



# Affimer Therapeutics: A Novel Human Scaffold for the Generation of Bi-specific Molecules

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Chief Scientific Officer

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# Avacta Life Sciences

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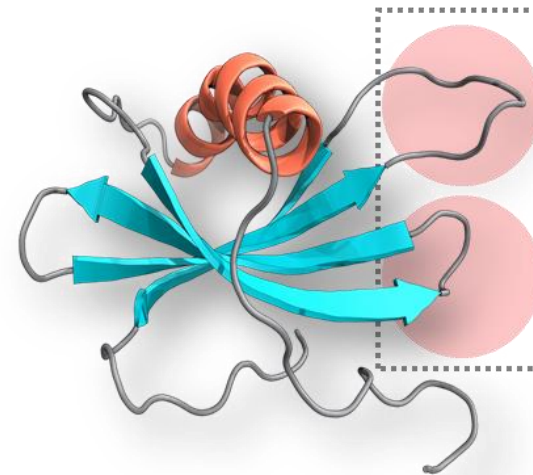
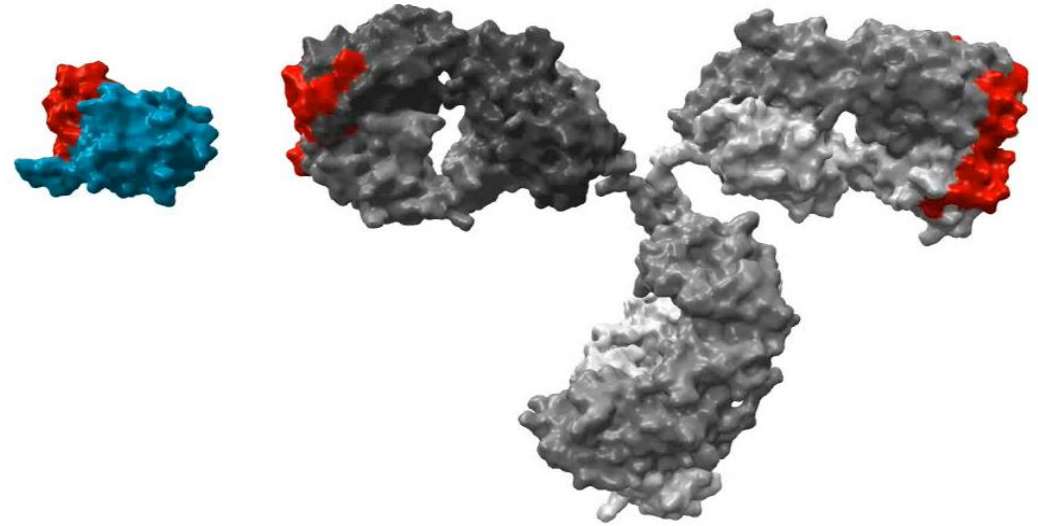
- Avacta Life Sciences (AIM listed) established in 2012 to exploit Affimer IP
- Sites in Cambridge (~35 staff) and Wetherby (~40 staff)
- To date, raised £33.4 m (\$43.9m) to develop the Affimer platform
- Research collaborations and license deals with Moderna Therapeutics, LG Chem and others



# Affimer Technology

Affimer®

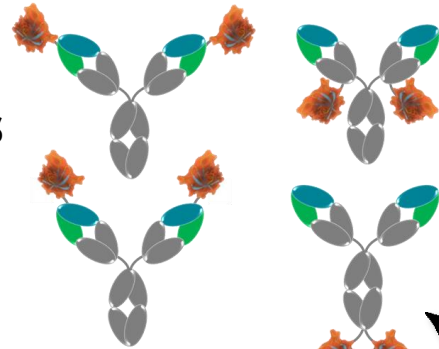
- Based on Stefin A, a human intracellular protease inhibitor
- 1/10<sup>th</sup> size of a mAb
- No disulphide bonds or post translational modifications
- Expressed at high levels
- We have freedom to operate
- Engineered to create vast peptide libraries ( $1 \times 10^{10}$ )
- Utilise phage display to identify binders



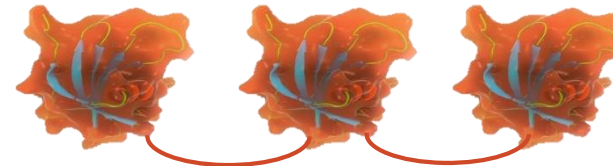
Two surface loops “display”  
the engineered peptide  
library

# Immuno-oncology Strategy

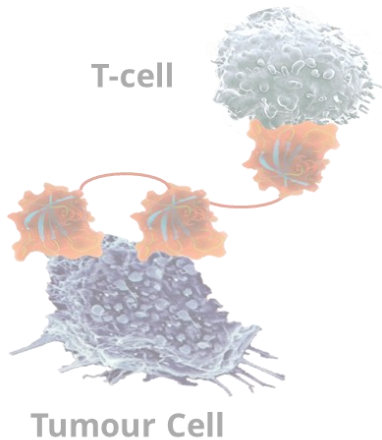
**Bispecific Antibodies  
Biparatopic Antibodies**



**Combination Therapies  
and Agonists**



**T-cell Recruitment**



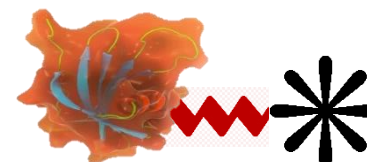
**CAR-T**



**Intratumoral  
Expression**



**Drug Conjugates**

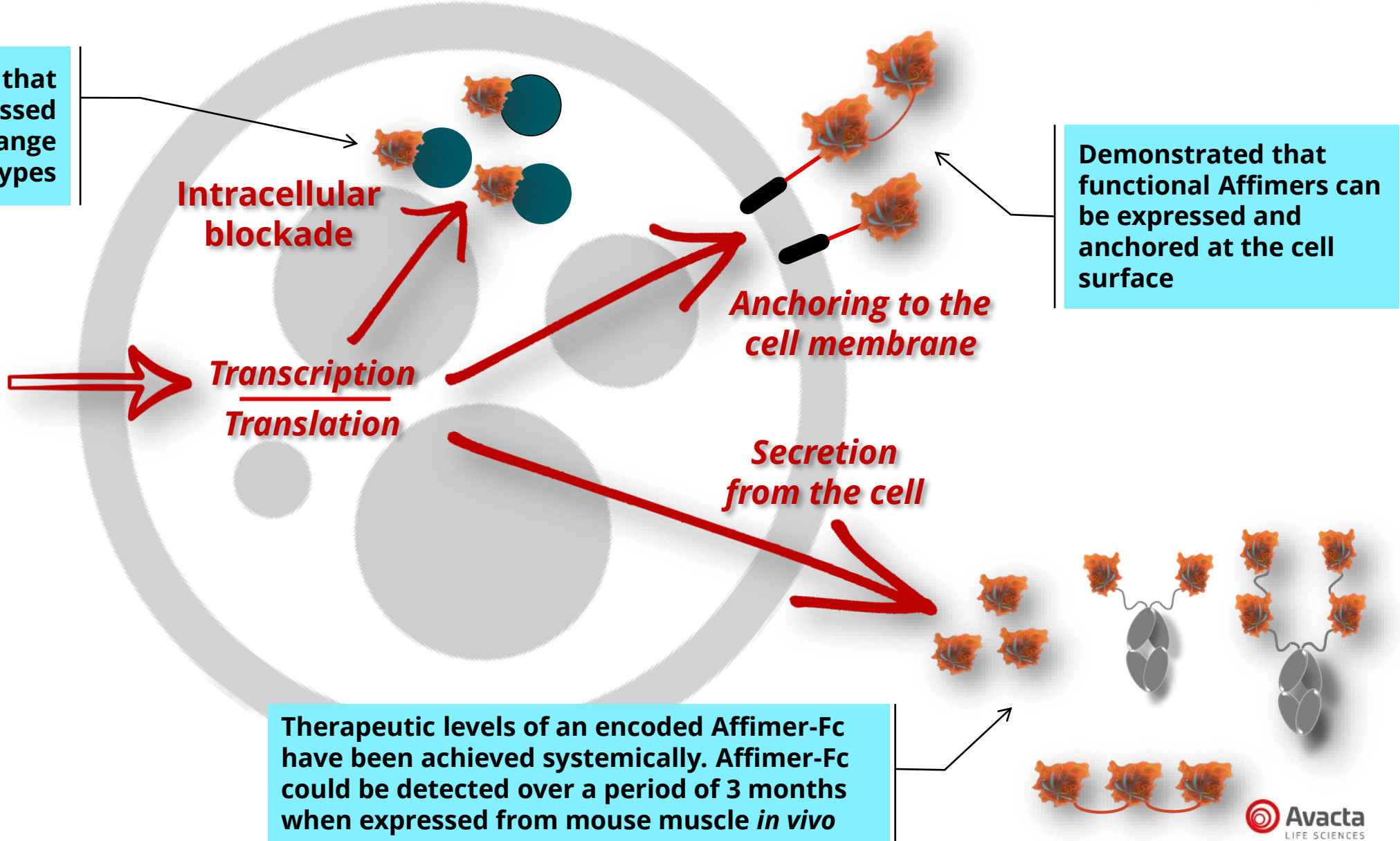


# Encoded Affimers : Examples

Affimer®

Demonstrated that Affimers can be expressed intracellularly in a range of human cell types

DNA, RNA or viral delivery of "Encoded Affimer"



Demonstrated that functional Affimers can be expressed and anchored at the cell surface

Therapeutic levels of an encoded Affimer-Fc have been achieved systemically. Affimer-Fc could be detected over a period of 3 months when expressed from mouse muscle *in vivo*

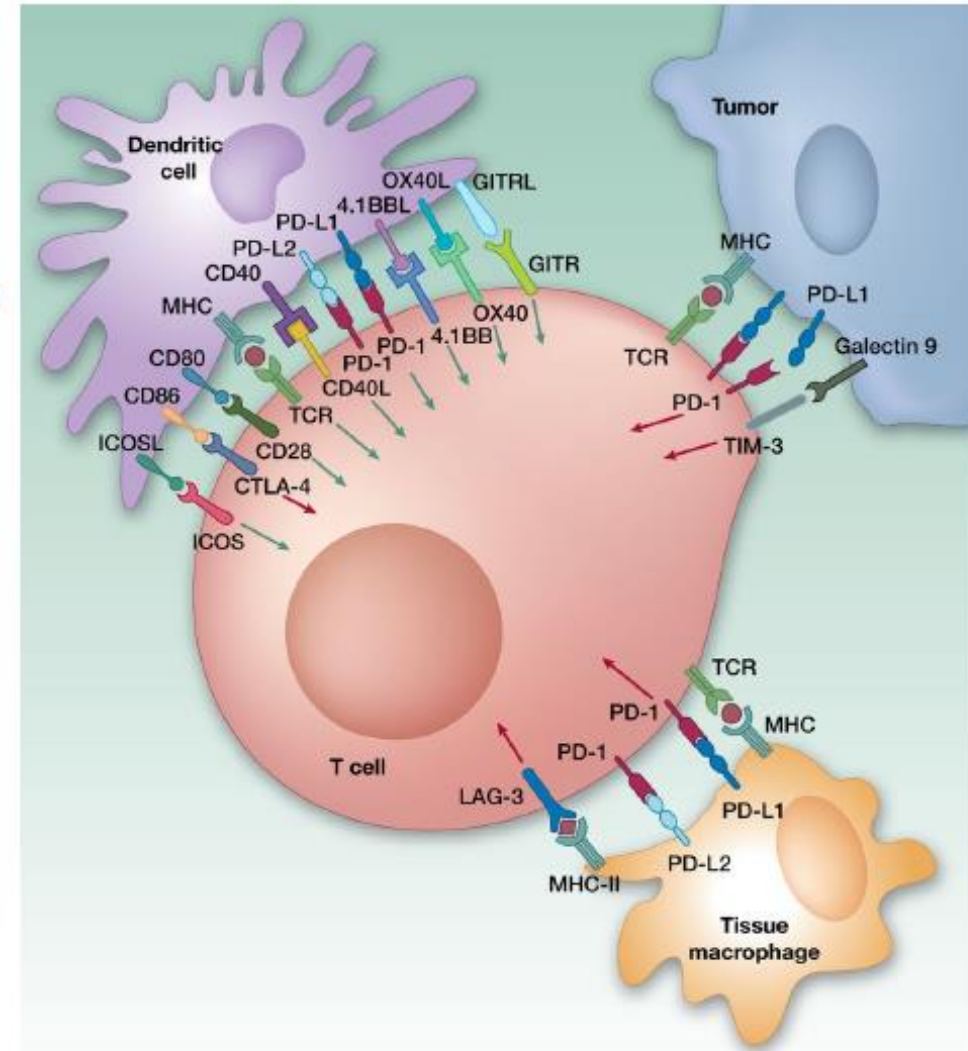
# Affimer<sup>®</sup>

Affimer<sup>®</sup>

## PD-L1 (AVA04) Programme

# Immune Checkpoint Inhibitors

- PD-L1 is an immune checkpoint receptor that helps the immune system (T cells) recognise normal cells and avoids attacking them.
- Tumour cells express PD-L1 on their surface to make themselves appear “normal” and therefore invisible to the immune system.
- Blockade of the PD-L1/T-cell (PD-1) interaction reactivates the immune system
- Numerous immune check-point proteins and they are attracting huge interest as targets for cancer immunotherapy.

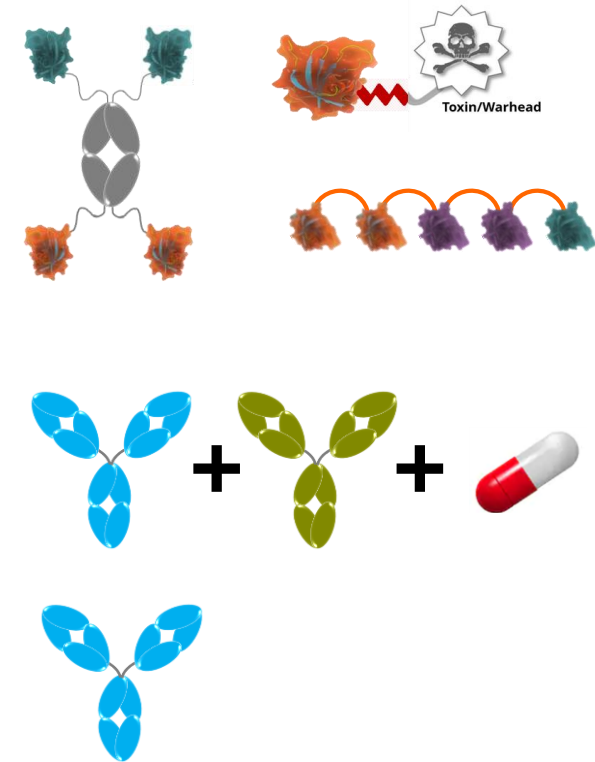
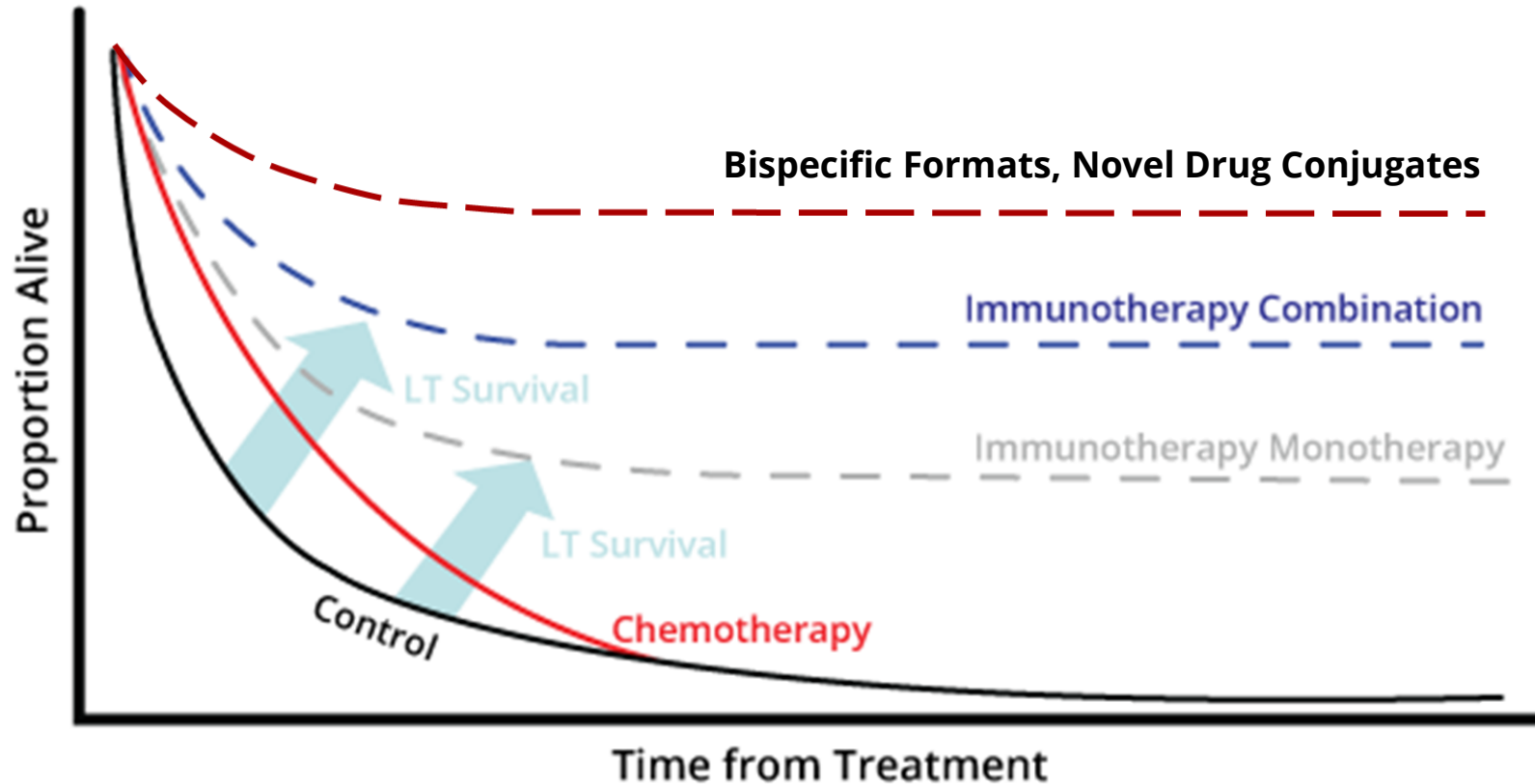


Ott, *et al.*, Clinical Cancer Research, 2013



# The Challenge for Cancer Therapies

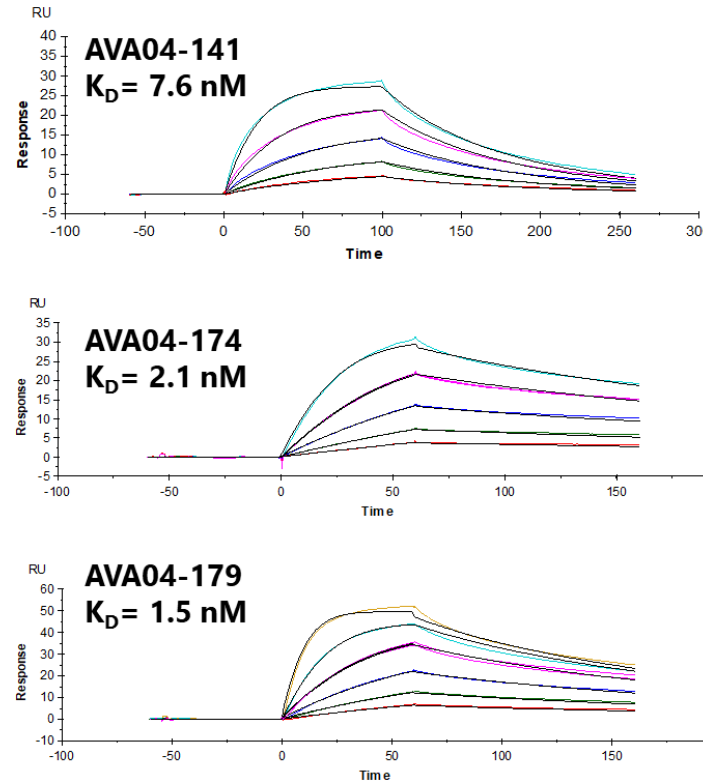
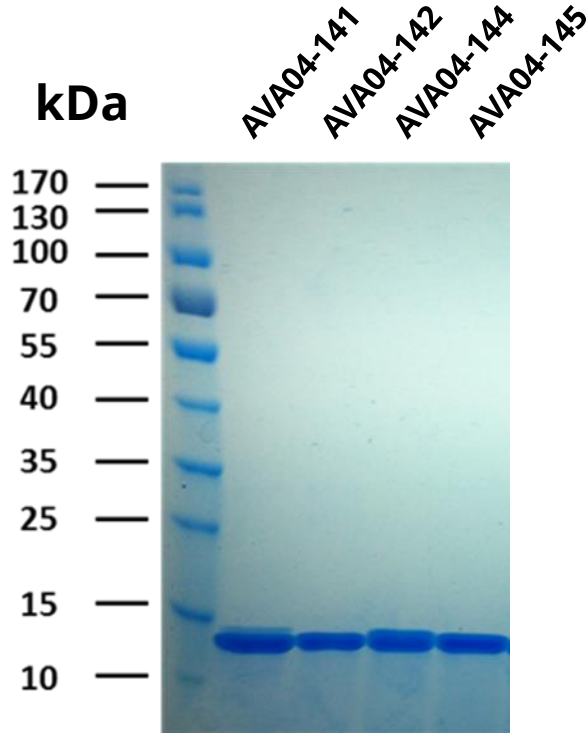
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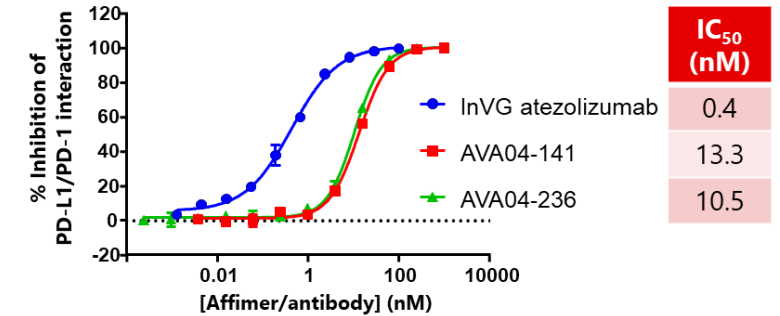
Increasing safety and efficacy?

Adapted from <https://obroncology.com/>  
Doyle, C., October 2015 Edition Vol.11, Issue 10

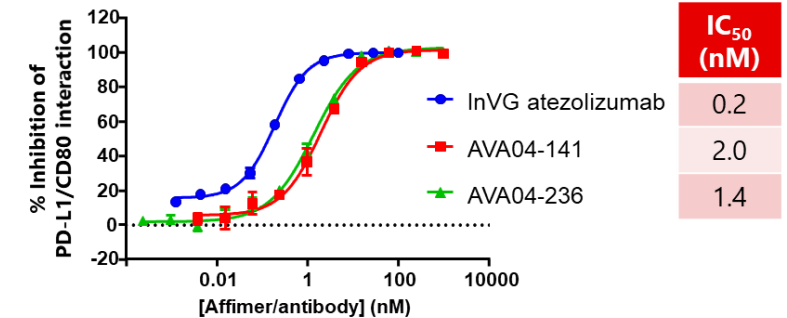
# AVA04 Lead Characterisation



PD-L1/PD-1 Competitive ELISA



PD-L1/CD80 Competitive ELISA



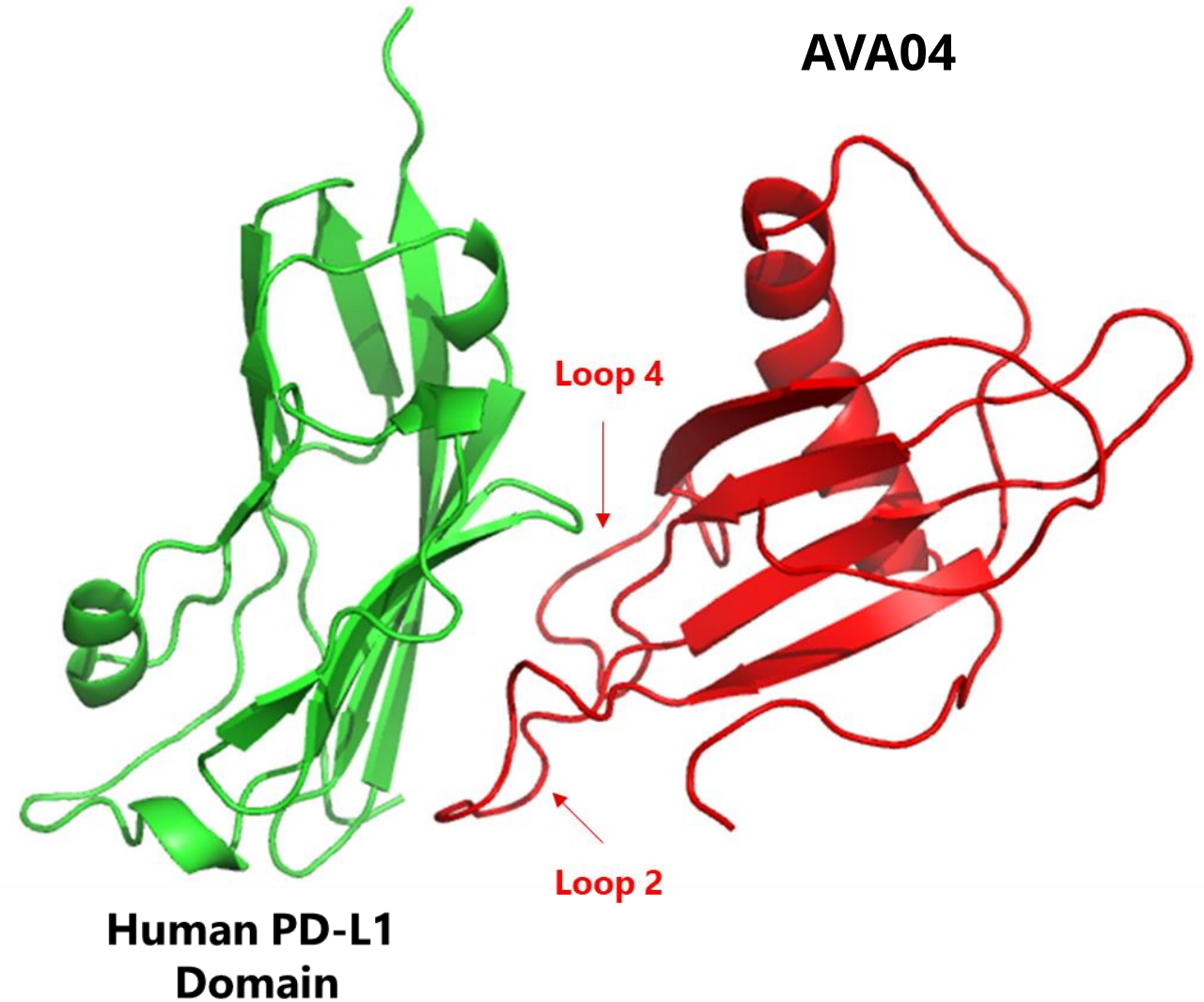
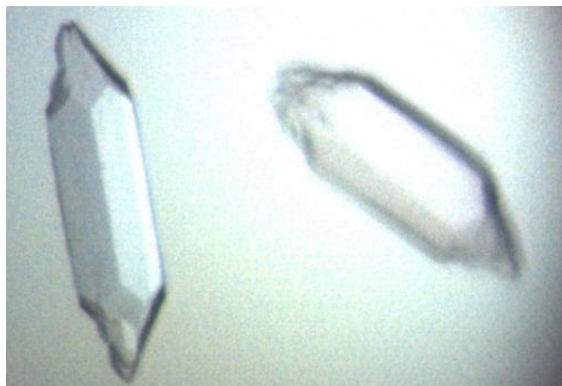
- Identified >70 unique sequences and expressed intracellularly in *E. coli*
- Ni-NTA purified (>95%) and expression levels ~200-350 mg/L at 15 ml scale
- Affimer binders compete for human PD-1/CD80 epitopes on PD-L1

# PD-L1/Affimer Protein Co-crystal Structure

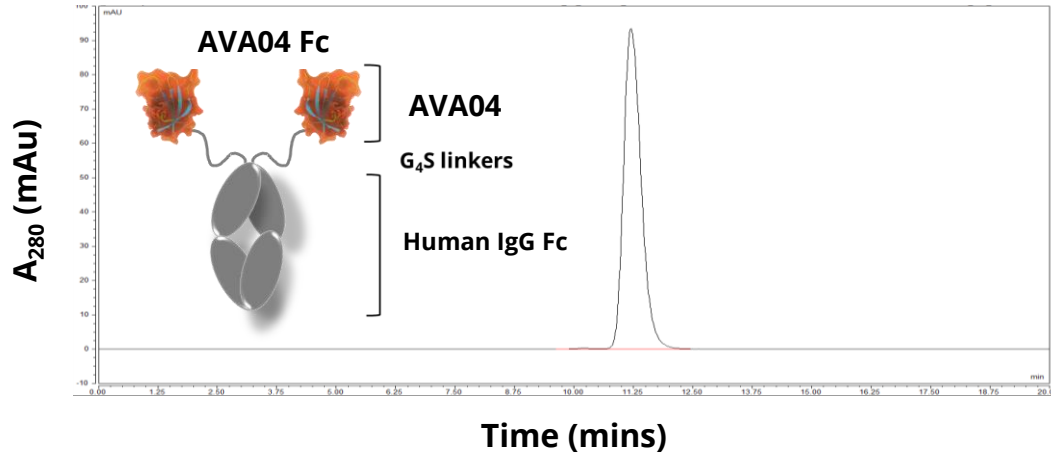
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- Co-crystallised Affimer protein with PD-L1 (N-terminal IgV domain 18-134)
- Structure solved to 2.1 Å
- Confirms main binding interactions are via loop 2
- Epitope binding site similar to Atezolizumab

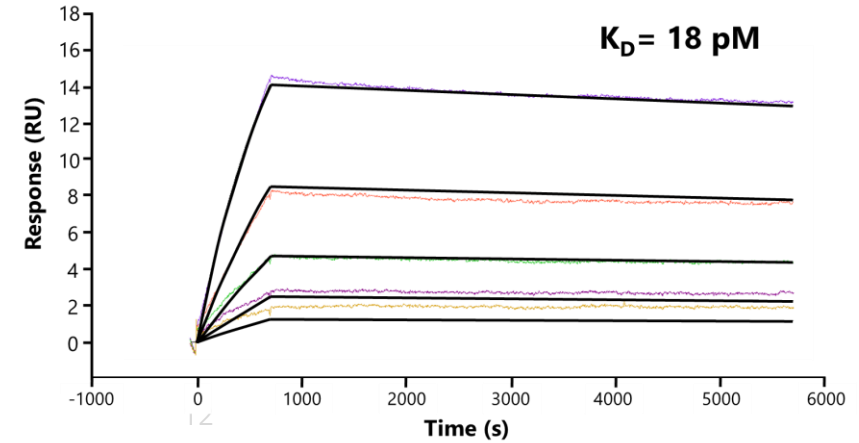
**AVA04/PD-L1 crystals**



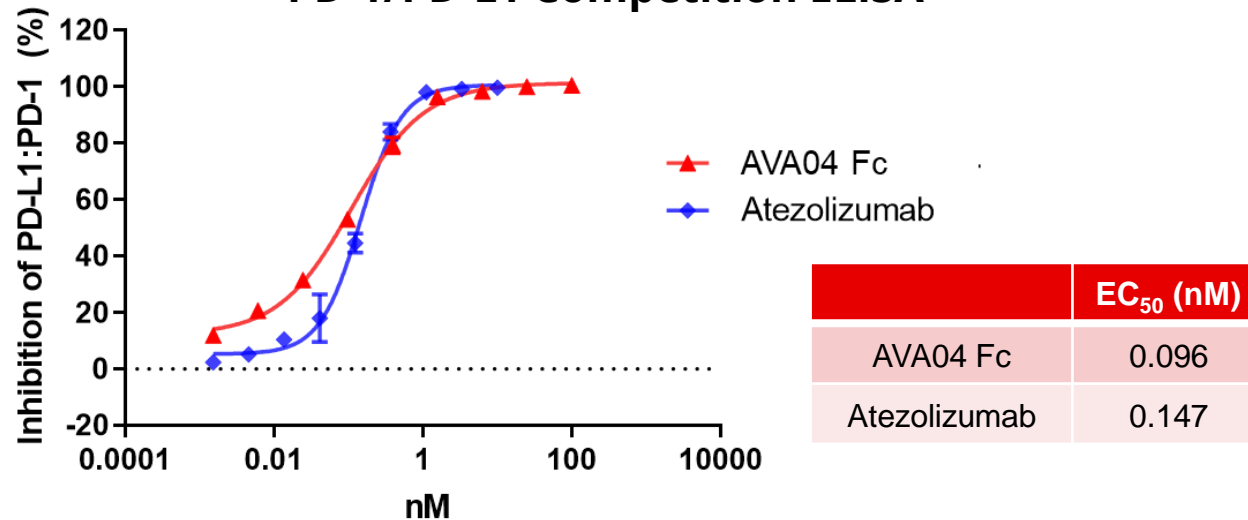
## AVA04 Fc SEC-HPLC



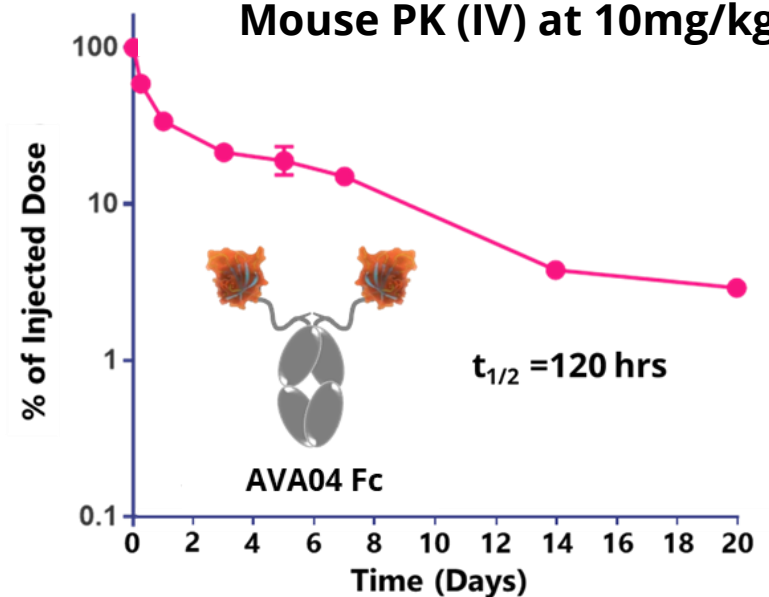
## AVA04 Fc Biacore Kinetics



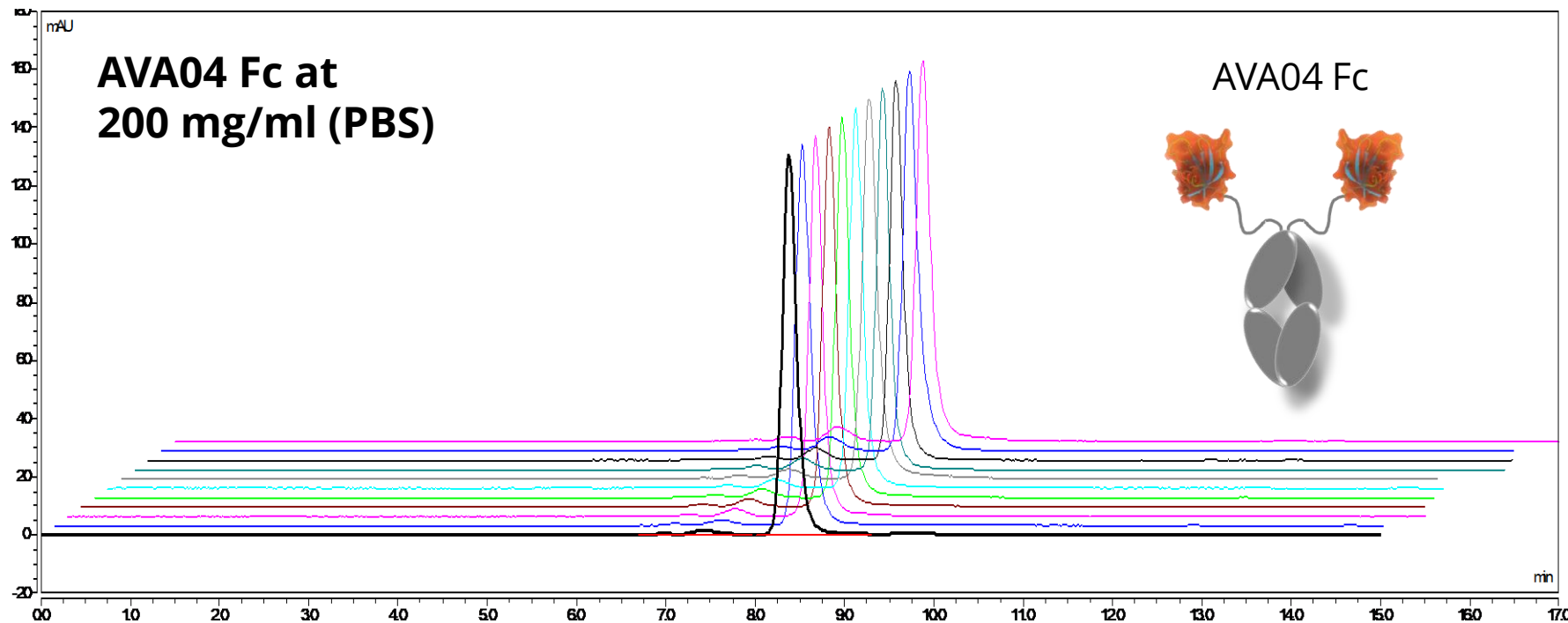
## PD-1/PD-L1 Competition ELISA



## Mouse PK (IV) at 10mg/kg



# AVA04 Fc Stability at 200 mg/ml at +4 °C

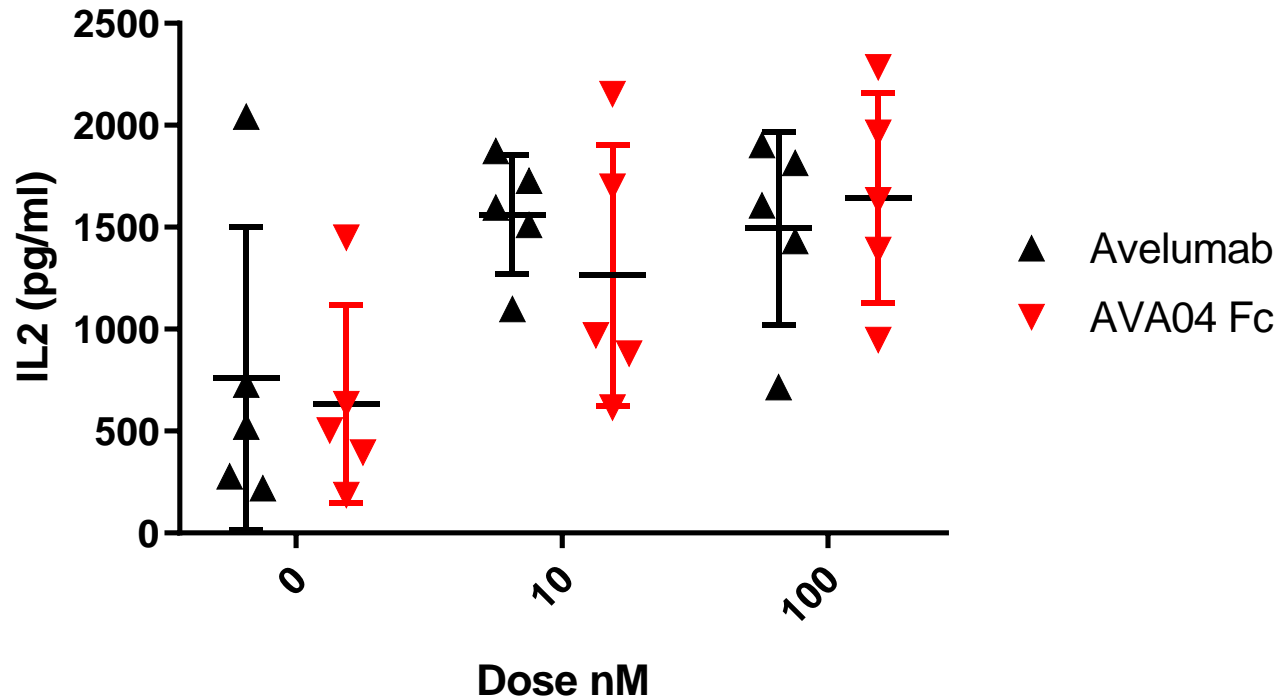


Sample	% Monomer
Day 1	97.9
Day 7	97.2
Day 21	96.0
Day 28	95.7
Day 47	95.8
2 Months	95.2
3 Months	95.7
4 Months	93.3
5 Months	92.9
6 Months	92.0
7 Months	92.2

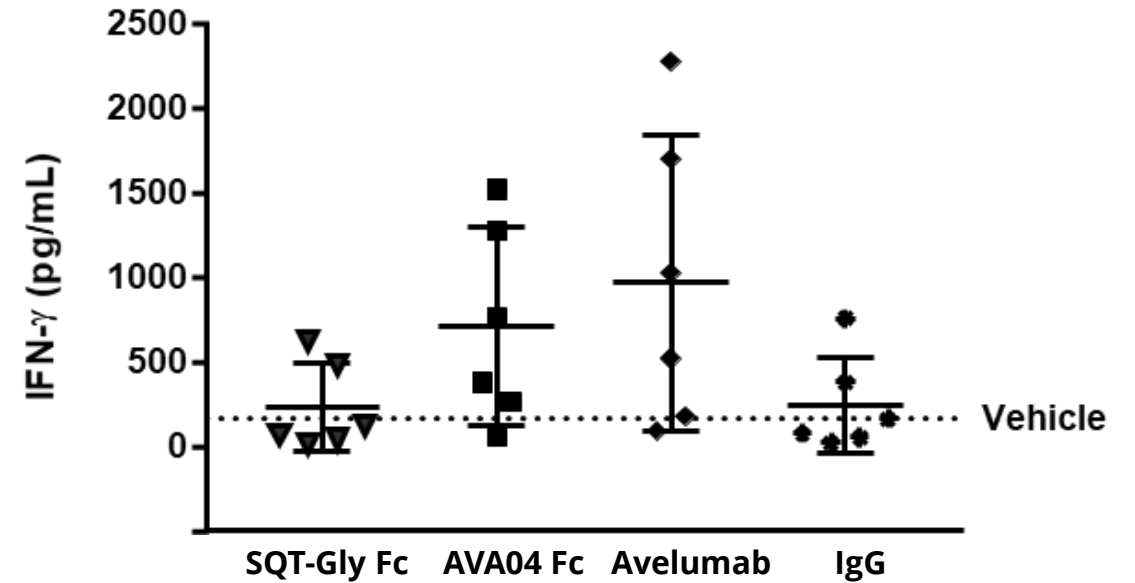
- AVA04 Fc is highly soluble and good stability at + 4 °C at high concentrations

# AVA04 Fc SEB and MLR Assays

### T-cell Activation using Staphylococcus enterotoxin B (SEB)



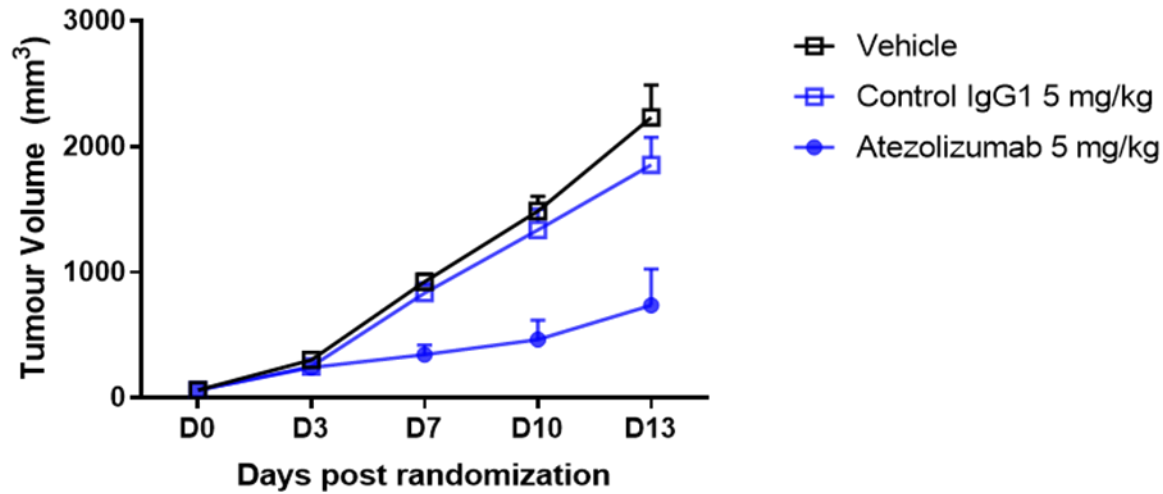
### T-cell Activation Activity by MLR



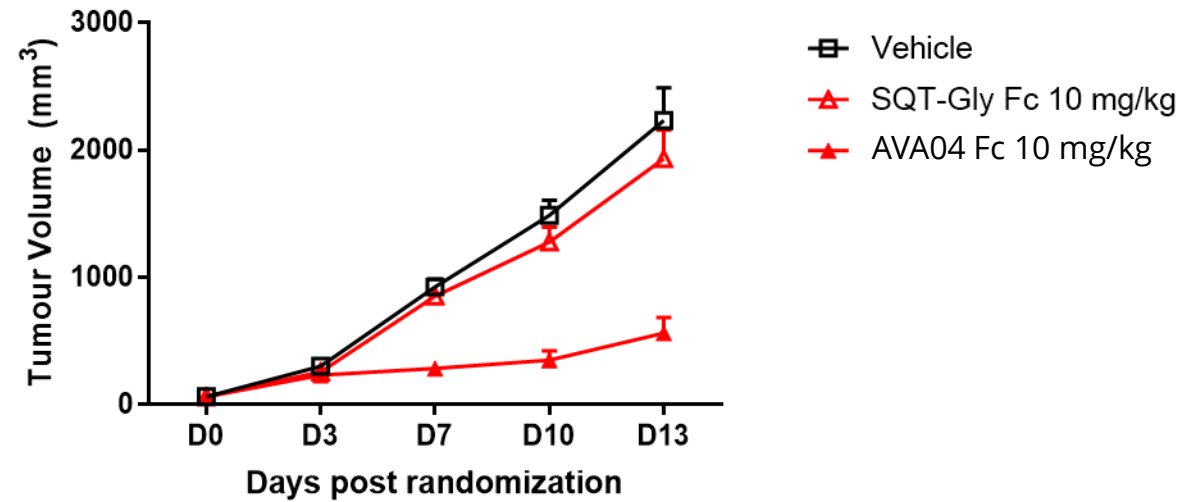
All proteins are at 70 nM

# hPD-L1 MC38 Syngeneic Model

huMC38 Syngeneic model

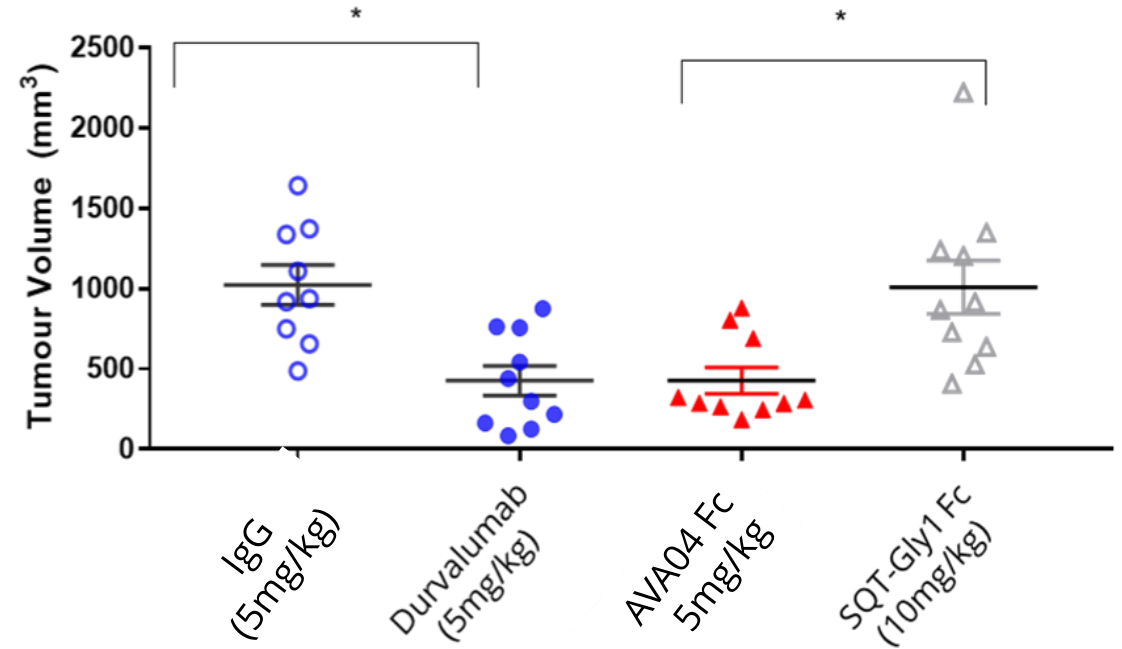
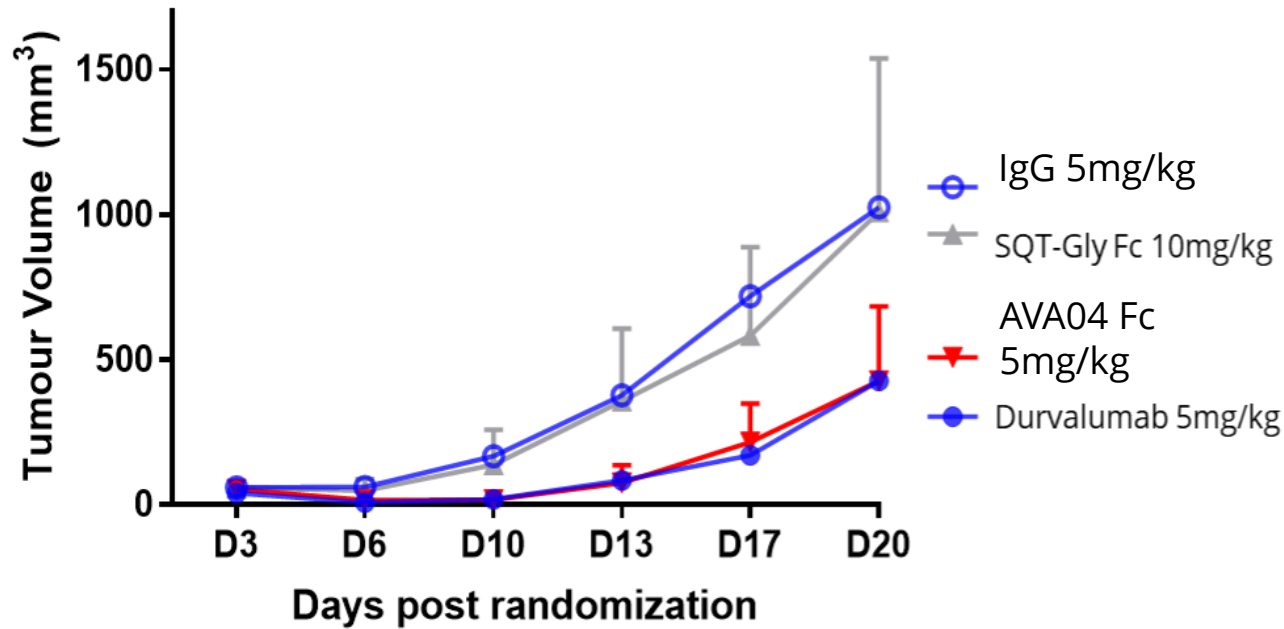


huMC38 Syngeneic model



# A375 Mouse Xenograft Model Results

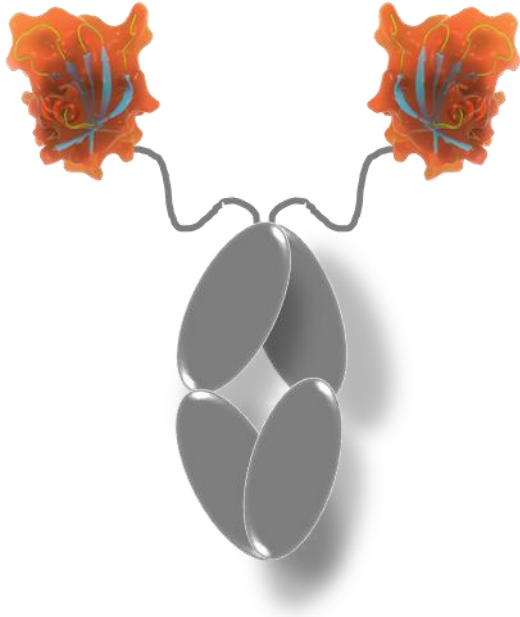
### Xenograft Model purified CD3+





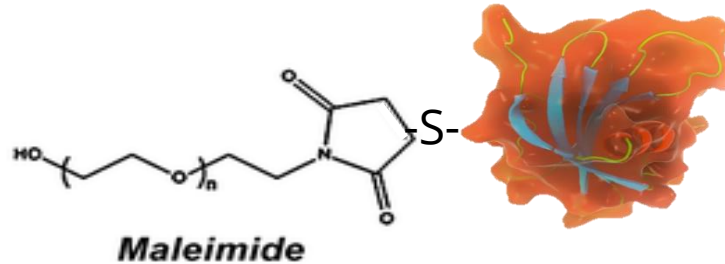
# Serum Half-life Extension Technologies

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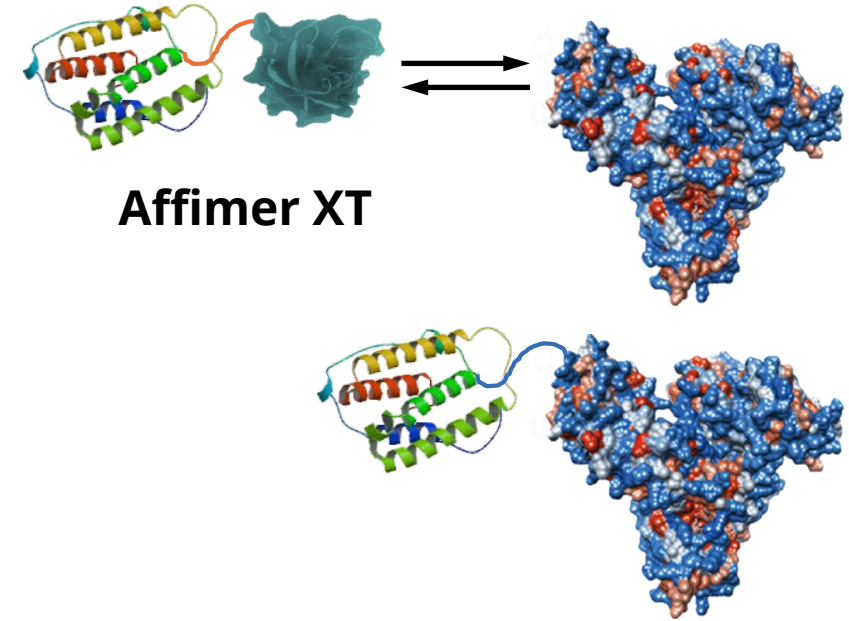
## Fc Fusions

*Utilising IgG FcRn recycling to maintain high serum levels*



## PEGylation

*Increased hydrodynamic size of the protein to prevent clearance via the kidneys*

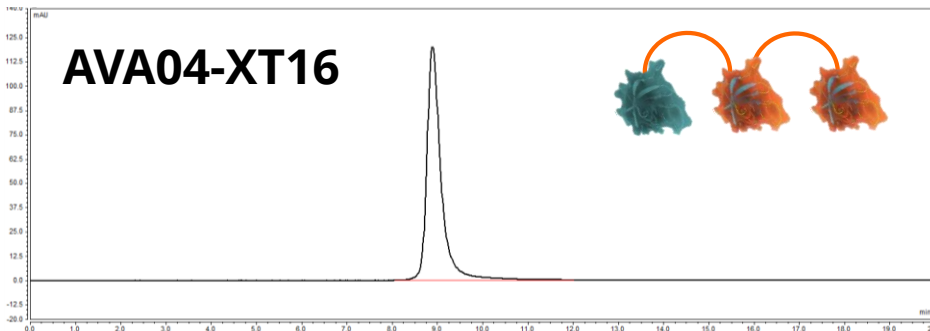
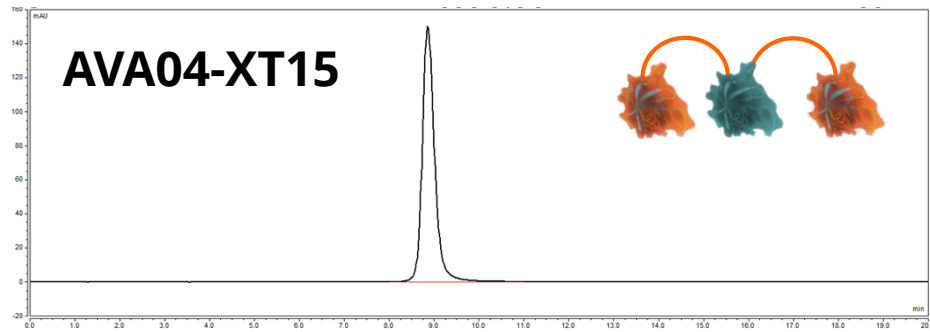
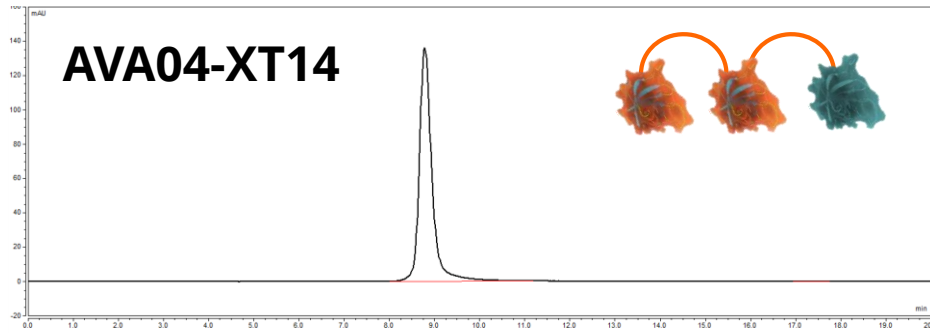


## Serum Albumin

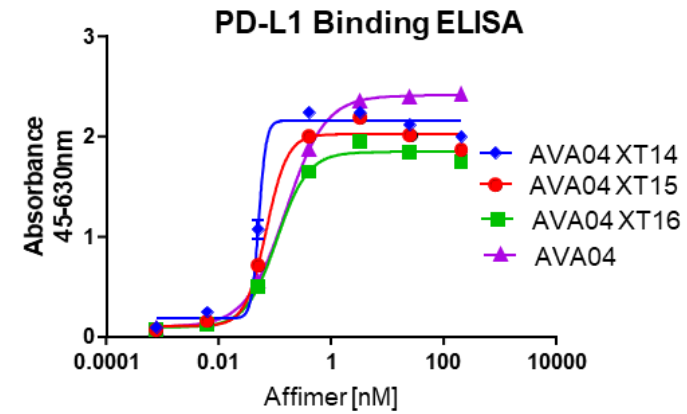
*Affimer biotherapeutic binds to SA in the circulation*

*Direct genetic fusion to SA*

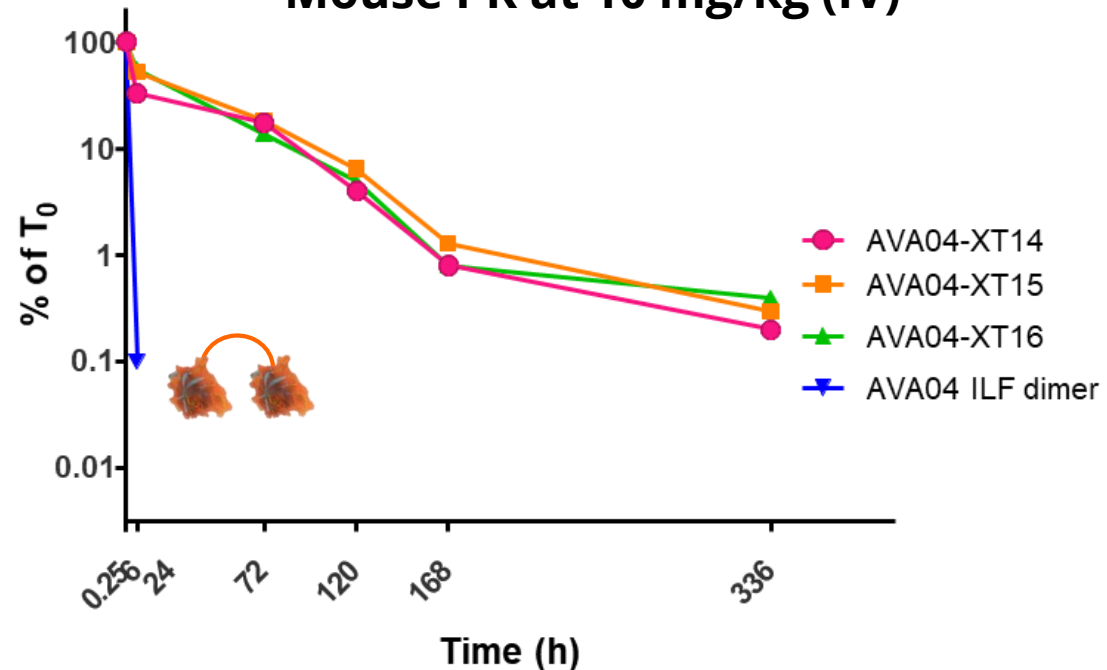
# Affimer XT Formatting and Half-Life Extension



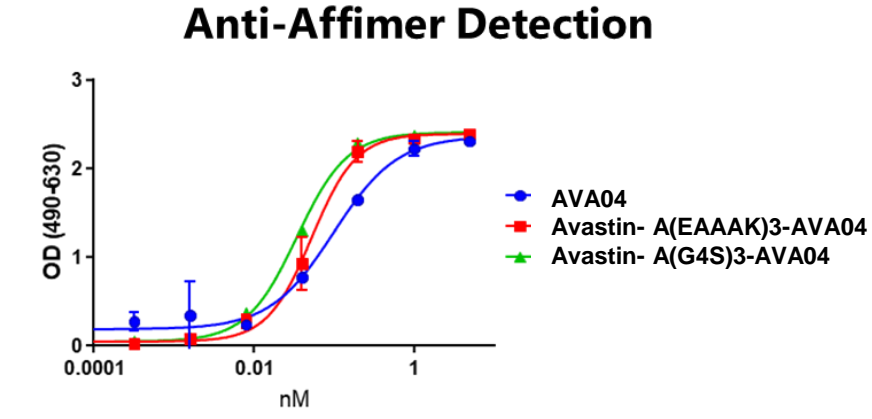
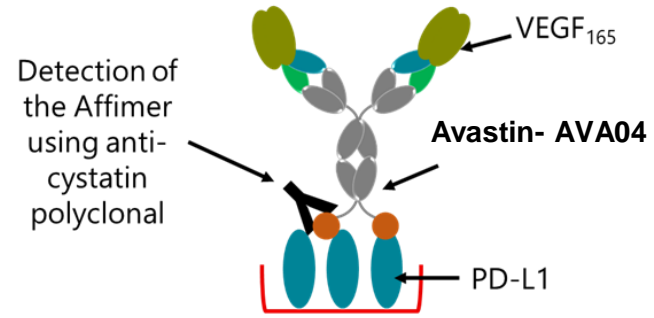
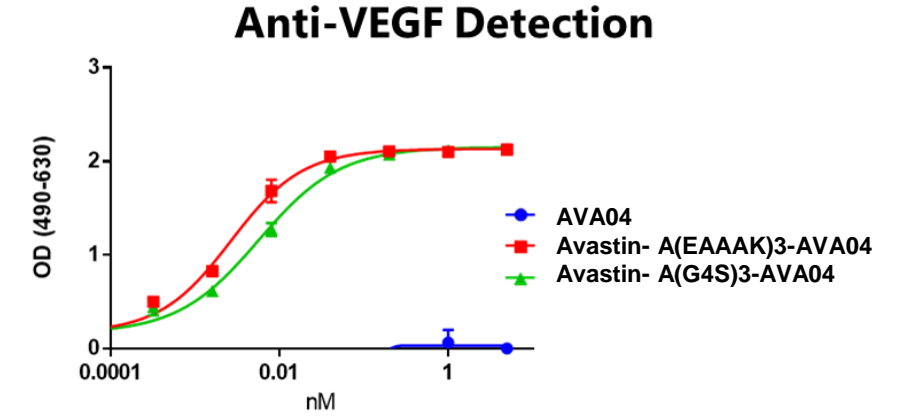
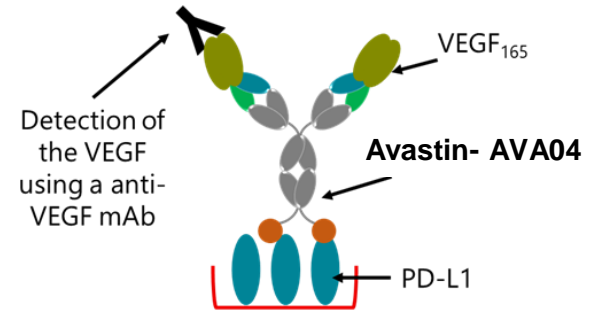
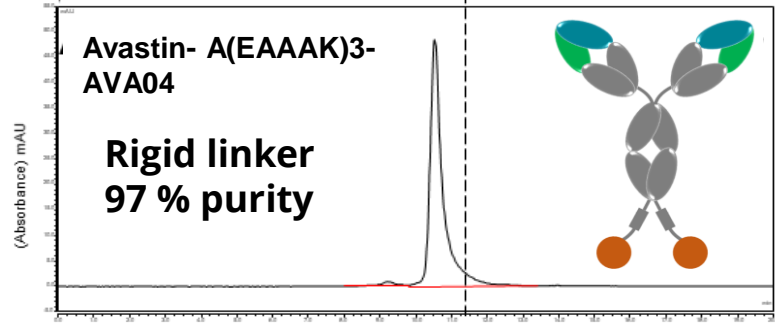
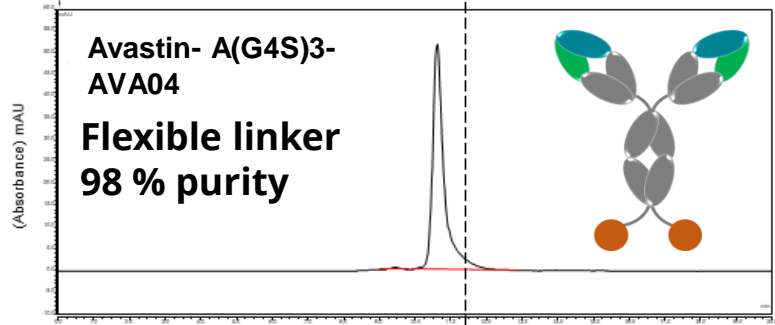
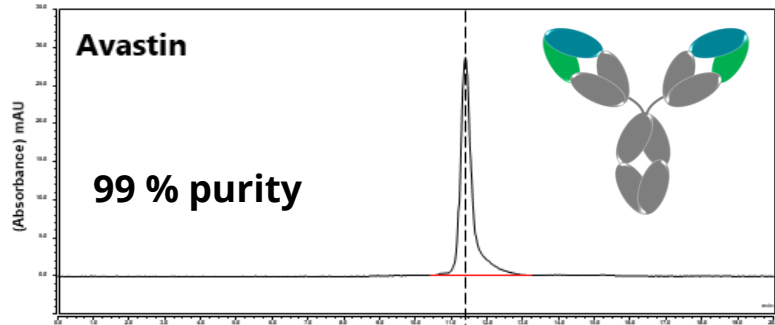
Expression levels >200 mg/L in *E. coli*



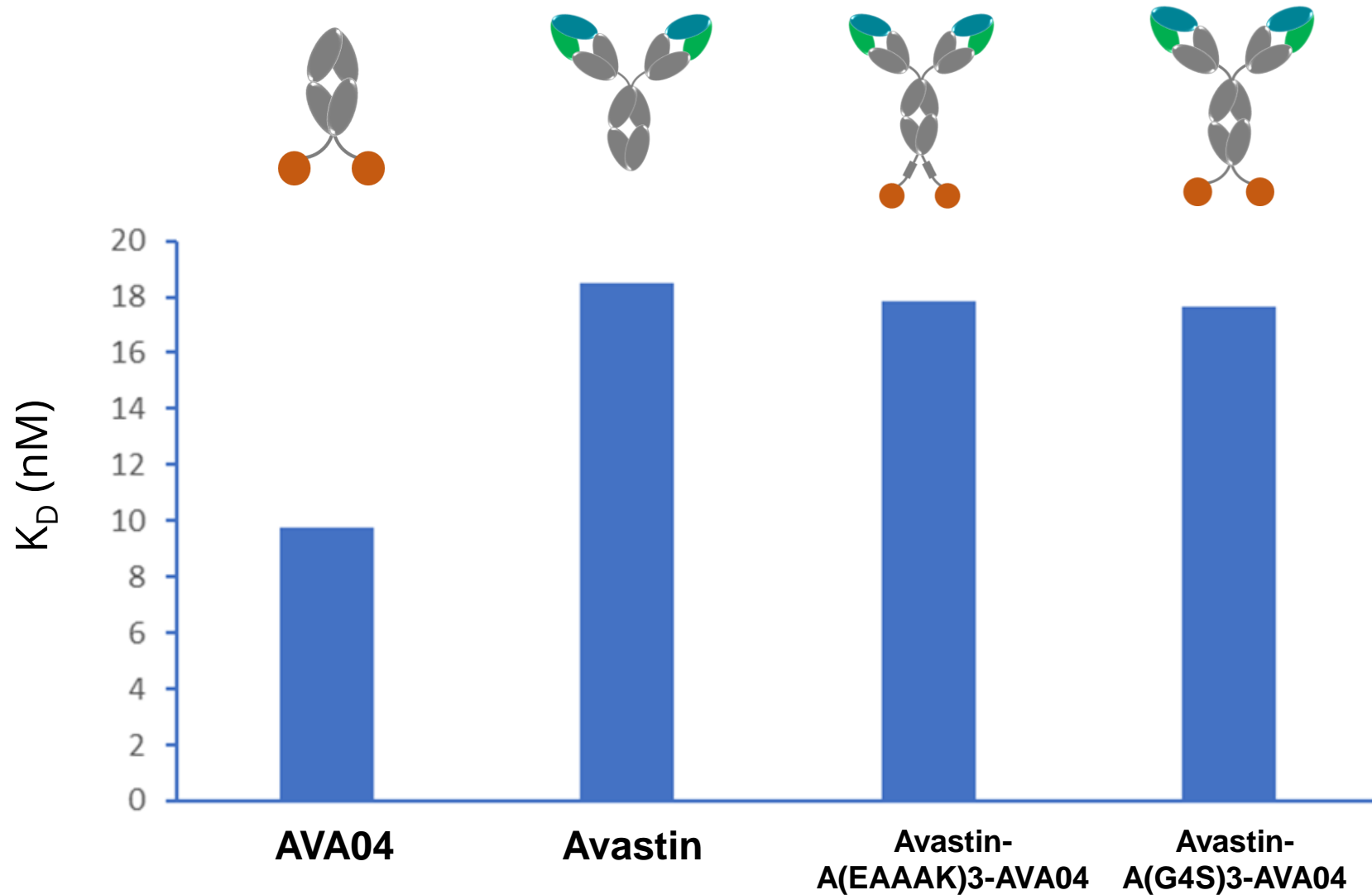
## Mouse PK at 10 mg/kg (IV)



# Avastin-AVA04 Formatting

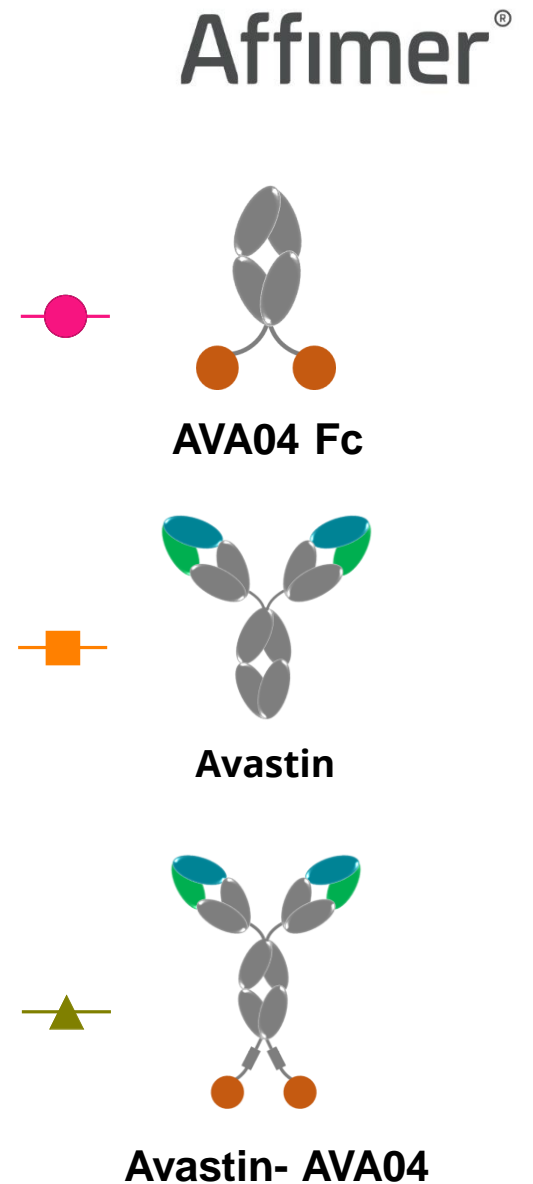
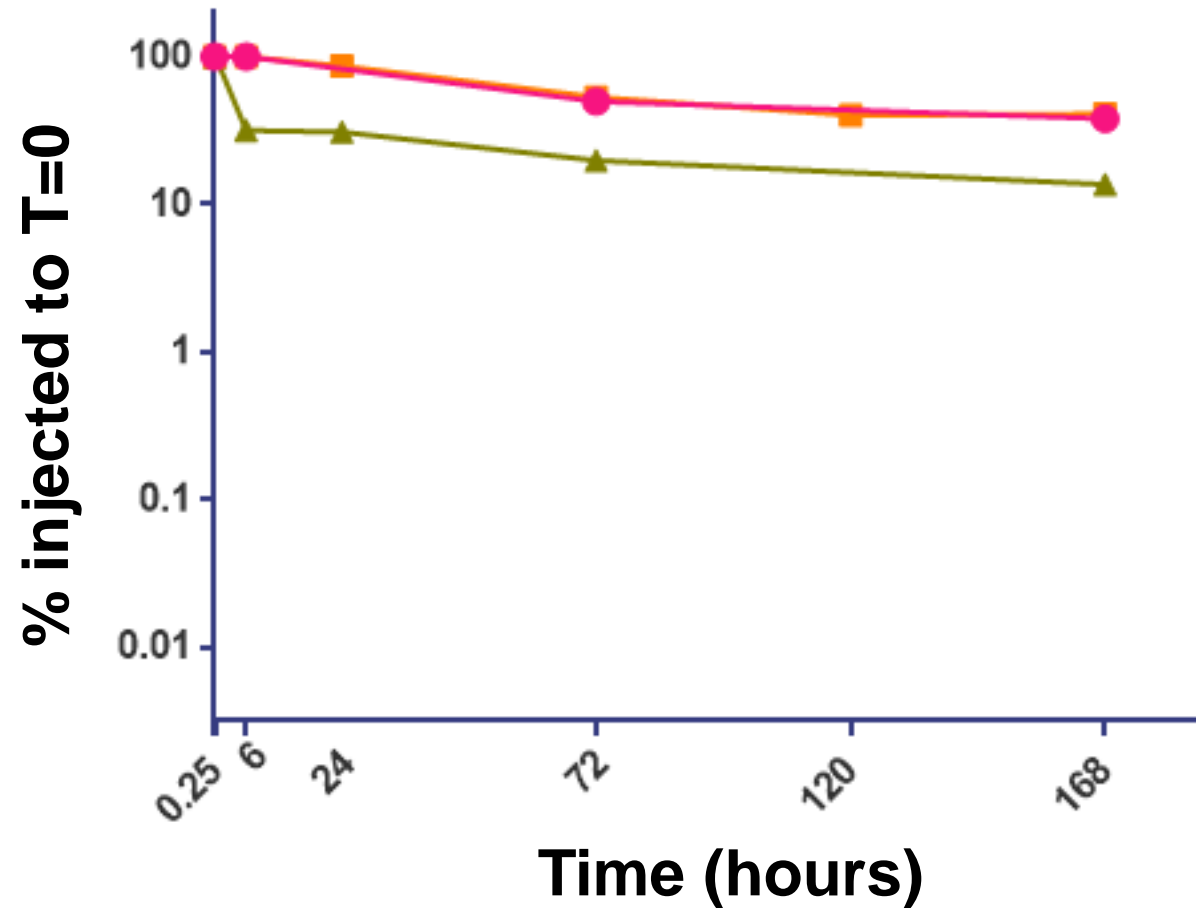


# Fc/FcRn Binding by Biacore



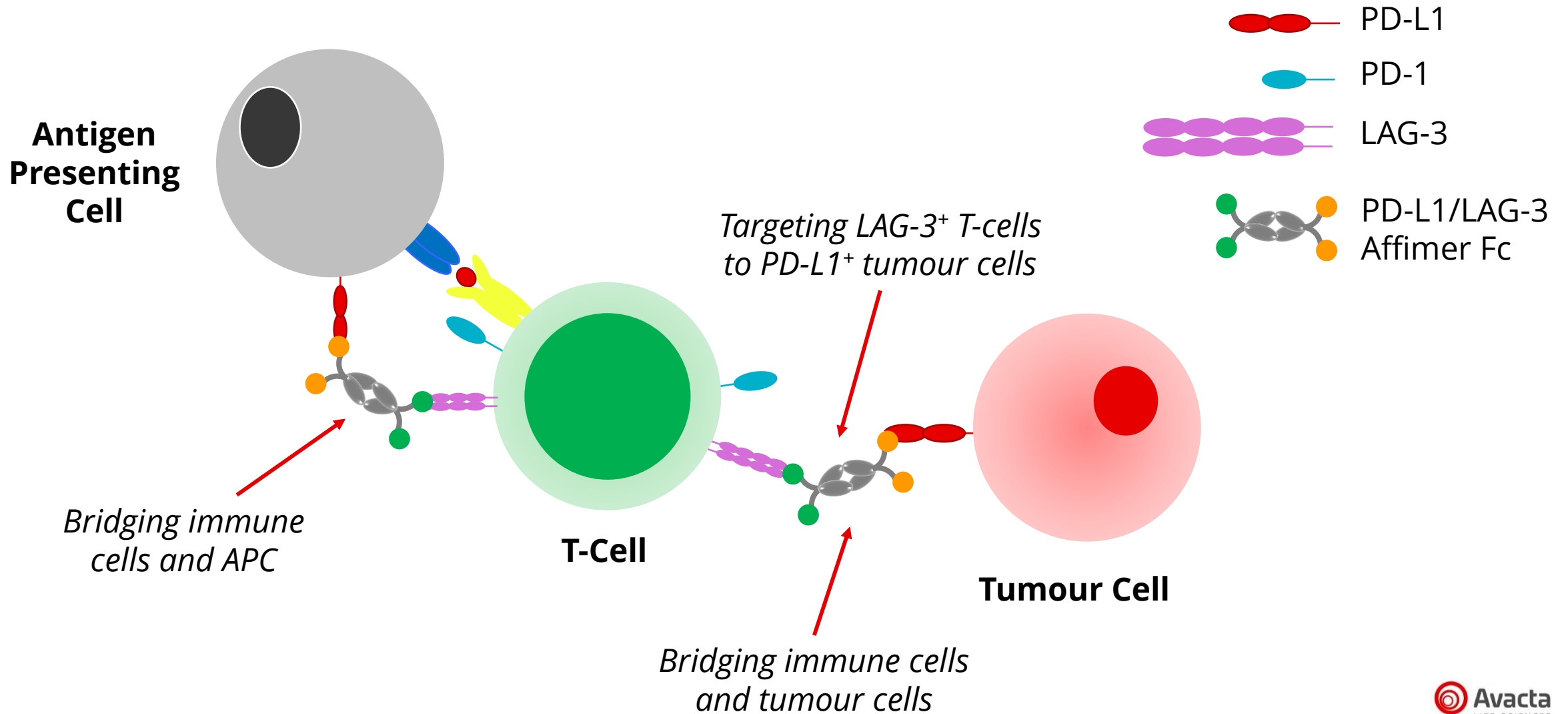
# Preliminary Mouse PK

- Do we compromise the FcRn binding and/or recycling by making Affimer-Fc fusion proteins *in vivo*?
- Molecules dosed at 10 mg/kg IV
- Affimer-Fc protein fusions do not significantly impact *in vivo* PK

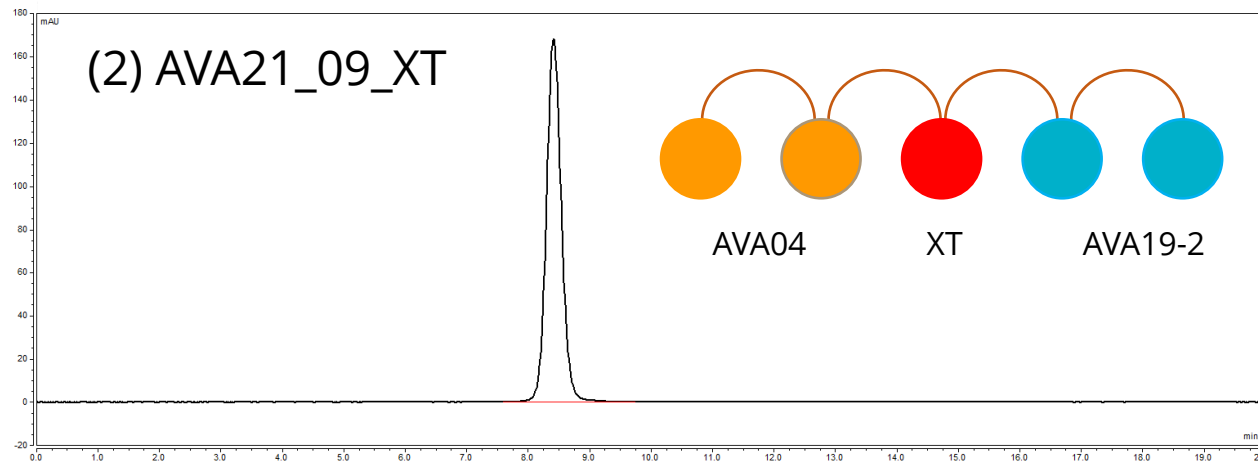
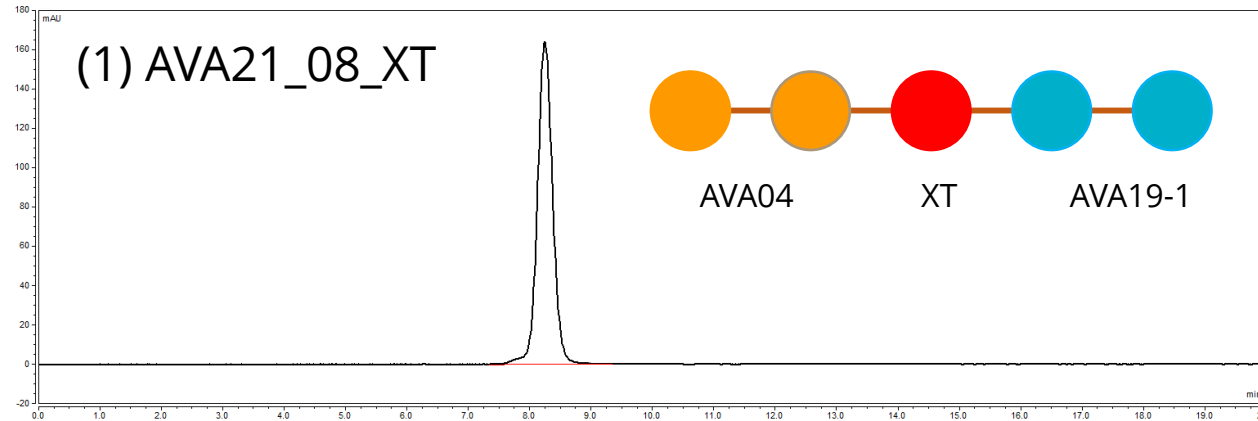
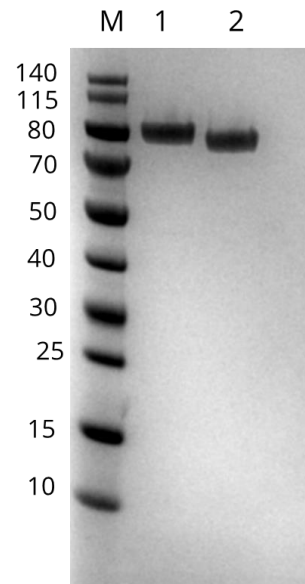


# Scientific Rationale for Targeting PD-L1 and LAG-3

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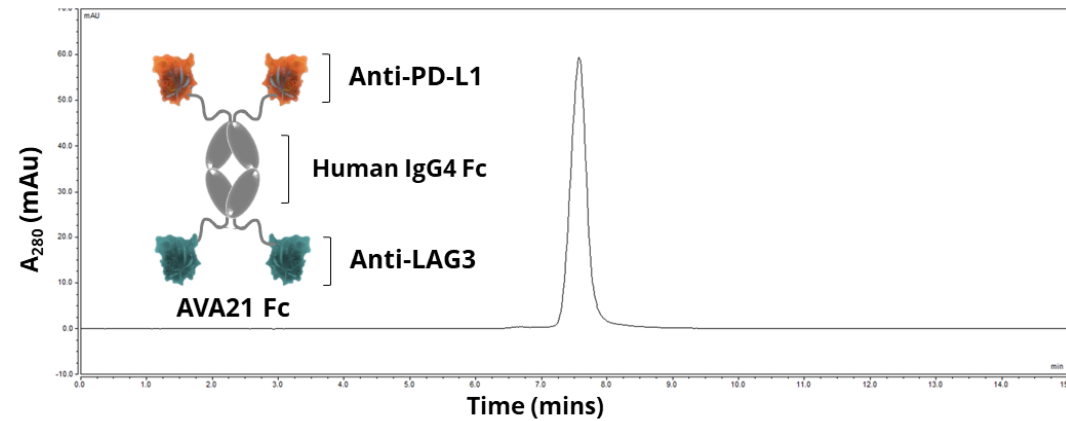


# AVA21 ILF XT Format

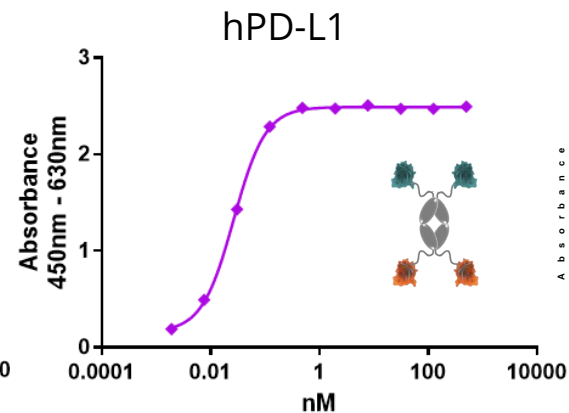
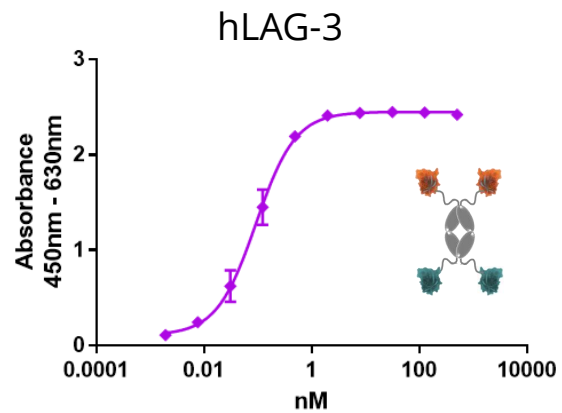


# AVA21 (PD-L1/LAG-3) Formatting

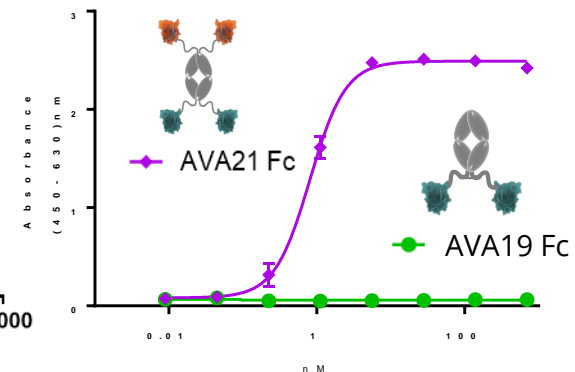
Analytical SEC-HPLC



AVA21 Fc Target Antigen Binding ELISAs

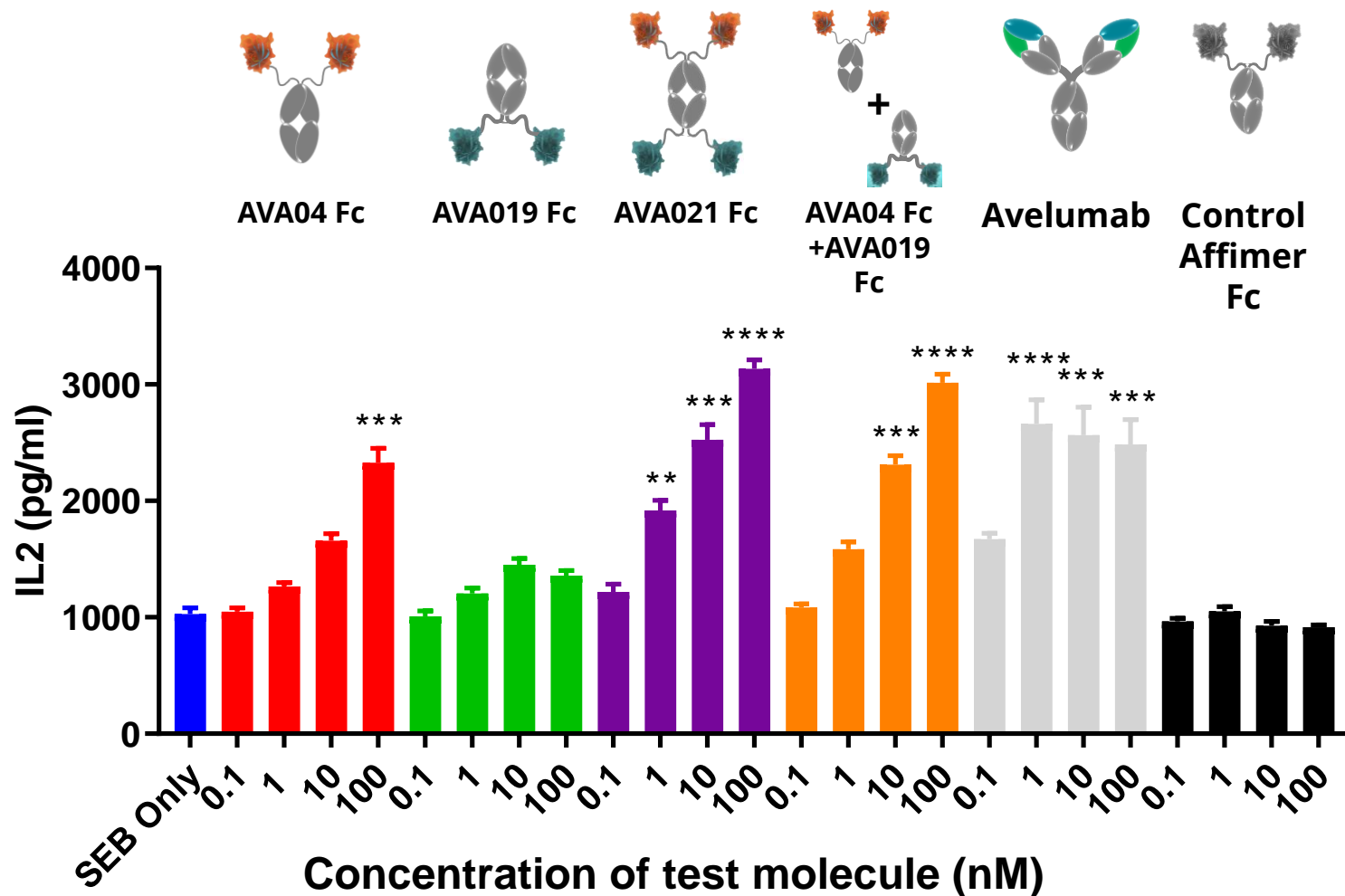


Human PD-L1/LAG-3 Bridging ELISA





# Human PBMC SEB Assay (3 Donors)



Data for the pooled donors are presented as mean +/- S.E.M. pg/ml (n=3). \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001, using two-way ANOVA with Dunnett's post-test comparing test substances to SEB only.

# Acknowledgements

## Discovery Team

- Celeste Letellier
- Hannah Wall
- Bruno Gomes
- Mingkui Zhou
- Michele Writer

## Protein Sciences Team

- Floriane Laurent
- Derina Sweeney
- Katherine Carr
- Agata Oruba
- Emma Jenkins

## Bioassay Team

- Jennifer Bate
- Maureen West
- Marine De Jaeger
- Jyrki Sivula
- Dino Ossola
- Estelle Adam

## Project Management

- Emma Stanley

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