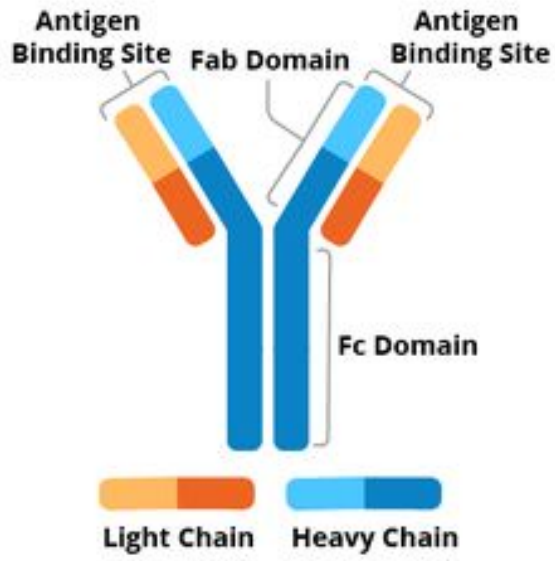
- Produced in a lab
- Used to mimic the antibodies that our body makes
- Inactivate cells or viruses
- Popular References to mAbs
  - Neuroinflammatory conditions, like multiple sclerosis (ofatumumab)
  - Rheumatoid arthritis (adalimumab)
  - HER2-positive breast cancer (trastuzumab)
  - Treatment for COVID-19 infection (Paxlovid; Ritonavir)



mAbs are also known as immunoglobulins (Ig)



mAbs can be separated into **Light Chain** and **Heavy Chain**



⬅️**Heavy Chain tells you what kind of Ig it is**

🦠**Light Chain binds the antigen**

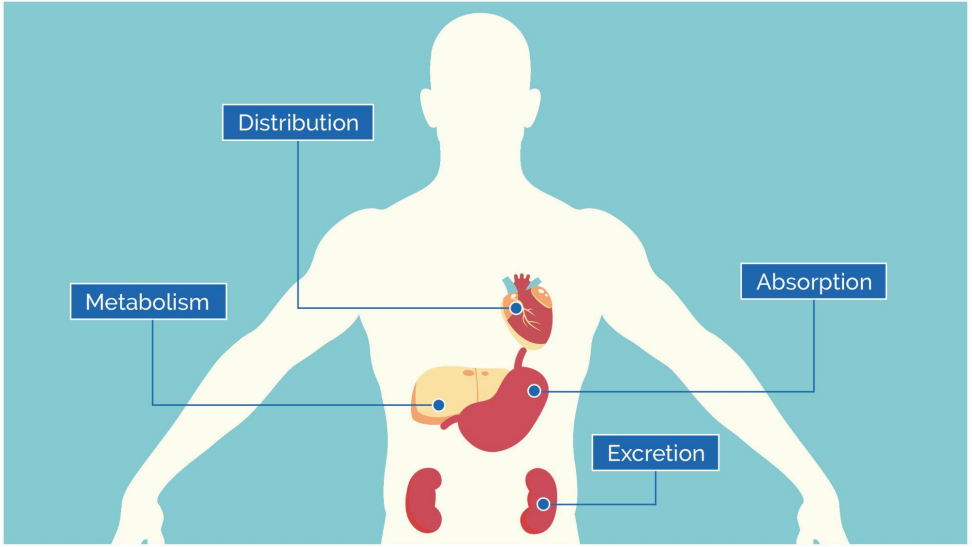
Pharmacokinetic (PK) profiles

- are a collection of values that describe the movement of a therapeutic through an organism (eg. clearance, volume of distribution)

- ADME

- To predict systemic levels

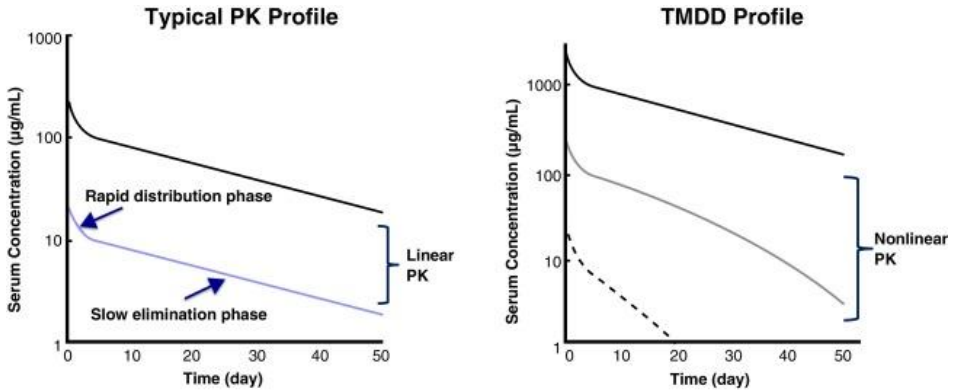
  (exposure)



PK profiles of mAb

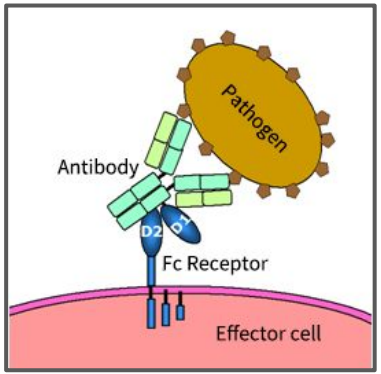
- Are important because FDA average annual approval rates for mAb therapeutics increased ~325% over last decade

- However, biologics like mAbs exhibit fundamentally different, and harder to predict exposure levels *in vivo* than small molecules



Tg32 Mice

- Commercially available through Jackson Laboratories (JAX)
- A humanized mouse, where the mouse immune cells now express **a human Fc receptor which binds to the heavy chain Fc domain of human IgG**
- JAX: *“Useful in evaluating the pharmacokinetics and pharmacodynamics of human IgG and Fc-domain based therapeutics”*
- In the paper, *in vivo* pharmacokinetics are quantified using these mice



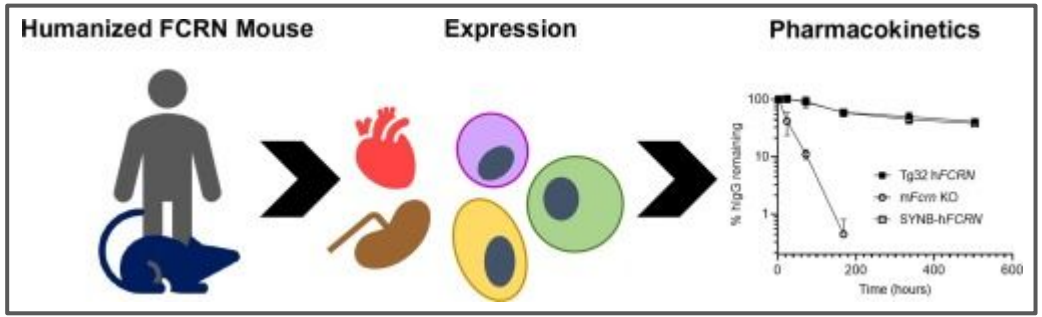
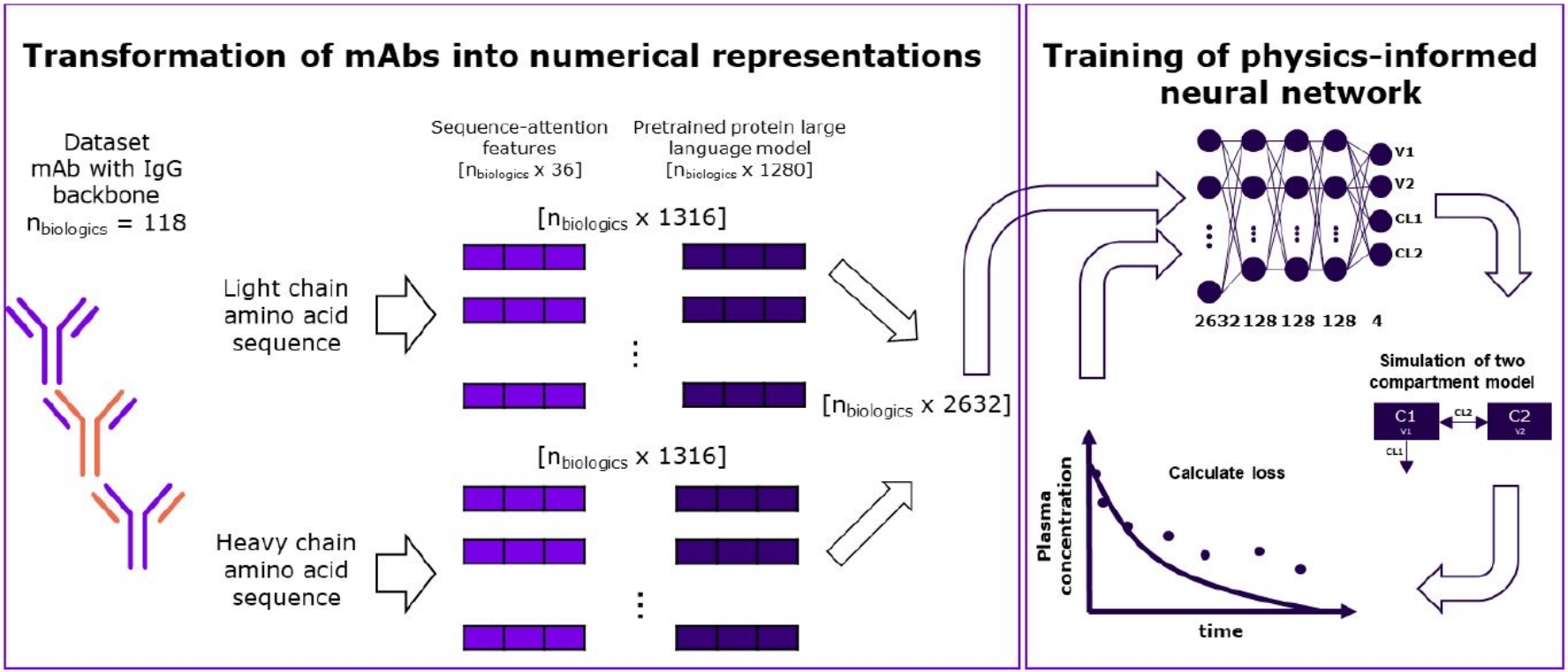


Figure 1: Schematic presentation of deep learning architecture for numerical representation of amino acid sequence and physics-informed neural network framework



The primary structure of IgG contains two heavy (each of 450–550 amino acids) and two light chains (each of 211–217 amino acids).[Ref]

Entire IgG: 1,322–1,534 amino acids

Figure 2: Predicted vs observed concentration data points separated into training, validation, and test data sets.

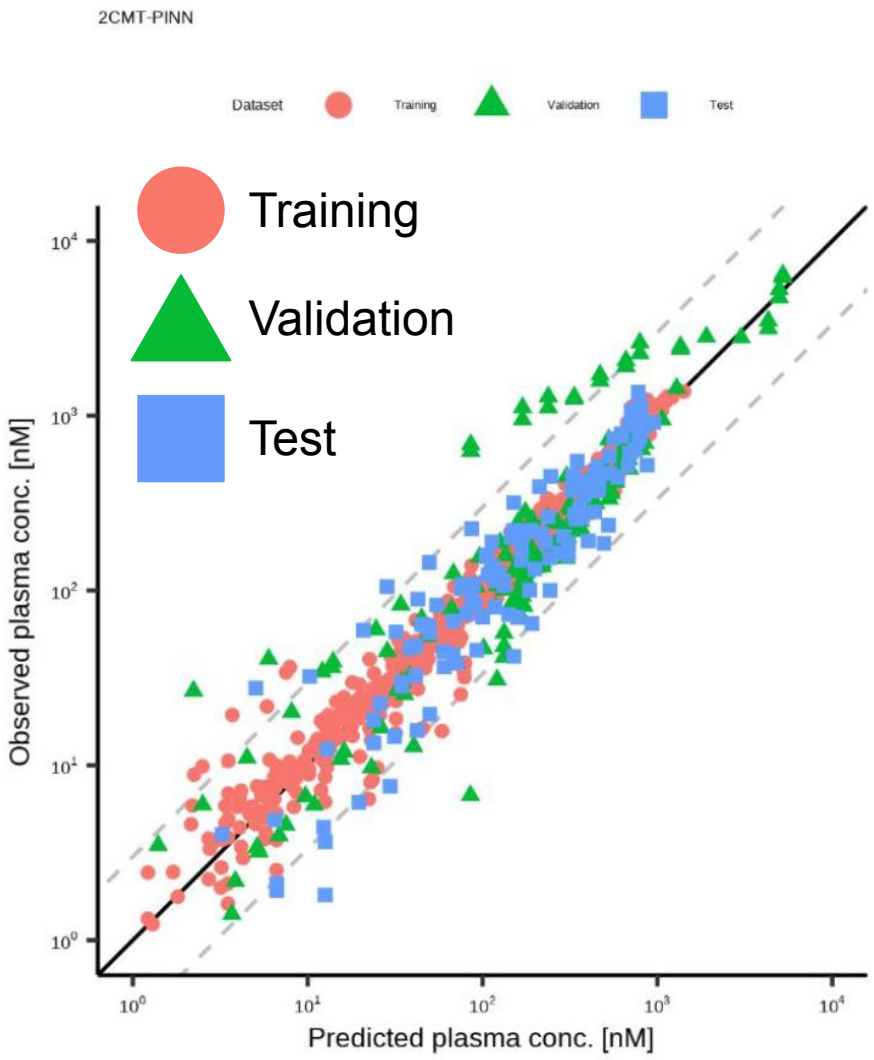
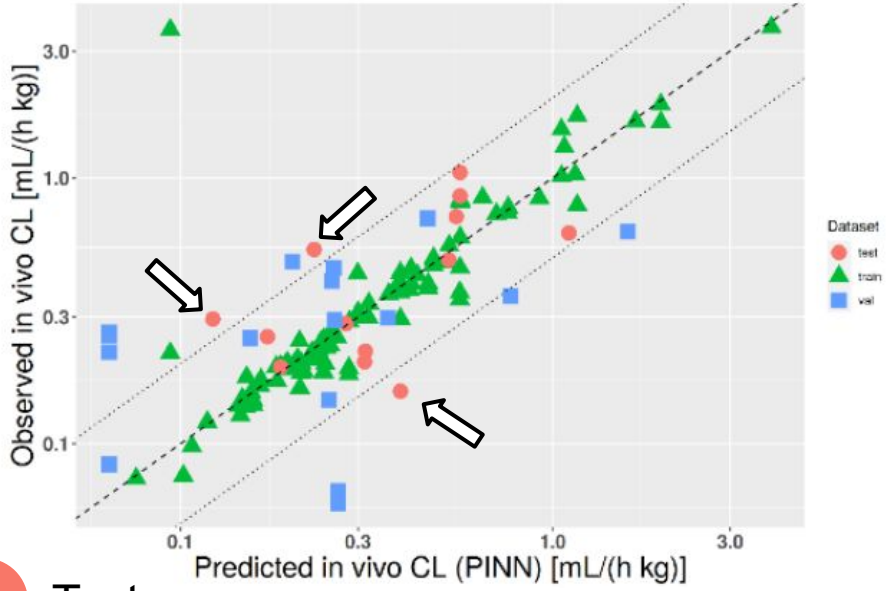
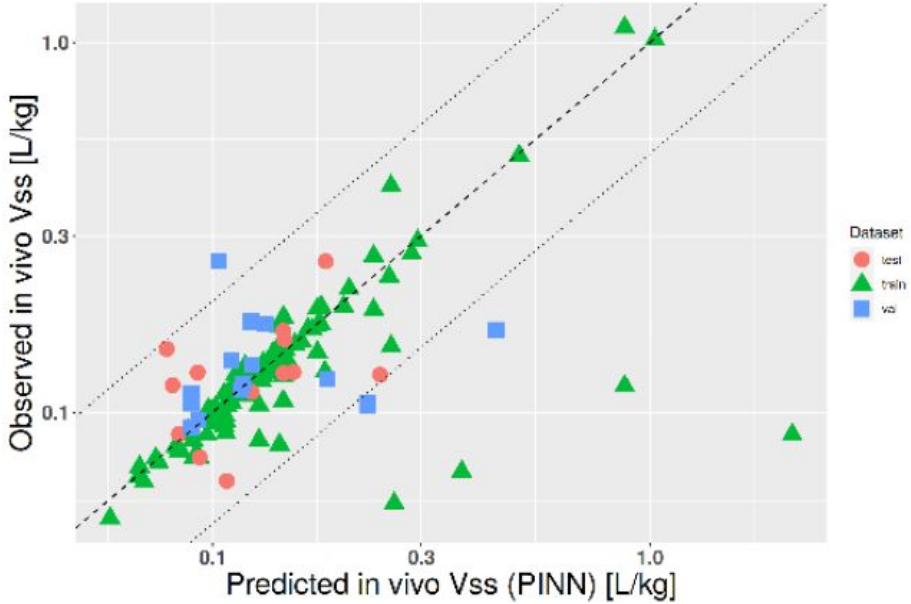


Figure 3: Predicted vs observed *in vivo* clearance (**CL**) and volume of distribution at steady state (**Vss**) separated into training, validation, and test data sets





Test

Training

Validation

CL represents the volume of blood plasma completely cleared of the antibody per unit of time

Vss is a theoretical volume that relates the total amount of drug in the body to its concentration in the plasma once the drug has reached equilibrium (steady state) between the blood and bodily tissues.

Conclusions, Implications, and Future Directions

- The authors have presented a novel method of *in silico* development of mAbs prior to production and validation
- The concept of (Input) amino acids ➡️ (Output) PK prediction is exciting and potentially translatable in other contexts
- Future Directions
  - *"[...] future investigations should consider incorporating datasets with **multiple dose groups for each mAb**, enabling the characterization of individual target mediated drug disposition profiles."*
  - Explicitly use some of the on-the-market mAbs in this PINN for further validation

	Known Parameters	**Unknown Parameters**
In the paper	Amino Acid Sequence + [Target]	PK profile
Potential application	Amino Acid Sequence + PK Profile	Target

Strengths

- *In silico* justification prior to mAb production is a definitive strength
- Lays framework for possible future biologic PK predictions

Weaknesses

- **There's no actual data for the reader to interpret**
- They could have offered a sample of some of the mAb targets, or if any on-the-market Sanofi mAbs were used
- The CL of the 3 majorly mis-predicted mAbs were not named or analyzed
- Figures have titles, but not informative captions. Explanations in the text are minimal. Linear data presentation with non-linear axes.