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Bispecific Molecules: Promises and Challenges

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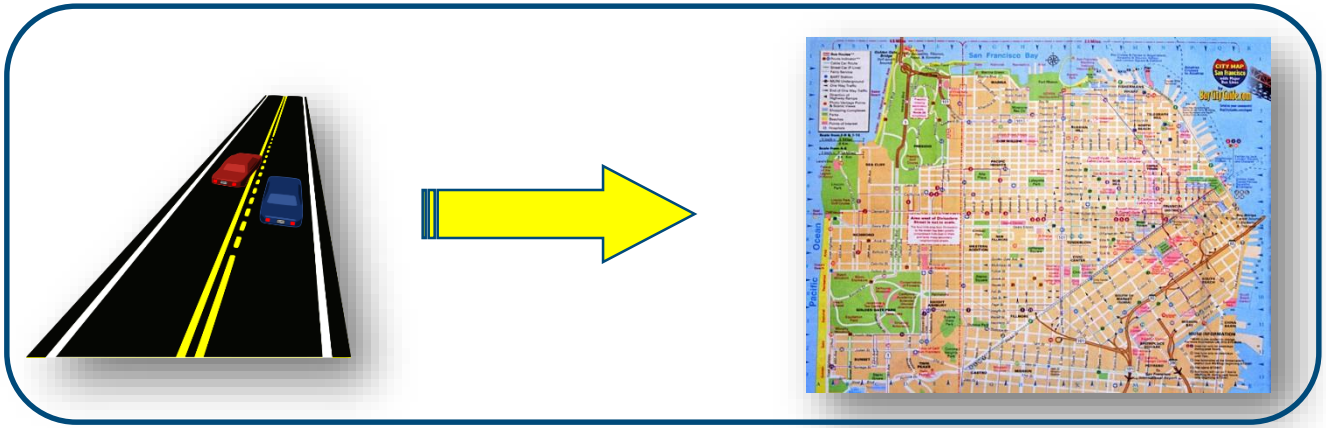
Bispecific Molecules: 1 + 1 > 2

- Simultaneously modulating two targets renders an extra dimension of therapeutic possibilities



- Two epitopes on one target
- Two targets on one cell
- Two targets in the same pathway
- Two targets in different pathways
- New mechanisms
  - T cell redirecting, BBB penetration…

↑ Efficacy

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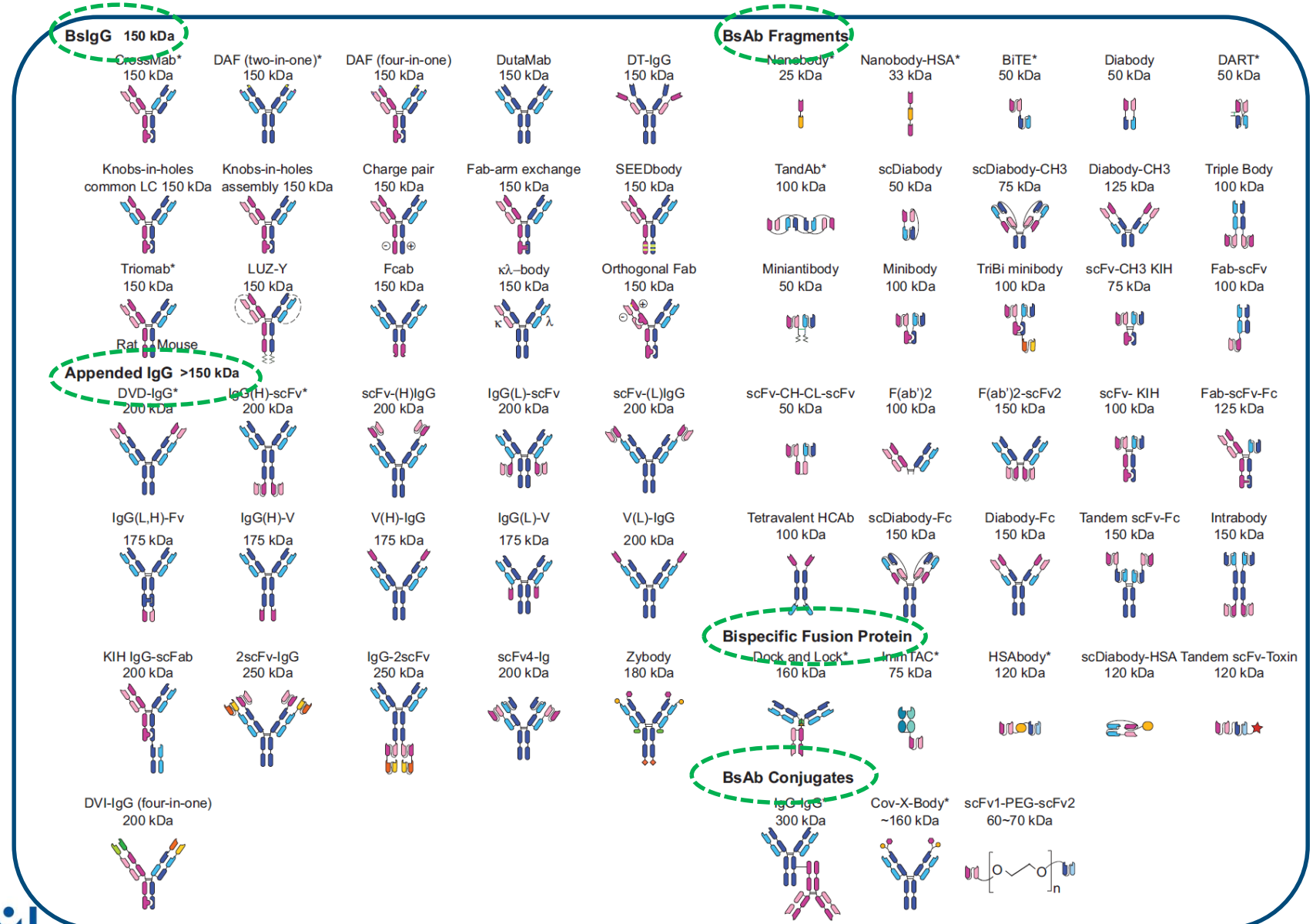
Bispecific: a Multitude of Structural Diversity



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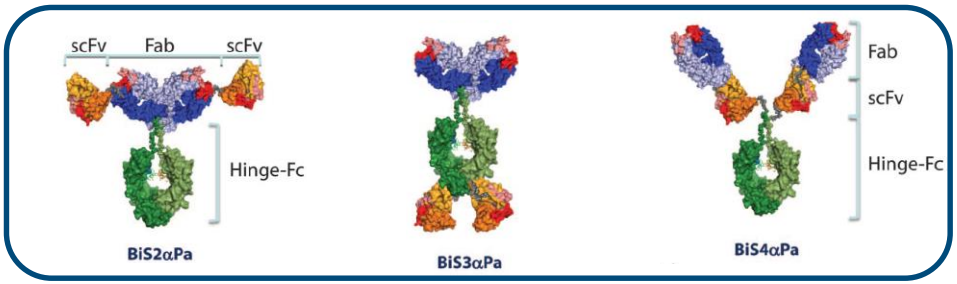
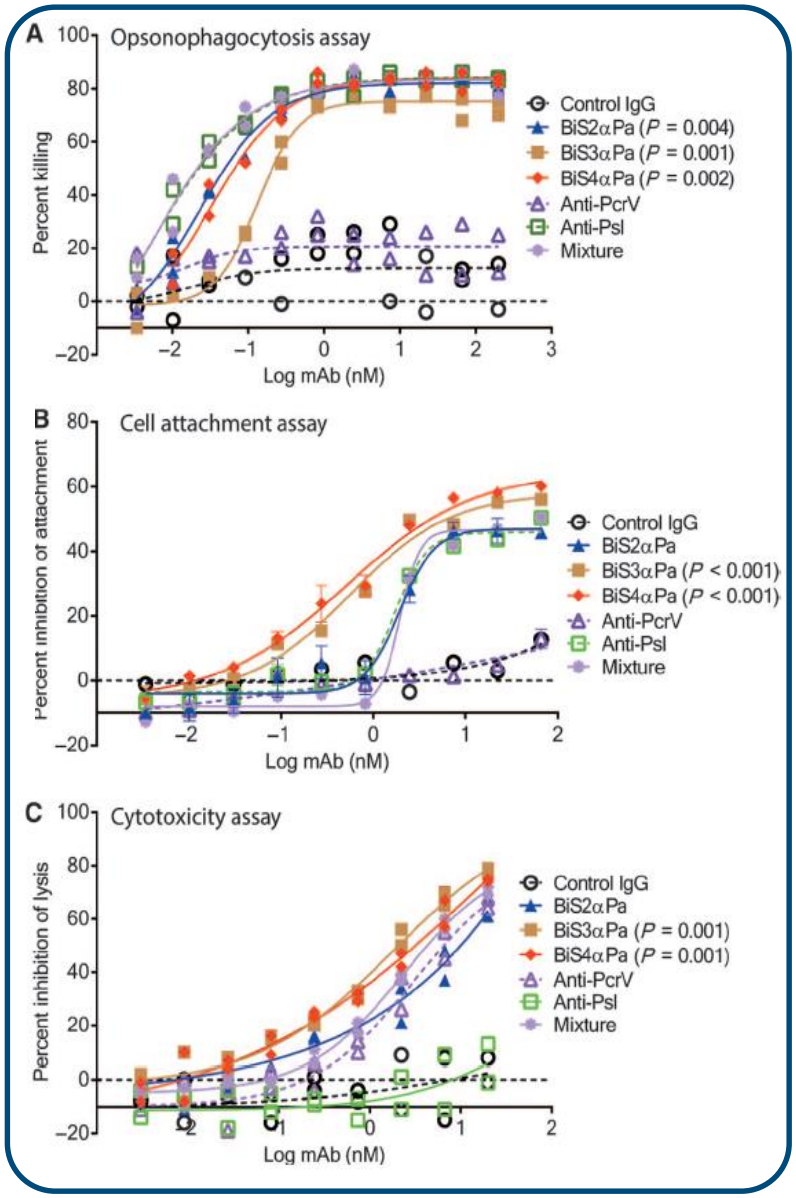
Spiess C eta al, *Mol Immunol* 2015; 67: 95-106

Scaffold-Dependent Activity of BsAb > Mixed mAbs

- BsAb targeting *Pseudomonas aeruginosa*
- Anti-PcrV to prevent toxin injection into host cells
  - High affinity for low density target
- Anti-Psl to promote OPK and block cell adherence
  - Low affinity for high density target



	Mediate OPK	Inhibit Cell Attachment	Inhibit Cytotoxicity
Anti-Psl			
Anti-PcrV			
Mixture			
BiS2Ab			
BiS3Ab			
BiS4Ab MEDI3902			



DiGiandomenico A eta al, Sci Transl Med 2014;6:262ra155

Gao C, AAPS 2015

Clinical Pharmacology Considerations for BsAb

- Target evaluation
  - Disease association
  - Expression and turnover rate; up/down-regulation
- Affinity
  - Tug war between two targets
  - Optimal affinity ≠ high affinity
- PK
  - Serum half-life vs. tissue penetration
  - Interspecies scaling
- (Immunogenicity)
- Dose
  - Hook Effect
- (PD Biomarker)

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Systems Pharmacology: MEDI3549 (Ang2-TNF bispecific)

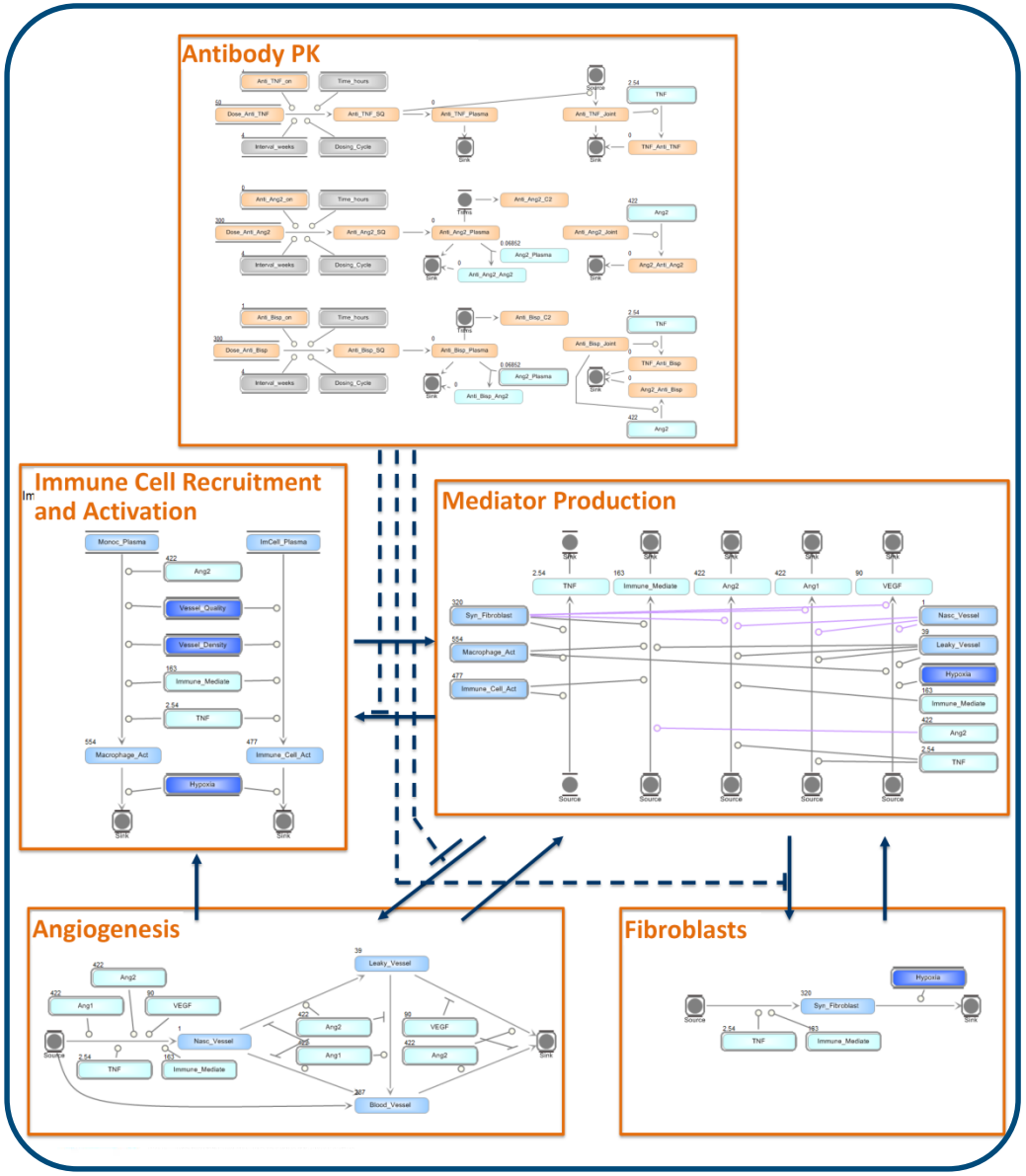
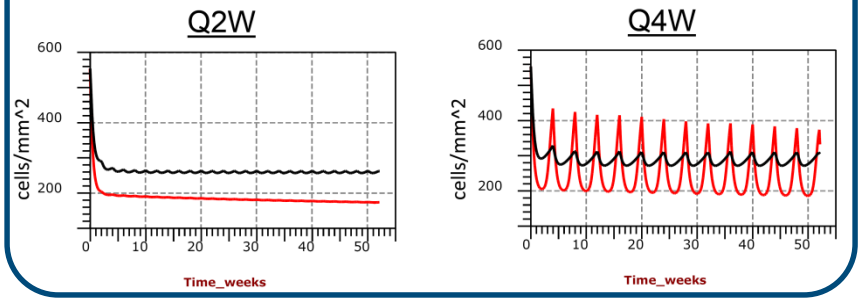
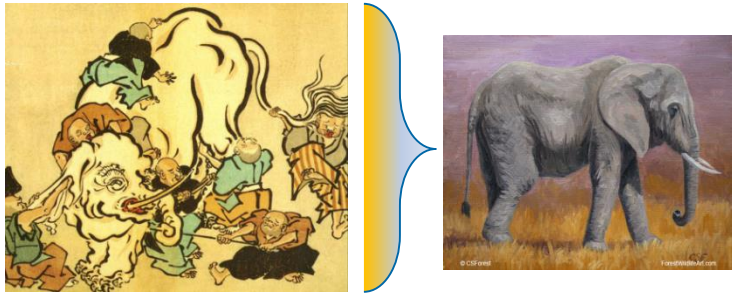


Table 1: Summary of pathophysiological differences explored with three virtual patients.

	VP1	VP2	VP3
TNF effect on Ang2	No	Yes	Yes
Leaky vessel conversion to normal	No	Yes	Yes
VEGF effect on normal vessels	Yes	Yes	No
Matches steady-state data	Yes	Yes	Yes
Matches Golimumab effect on cell numbers	Yes	Yes	Yes
Golimumab effect on leaky vessels	Reduced growth	Significant decrease	Significant decrease
Golimumab effect on mature vessels	Regression	Stabilization	Increase

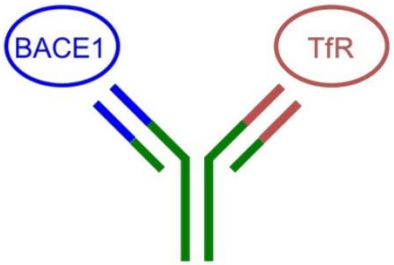


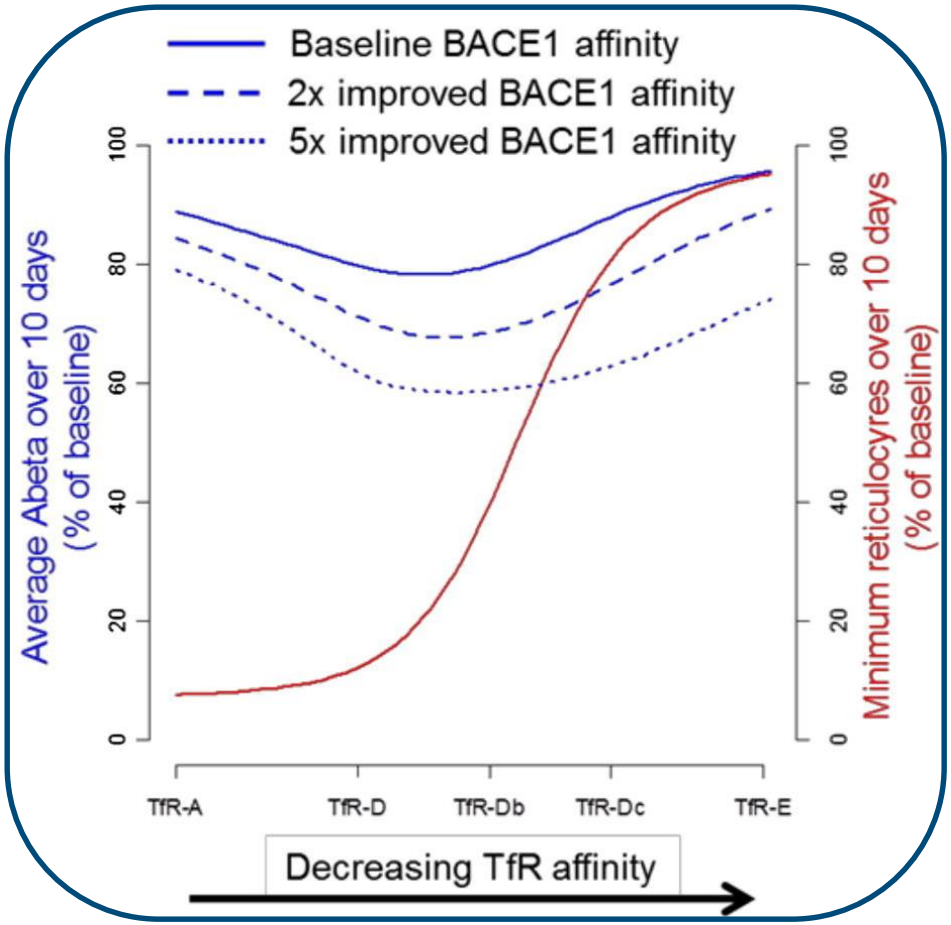


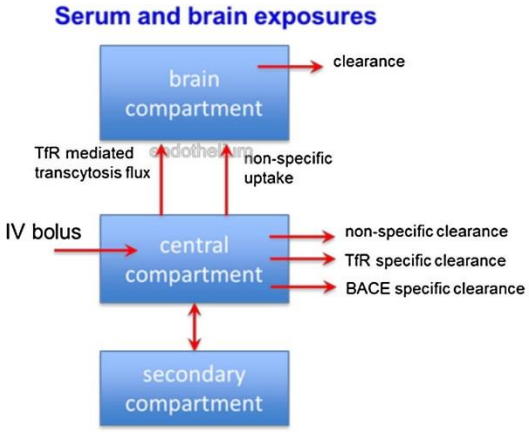
Yan L, ASCPT 2014

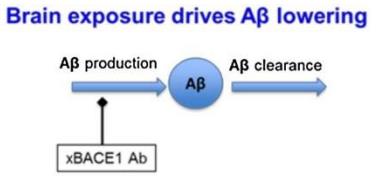
Bispecific Molecule: Optimal Affinity ≠ High Affinity

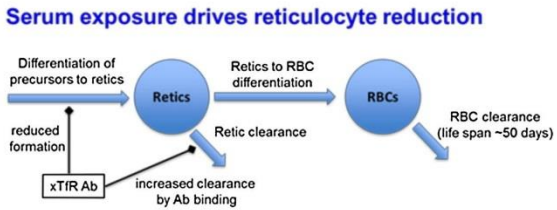
- Transferrin Receptor (TfR)
  - To enhance BBB uptake
- β-secretase 1 (BACE1)
  - To reduce amyloid β peptides







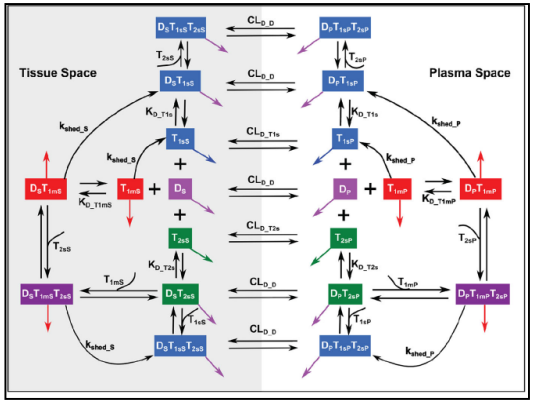


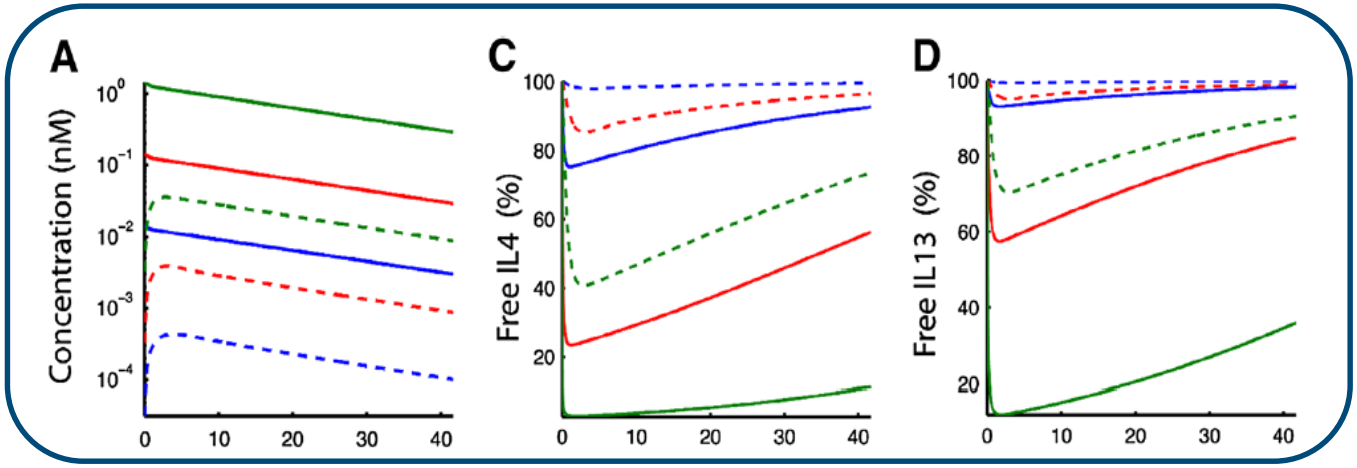


Gadkar K eta al, *Eu J Pharmceutics Biopharm* 2016; 101: 53-61

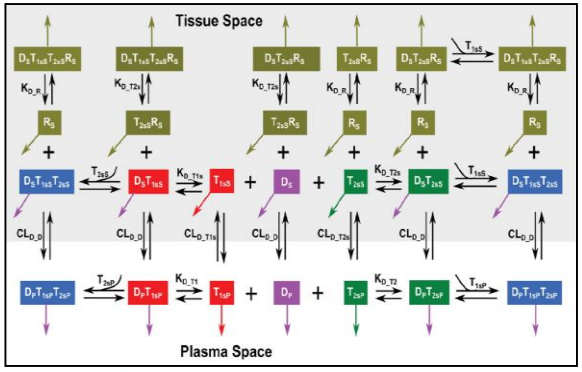
Bispecific Antibody: PK-PD

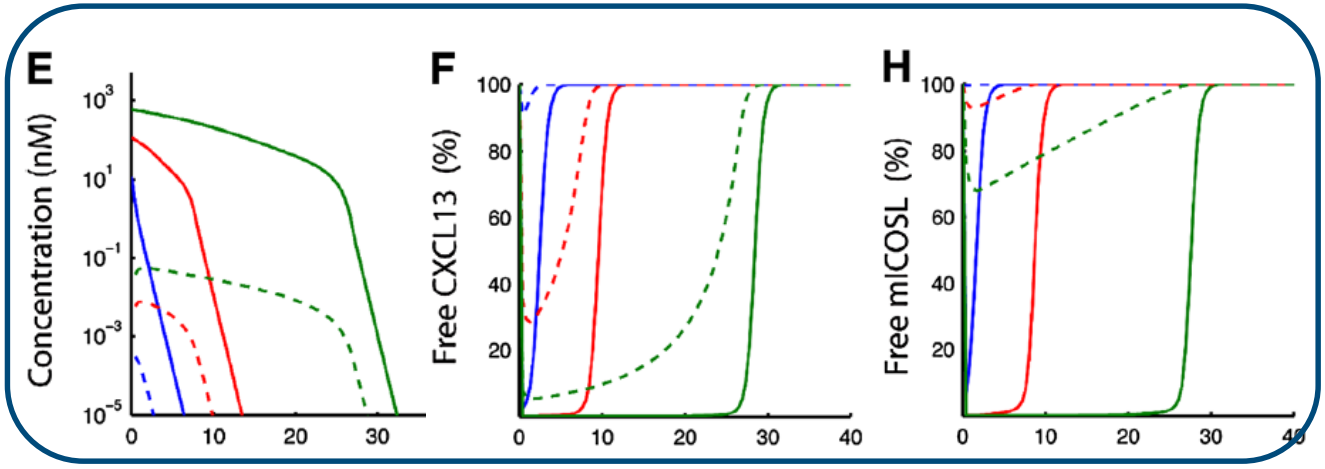
- BsAb anti-IL4/anti-IL13 (soluble targets)





- BsAb anti-CXCL13IL4/anti-ICOS (soluble/membrane-bound)





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Chudasama V eta al, *J Pharmacokinet Pharmacodyn* 2015; 42:1-18

FIH Dose Selection: No Relevant Animal Species for Tox

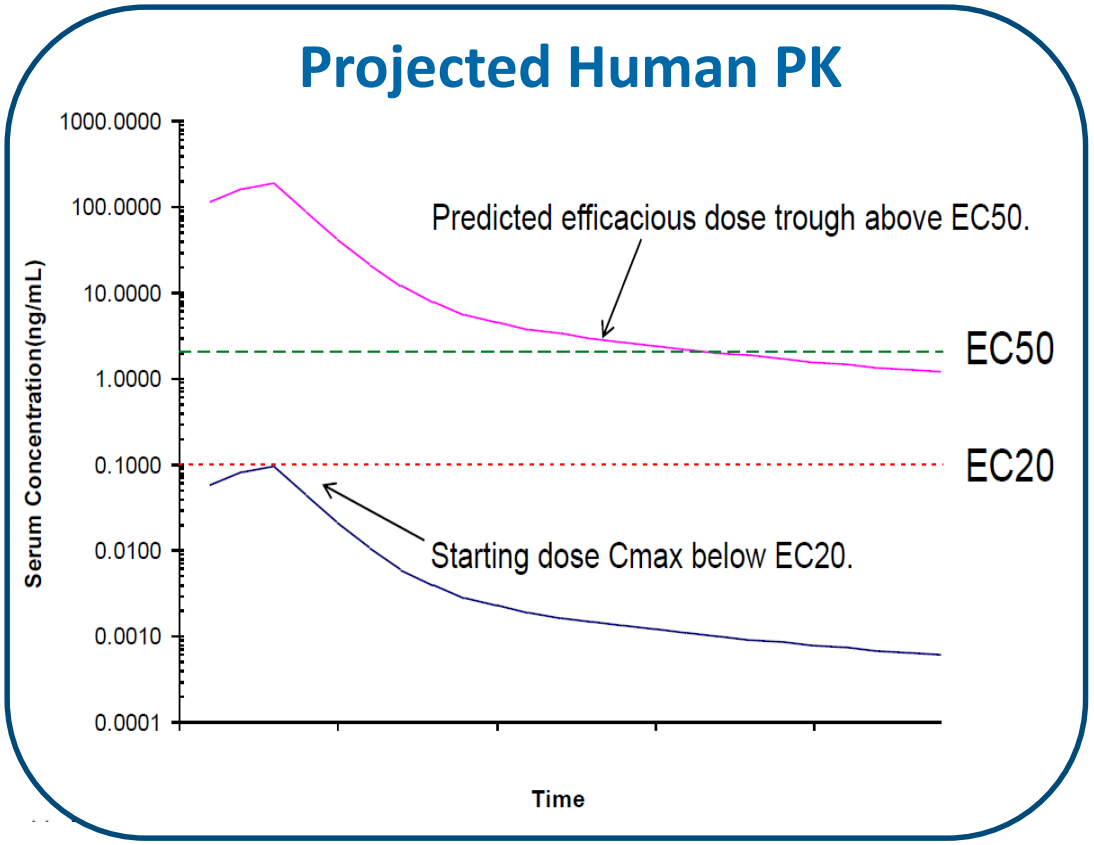
- M&S based MABEL Dose Selection

In Vitro Activity

- T Cell Activation
- Cytotoxicity
- Cytokine Release

NHP PK

- Single-dose study
- Population modeling
- Allometric scaling



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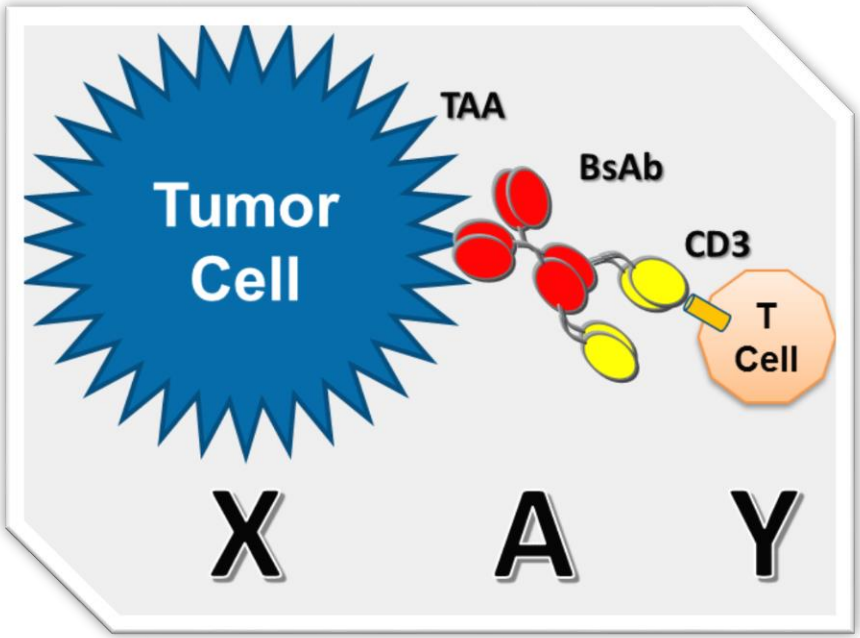
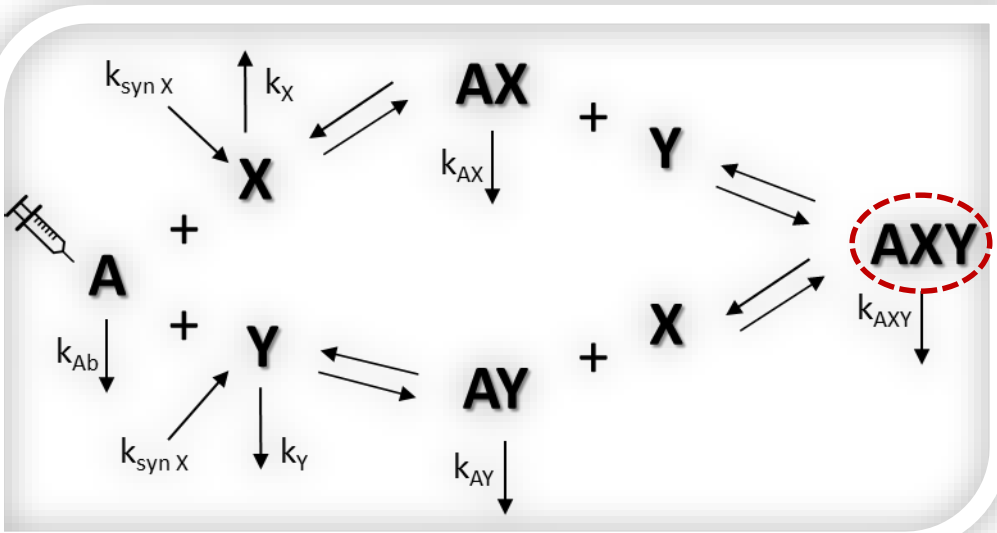
Bispecific Antibody: Dose-Response Simulation #1



Model Diagram



- A: BsAb
- X: TAA
- Y: CD3

- AX: BsAb-TAA
- AY: BsAb-CD3
- AXY: BsAb-TAA-CD3 triplex
  - Primary interest for simulation (response)

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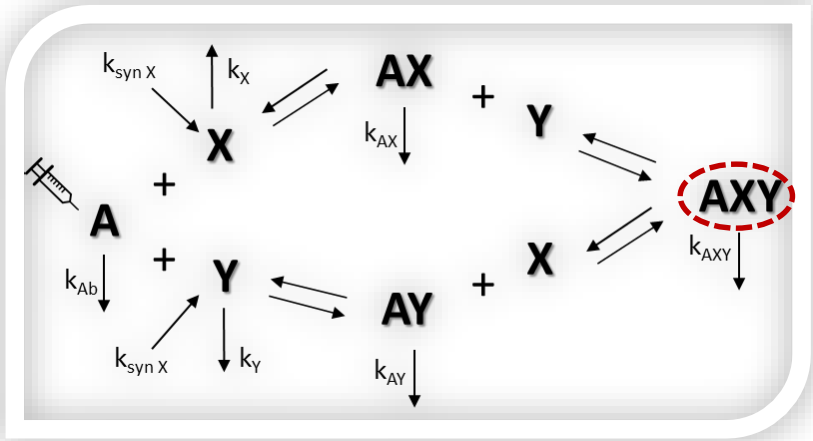
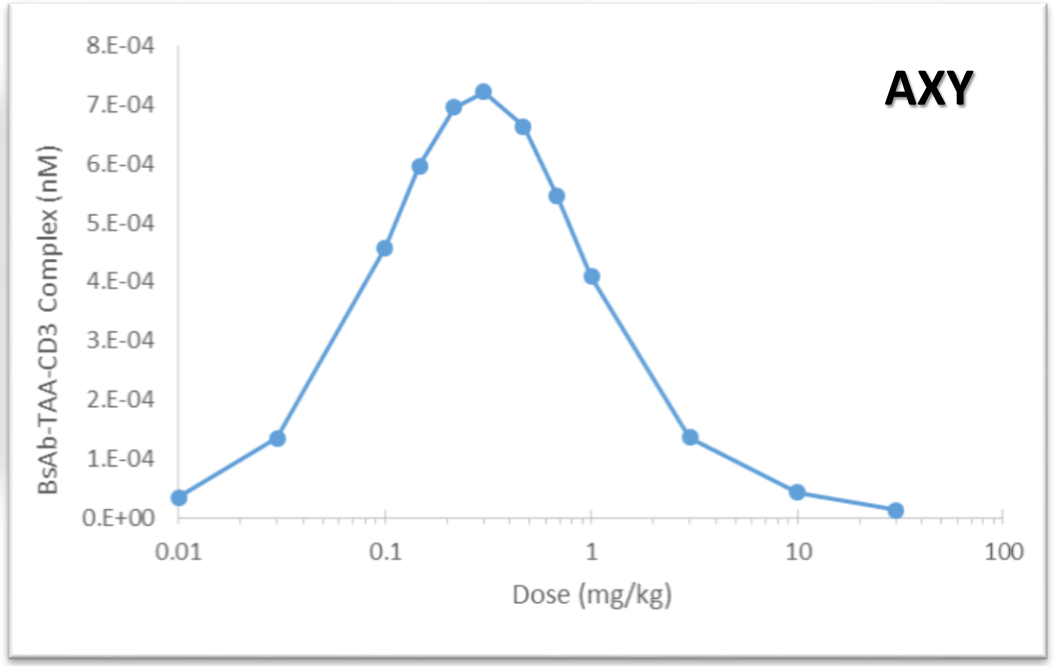
Bispecific Antibody: Dose-Response Simulation #1





- **Prozone Phenomenon (Hook Effect)**
  - Excess BsAb impedes BsAb-TAA-CD3 triplex formation
  - Majority forms are AX and AY, with minimum free X and Y for further binding
- **For illustration purpose only**
  - Tissue penetration is not considered

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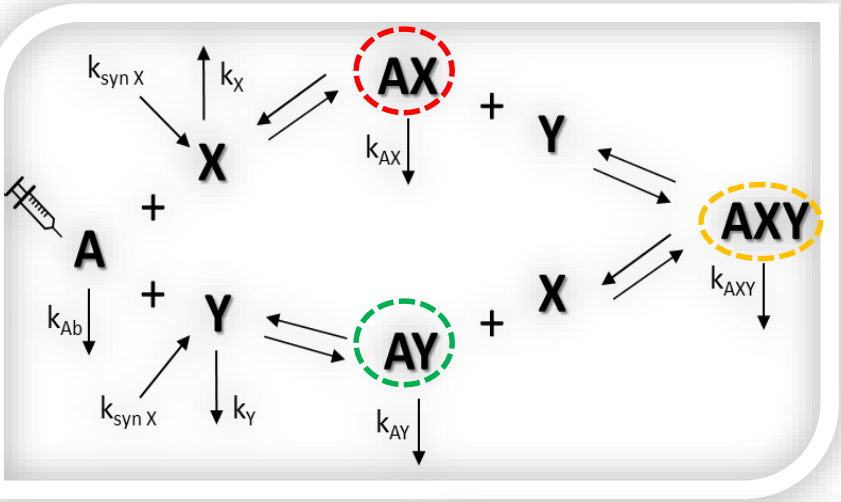
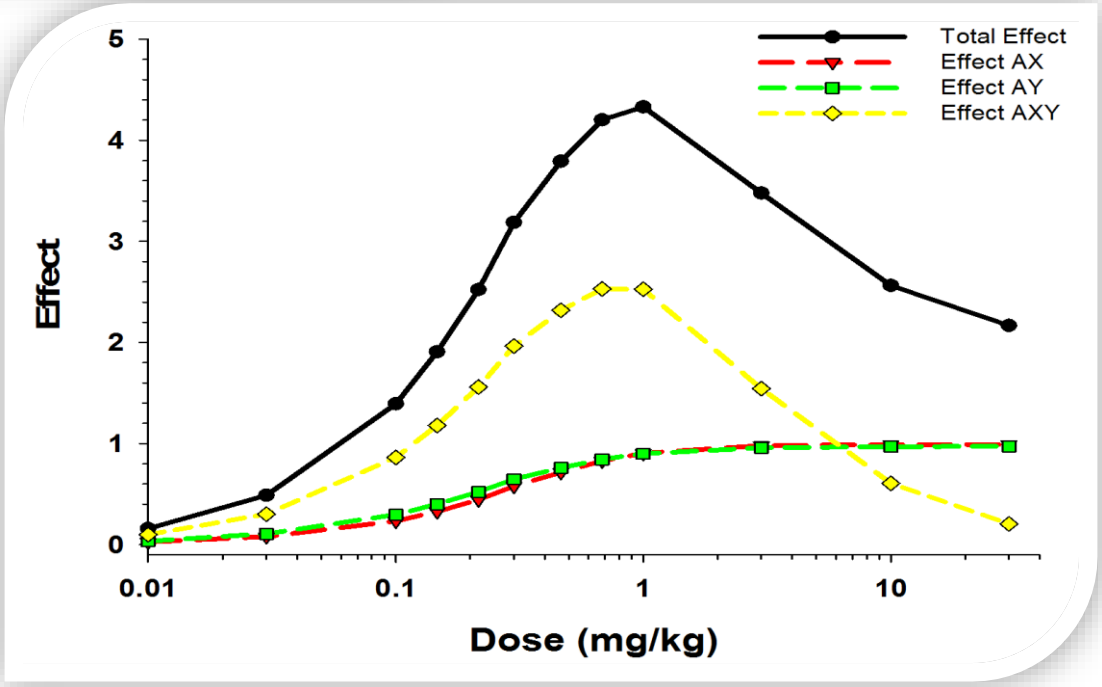
Bispecific Antibody: Dose-Response Simulation #2



- **Effect $_{total}$ = E_{AX} + E_{AY} + E_{AXY}**
- **Synergistic efficacy**
  - E_{max} = 1 for AX & AY; E_{max} = 6 for AXY
- **BsAb:** 5 nM Kd for X, 3 nM for Y
- **X:** 0.5 h $t_{1/2}$, 0.1 nM baseline
- **Y:** 15 h $t_{1/2}$, 0.3 nM baseline



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Summary

- Bispecifics introduces a new dimension for biotherapeutics
- Purpose-engineered for optimal activity
  - Mechanism, target, scaffold, affinity, FcγR, ADC…
- Potential development challenges
  - Affinity tuning
  - Manufacturing and characterization
  - PK, Tox and Immunogenicity assessments
  - Exposure-response relationship
- M&S may facilitate the design and development of bispecific molecules

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