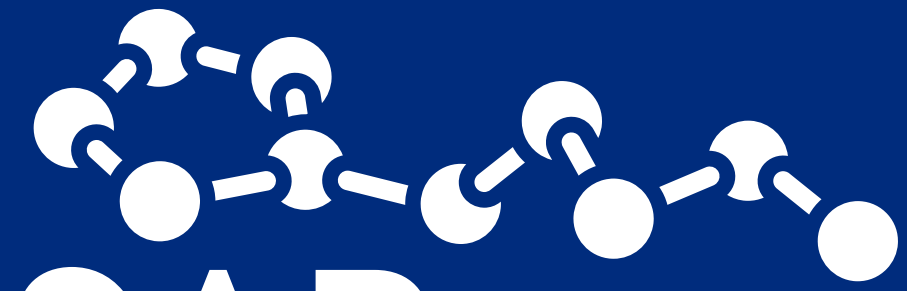


SARomics

v.230207

Antibody-antigen complex structures

ANTIBODY-ANTIGEN
STRUCTURES

Fab-antigen Structures

Don’t work in the dark!

Access to structural information increases your understanding and enables you to execute projects faster.

Use structural information for:

- Epitope definition to file stronger IP
- Understanding MoA
- Structure-based design
- Structural characterization of protein drugs (HOS)
- Antibody engineering: affinity maturation
- Antibody engineering: humanization
- Antibody engineering: ADC

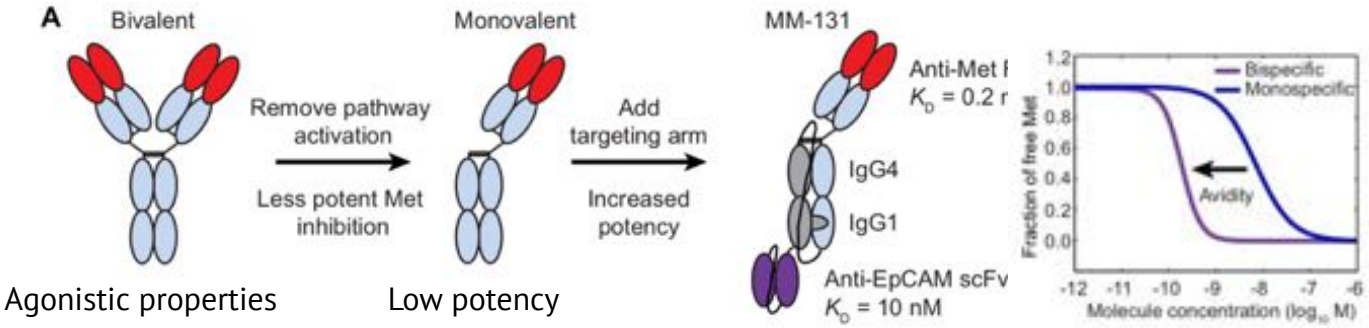
MM-131 – Antigen Structures Case Study

Client project: Bispecific anti-Met/EpCAM mAb MM-131 in complex with its antigens

Collaboration with **Merrimack Pharmaceuticals**, Cambridge, MA


MM-131, a bispecific anti-Met/EpCAM mAb, inhibits HGF-dependent and HGF-independent Met signaling through concurrent binding to EpCAM

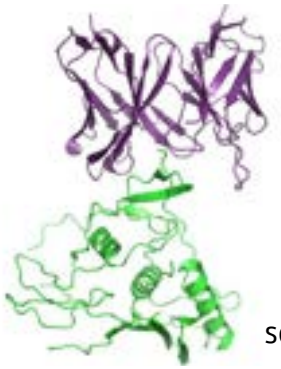
Published in PNAS!



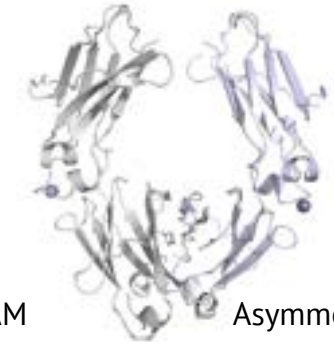
Agonistic properties

Low potency

Antagonistic with high potency



scFv-EpCAM



Asymmetric Fc

Fab-Met

PDB codes: 6I07, 6HYG, 6I04

Casaletto *et al.*, 2019, *PNAS*, 116, 7533-7542.

Davoceticept (ALPN-202) - An engineered CD80 variant fusion therapeutic

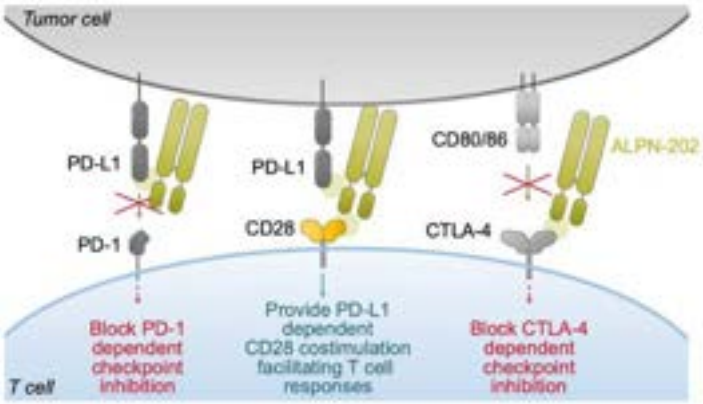
Client project: ALPN-202 in complex with PD-L1

Collaboration with **Alpine Immune Sciences**, Seattle, WA

ARTICLE

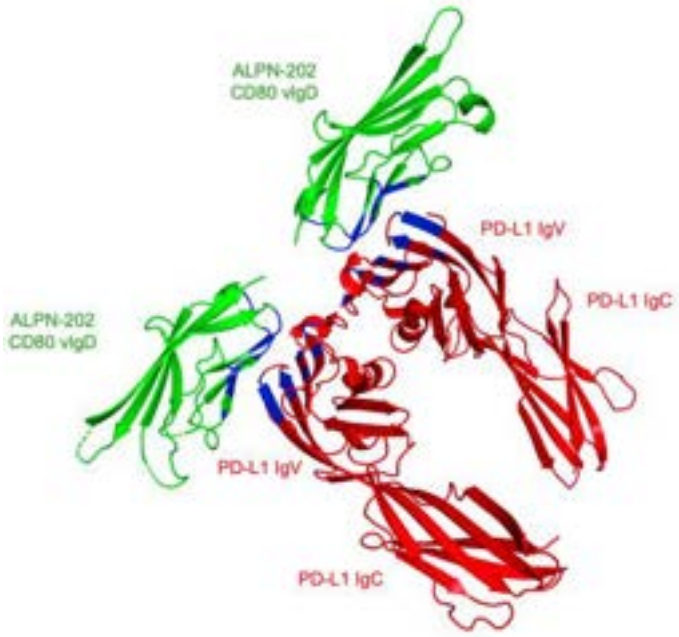
The engineered CD80 variant fusion therapeutic davoceticept combines checkpoint antagonism with conditional CD28 costimulation for anti-tumor immunity

Published in Nature Communications!



The three mechanisms of action of ALPN-202:

- Blockade of PD-1–PD-L1 interaction
- PD-L1-dependent CD28 costimulation
- Blockade of CTLA-4–CD80/CD86 interactions.



X-ray structure of ALPN-202 CD80 vIgD in complex with PD-L1

PDB code: 7TPS

Maurer et al., 2022, Nat Comm, 13:1790.

Structural basis of activation and antagonism of receptor signaling mediated by interleukin-27

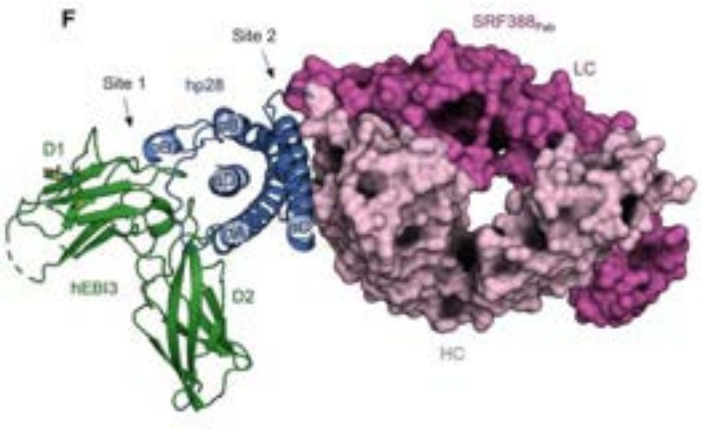
Client project: SRF388 Fab in complex IL-27

Collaboration with **Surface Oncology**, Cambridge, MA


Cell Reports

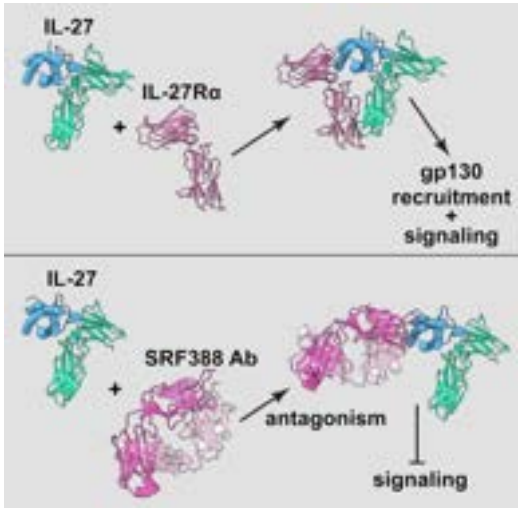
CellPress

Structural basis of activation and antagonism of receptor signaling mediated by interleukin-27



X-ray structure of SRF388 Fab in complex with IL-27

PDB code: 7ZXK



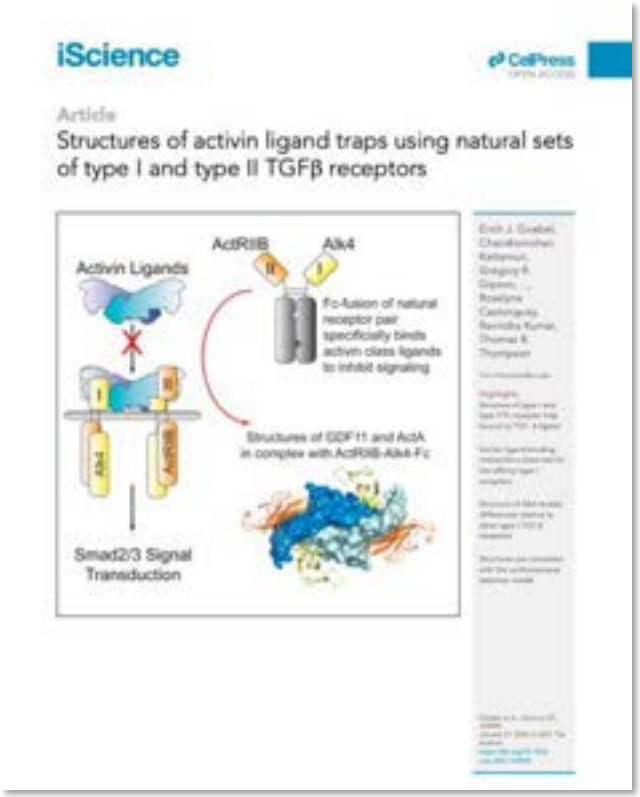
- IL-27Ra interacts both with the p28 and EBI3 subunits of IL- 27
- SRF388 and IL-27Ra occupy mutually exclusive binding sites on IL-27
- IL-27 mediates receptor assemblies distinct from IL-12 and IL-23

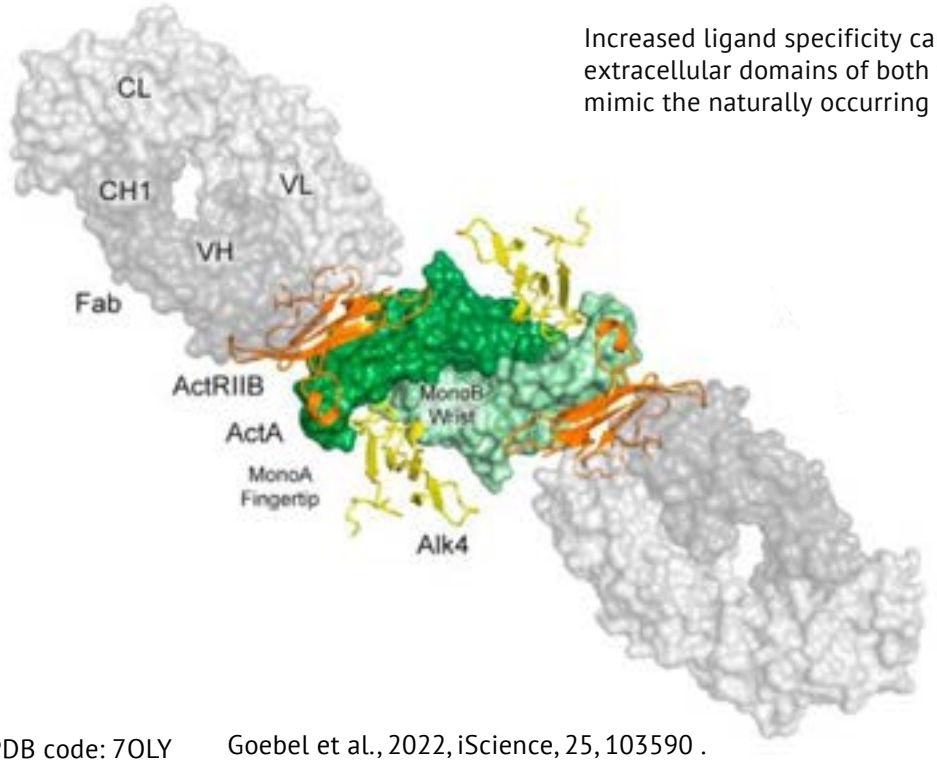
Skladanowska et al., 2022, Cell Reports, 41, 111490.

Activin ligand trap

Client project: ActRIIB-Alk4-Fc in complex with activin A and anti-ActRIIB Fab

Collaboration with **Acceleron Pharma**, Cambridge, MA





Increased ligand specificity can be accomplished by using the extracellular domains of both the type I and type II receptor to mimic the naturally occurring signaling complex.

Structure of ActA/ActRIIB: Alk4/anti-ActRIIB Fab complex

PDB code: 7OLY

Goebel et al., 2022, iScience, 25, 103590 .

The bispecific 4-1BB x 5T4 agonist, ALG.APV-527, mediates strong T cell activation and potent anti-tumor activity

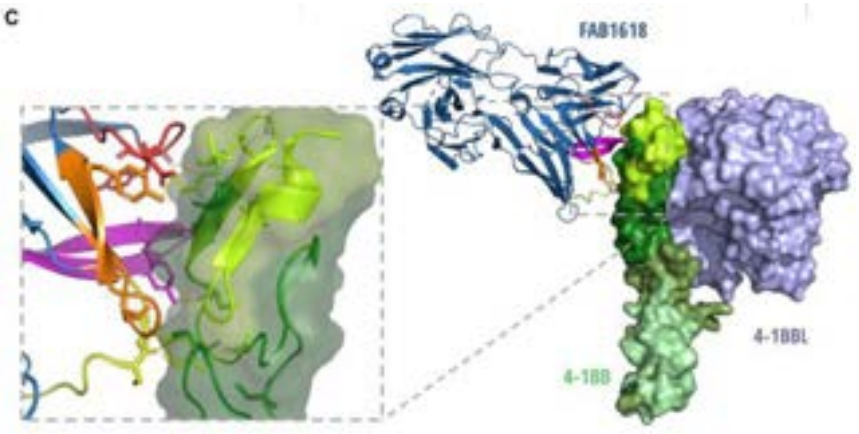
Client project: ALG.APV-527 (Fab1618) in complex with 4-1BB (CD137)

Collaboration with **Alligator Bioscience**, Lund, Sweden


MOLECULAR CANCER THERAPEUTICS

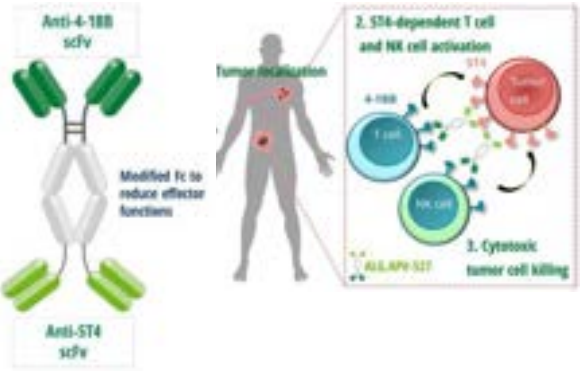
The bispecific tumor antigen-conditional 4-1BB x 5T4 agonist, ALG.APV-527, mediates strong T cell activation and potent anti-tumor activity in preclinical studies

Abstract



X-ray structure of Fab1618 in complex with 4-1BB

PDB code: 7YXU



- ALG.APV-527 directs the stimulation of T cells and NK cells to 5T4+ tumors and is designed to minimize the toxicity observed with other 4-1BB therapeutics
- Binding sites of ALG.APV-527 and the 4-1BBL on 4-1BB are distinct

Nelson et al., 2022, Mol. Cancer Ther., 22-0395.

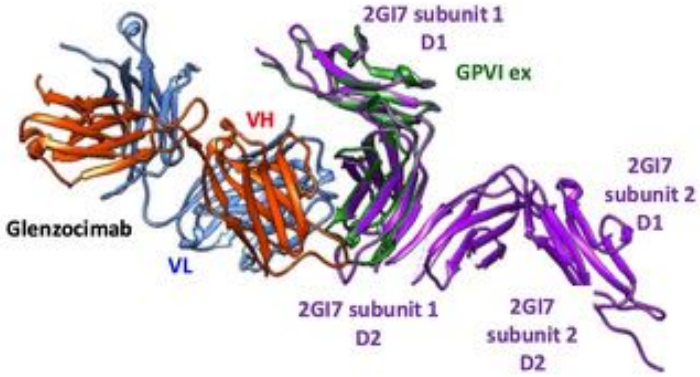
Targeting platelet GPVI with glenzocimab: a novel mechanism for inhibition

Client project: Glenzocimab Fab in complex with platelet glycoprotein VI

Collaboration with **Acticor Biotech**, Paris, France

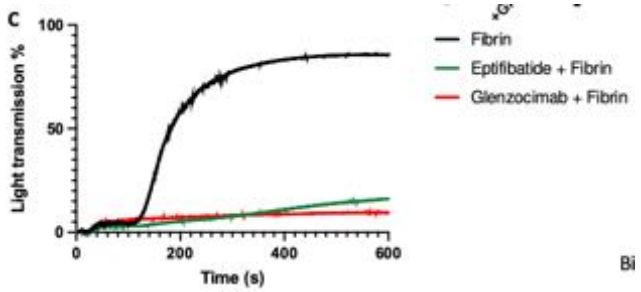

blood advances

Targeting platelet GPVI with glenzocimab: a novel mechanism for inhibition



X-ray structure of glenzocimab in complex with GPVI

PDB code: 7R58



Glenzocimab inhibits fibrin-induced platelet aggregation

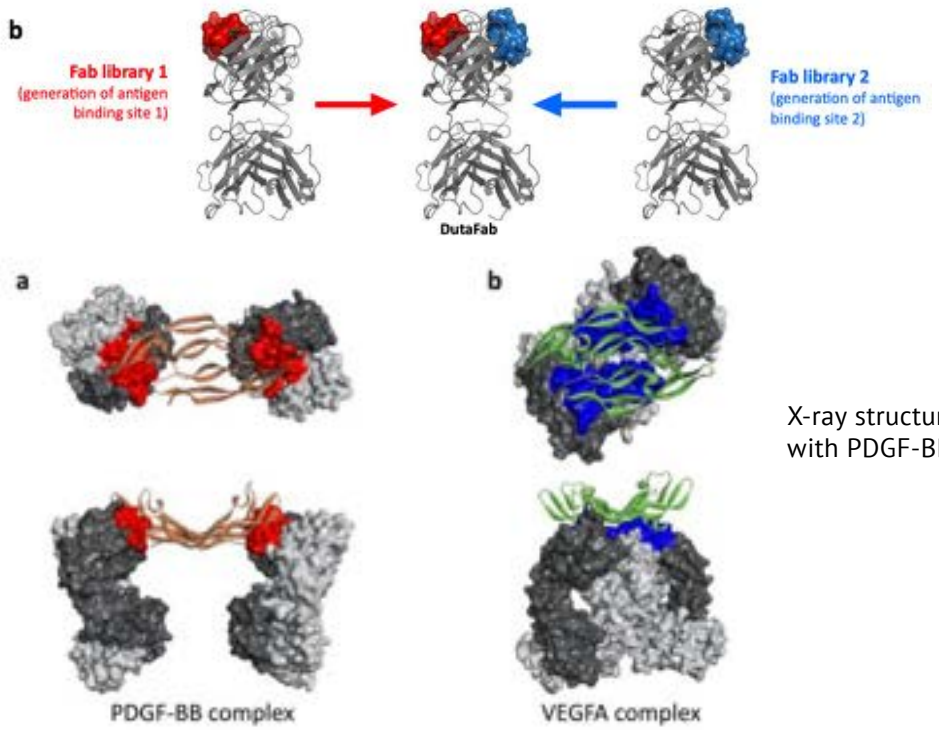
- GPVI binding to vascular collagen initiates thrombus formation and GPVI interactions with fibrin promote the growth and stability of the thrombus.
- Crystal structure information enables the **elucidation of a novel mechanism** for the powerful anti thrombotic effect of glenzocimab, in which both ligands are blocked through a combination of steric hindrance and structural change.

Billiald et al., 2022, Blood Adv., 007863R2.

DutaFabs - engineered Fab's that bind two antigens simultaneously

Client project: DutaFab (**Roche**) in complex with its antigens PDGF and VEGFA

Published in Nature Communications!



The DutaFab concept of separating paratopes on a single Fab

X-ray structure of the DutaFab in complex with PDGF-BB dimer and VEGFA dimer

PDB code: 6T9E 6T9D

Beckmann et al., 2021, Nat Comm, 12:708.

Dusquetide modulates innate immune response through binding to p62

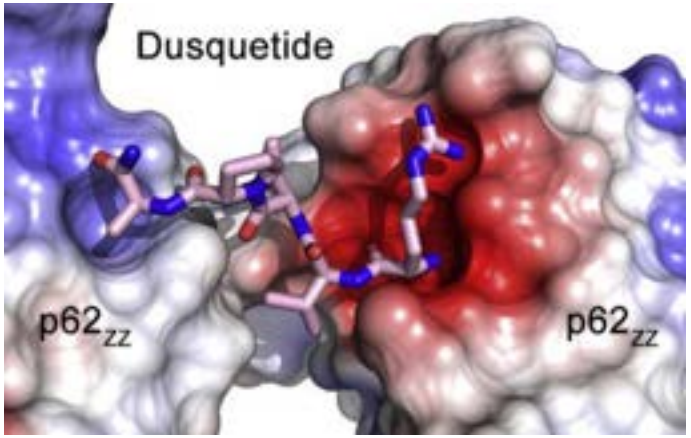
Client project: Dusquetide in complex with p62 (SQSTM1) ZZ domain

Collaboration with **Soligenix**, Princeton, NJ


Structure

CellPress

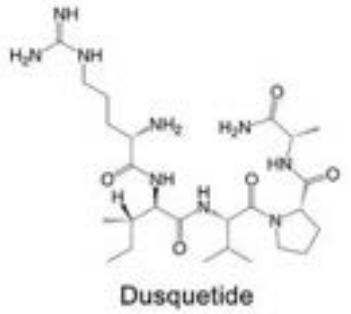
Dusquetide modulates innate immune response through binding to p62



X-ray structure of dusquetide in complex with $p62_{ZZ}$

PDB code: 7R1O

Zhang et al., 2022, Structure, 30, P1055.



- Next-generation IDR dusquetide penetrates the cell membrane
- Dusquetide targets the ZZ domain of p62
- Treatment of cells with dusquetide, which mimics arginylated ligands of $p62_{ZZ}$, leads to stabilization of the p62-RIP1 complex and an increase in p38 phosphorylation and CEBP/B expression

SARomics

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