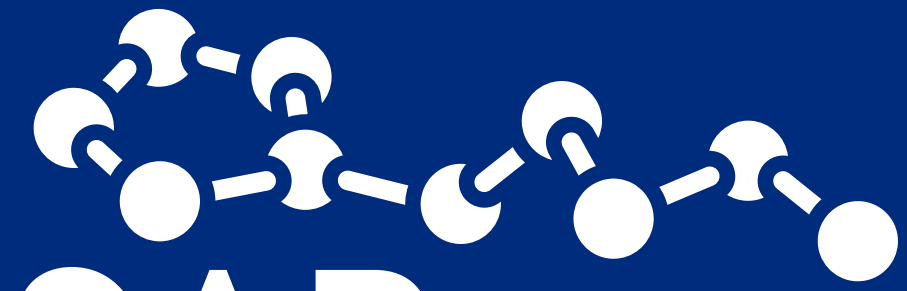


SARomics

v.230207

SARomics Biostructures at a glance

- Hybrid business model since 2006
  - Independent and founder owned
  - CRO generating revenues
  - Internal discovery projects (currently 2 oncology projects: NIK & BRD4)
- Proprietary discovery platform
  - Unique expertise in protein structure determination
  - Hit identification using proprietary WAC™ fragment screening technology
- Delivered hundreds of crystal structures to pharma, biotech and academic clients worldwide
  - Protein/small-molecule complexes
  - Antibody/antigen complexes
  - Industrial enzymes
- Experienced and skilled team of 25 (22 PhDs)
- Sales representatives in Boston & Japan

Broad spectrum of protein structure related services

- FastLane™ Premium
- FastLane™ Standard
- Gene-to-structure Platform
- NMR Services
- Antibody-antigen Structures
- Structure-Based Drug Design
- Fragment-Based Hit Generation
- Integrated Drug Discovery
- Industrial Enzymes
- Protein Shop

State-of-the-art Crystallization Lab

SARomics Biostructures performs high-throughput low volume crystallization using liquid handling, crystallization and imaging robotics

Crystallization robotics

Microlitre robotics

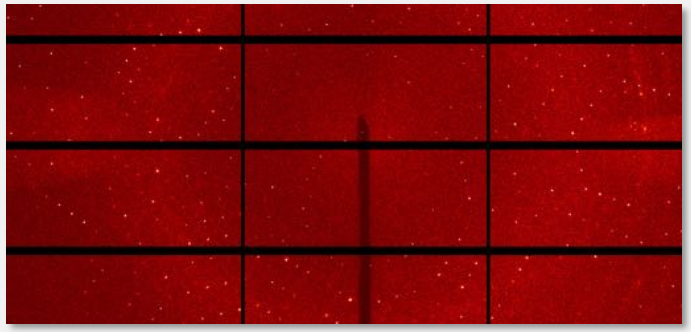
Plate hotel/imaging robotics

Synchrotron Access

- Our lab is located 2 km away from the world-leading MAX IV synchrotron
- Currently collecting data twice per month at DESY (Hamburg), Diamond (Oxford), Swiss Light Source or MAX IV, Lund

Our Local Light Source

- The MAX IV Laboratory is the new Swedish national synchrotron facility
- SARomics is in a very advantageous position for access to MAX IV (no need to ship crystals)
- Access to one of the world's most advanced synchrotron source substantially increases our competitiveness and shortens turnaround times
- We benefit from a smaller, more coherent and more brilliant beam and are thereby be able to collect superior data on smaller crystals




Our Local Light Source
ess
MAX IV
MEDICON VILLAGE
SARomics

Antibody-antigen complex structures

ANTIBODY-ANTIGEN
STRUCTURES

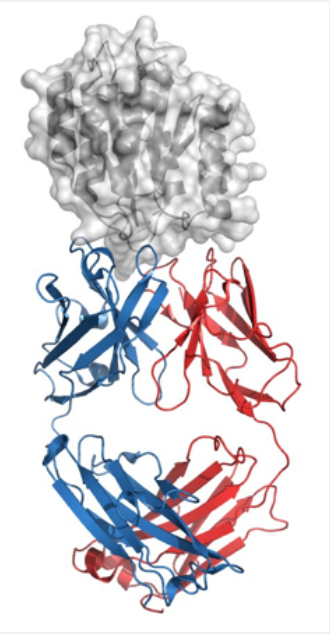
Fab-antigen Structures

Don’t work in the dark!

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

Use structural information for:

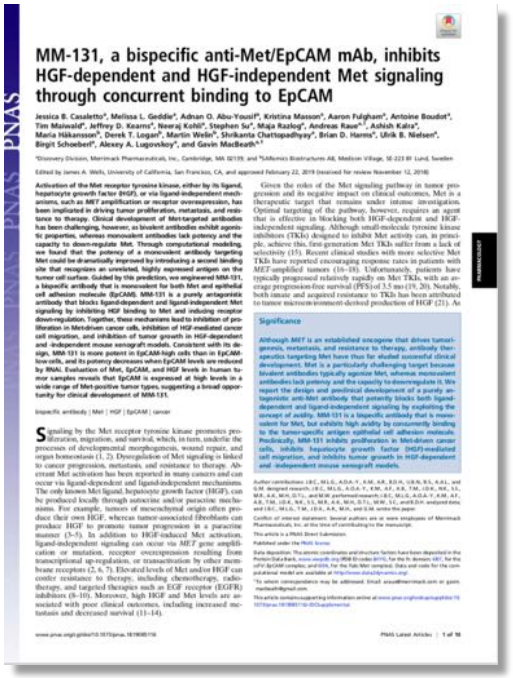
- Epitope definition to file stronger IP
- Understanding MoA
- Structure-based design
- Structural characterization of protein drugs (HOS)
- Antibody engineering: affinity maturation
- Antibody engineering: humanization
- Antibody engineering: ADC



MM-131 – Antigen Structures Case Study

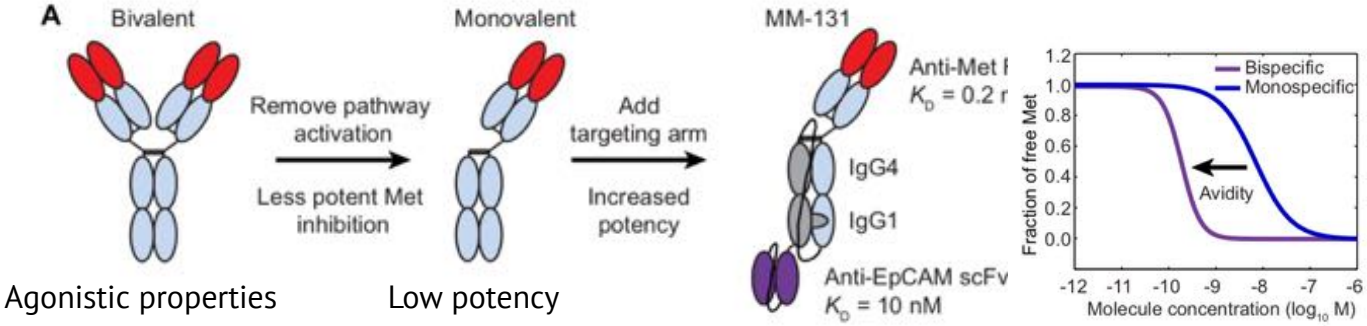
Client project: Bispecific anti-Met/EpCAM mAb MM-131 in complex with its antigens

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

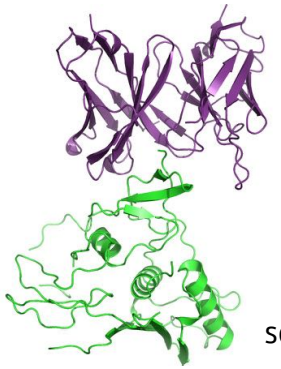
Published in PNAS!



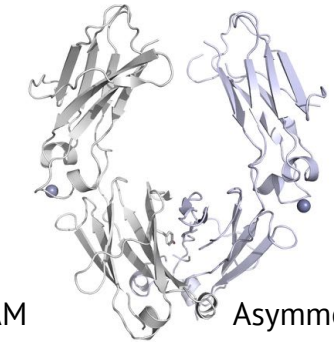
Agonistic properties

Low potency

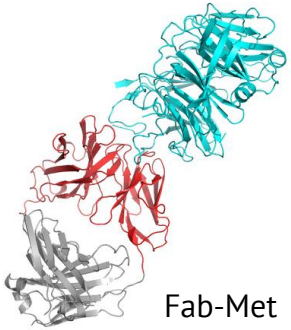
Antagonistic with high potency



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

nature COMMUNICATIONS

ARTICLE

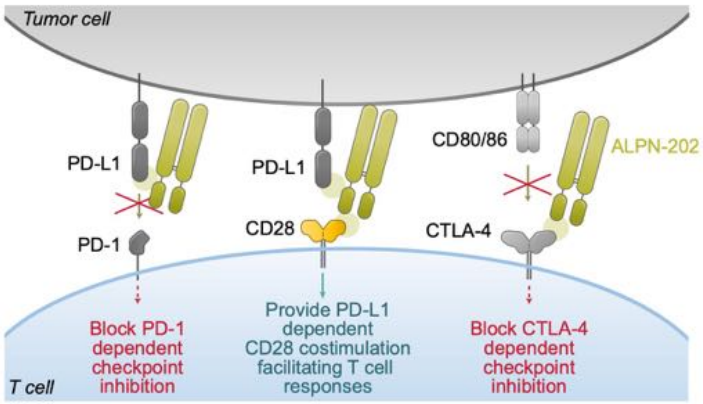
OPEN

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

Mark F. Maurer, Katherine E. Lewis, Joseph L. Kuijper, Dan Ardourel, Chelsea J. Gudgeon, Siddarth Chandrasekaran, Sherri L. Mudri, Kayla N. Kleist, Chris Navas, Martin F. Wolfson, Mark W. Rixon, Ryan Swanson, Stacey R. Dillon, Steven D. Levin, Yengo Raymond Kimbung, Masato Akutsu, Derek T. Logan, Björn Walse, Kristine M. Swiderek & Stanford L. Peng

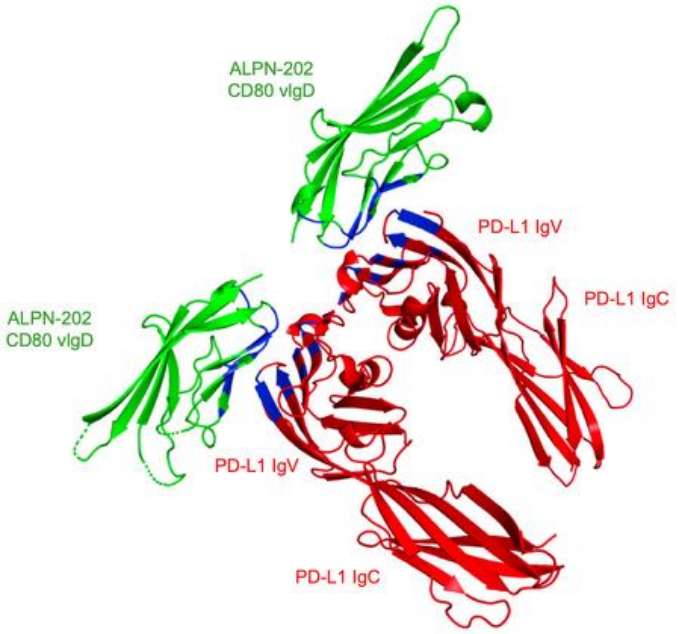
Despite the recent clinical success of T cell checkpoint inhibition targeting the CTLA-4 and PD-1 pathways, many patients either fail to achieve objective responses or they develop resistance to therapy. In some cases, poor responses to checkpoint blockade have been linked to suboptimal CD28 costimulation and the inability to generate and maintain a productive adaptive anti-tumor immune response. To address this, here we utilize directed evolution to engineer a CD80 IgV domain with increased PD-L1 affinity and fuse this to an immunoglobulin Fc domain, creating a therapeutic (ALPN-202, davoceticept) capable of providing CD28 costimulation in a PD-L1-dependent fashion while also antagonizing PD-1 – PD-L1 and CTLA-4–CD80/CD86 interactions. We demonstrate that by combining CD28 costimulation and dual checkpoint inhibition, ALPN-202 enhances T cell activation and anti-tumor efficacy in cell-based assays and mouse tumor models more potently than checkpoint blockade alone and thus has the potential to generate potent, clinically meaningful anti-tumor immunity in humans.

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

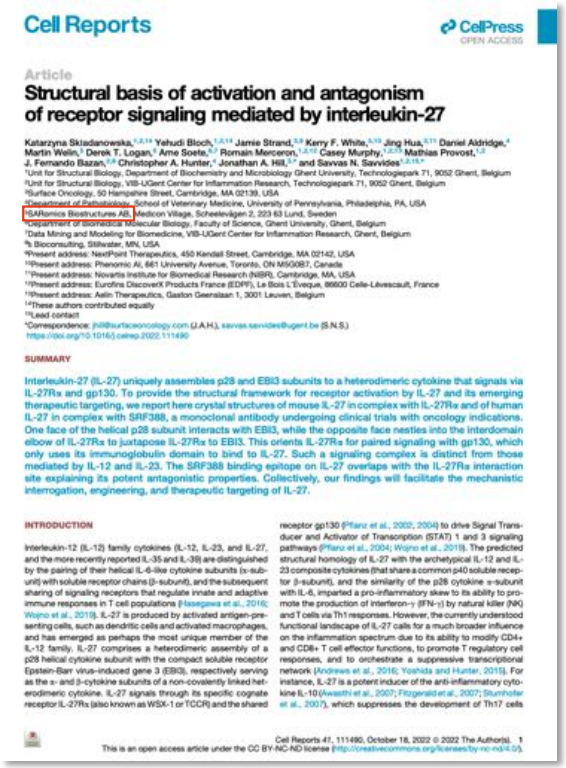
PDB code: 7TPS

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
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Article

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

Katarzyna Skladanowska,[1,2,14] Yehudi Bloch,[1,2,14] Jamie Strand,[3,4] Kerry F. White,[5,13] Jing Hua,[5,11] Daniel Aldridge,[4] Martin Welin,[3] Derek T. Logan,[3] Arne Soete,[6,7] Romain Mercenon,[1,2,12] Casey Murphy,[1,2,12] Mathias Provost,[1,2] J. Fernando Bazan,[5,8] Christopher A. Hunter,[4] Jonathan A. Hill,[5,*] and Savvas N. Savvides[1,2,15,*]

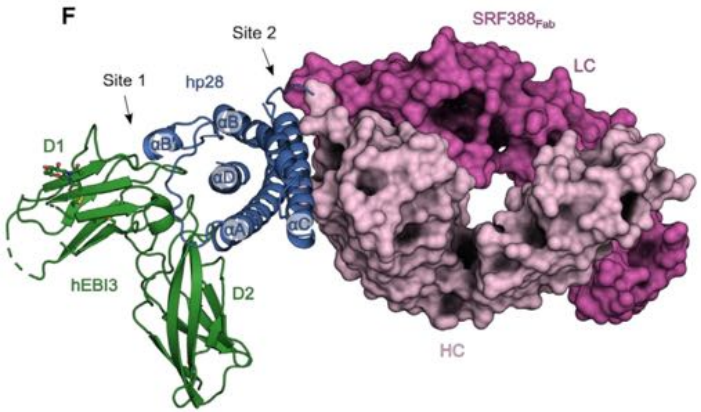
[1]Unit for Structural Biology, Department of Biochemistry and Microbiology Ghent University, Technologiepark 71, 9052 Ghent, Belgium
[2]Unit for Structural Biology, VIB-UGent Center for Inflammation Research, Technologiepark 71, 9052 Ghent, Belgium
[3]Surface Oncology, 50 Hampshire Street, Cambridge, MA 02139, USA
[4]Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA
[5]SARomics Biostructures AB, Medicon Village, Scheelevägen 2, 223 63 Lund, Sweden
[6]Department of Biomedical Molecular Biology, Faculty of Science, Ghent University, Ghent, Belgium
[7]Data Mining and Modeling for Biomedicine, VIB-UGent Center for Inflammation Research, Ghent, Belgium
[8]b Bioconsulting, Stillwater, MN, USA
[9]Present address: NextPoint Therapeutics, 450 Kendall Street, Cambridge, MA 02142, USA
[10]Present address: Phenomic AI, 661 University Avenue, Toronto, ON M5G0B7, Canada
[11]Present address: Novartis Institute for Biomedical Research (NIBR), Cambridge, MA, USA
[12]Present address: Eurofins DiscoverX Products France (EDPF), Le Bois L'Eveque, 86600 Celle-Lévescault, France
[13]Present address: Axlin Therapeutics, Gaston Geenslaan 1, 3001 Leuven, Belgium
[14]These authors contributed equally
[15]Lead contact
*Correspondence: jhill@surfaceoncology.com (J.A.H.), savvas.savvides@ugent.be (S.N.S.)
https://doi.org/10.1016/j.celrep.2022.111490

SUMMARY

Interleukin-27 (IL-27) uniquely assembles p28 and EBI3 subunits to a heterodimeric cytokine that signals via IL-27Rα and gp130. To provide the structural framework for receptor activation by IL-27 and its emerging therapeutic targeting, we report here crystal structures of mouse IL-27 in complex with IL-27Rα and of human IL-27 in complex with SRF388, a monoclonal antibody undergoing clinical trials with oncology indications. One face of the helical p28 subunit interacts with EBI3, while the opposite face nestles into the interdomain elbow of IL-27Rα to juxtapose IL-27Rα to EBI3. This orients IL-27Rα for paired signaling with gp130, which only uses its immunoglobulin domain to bind to IL-27. Such a signaling complex is distinct from those mediated by IL-12 and IL-23. The SRF388 binding epitope on IL-27 overlaps with the IL-27Rα interaction site explaining its potent antagonistic properties. Collectively, our findings will facilitate the mechanistic interrogation, engineering, and therapeutic targeting of IL-27.

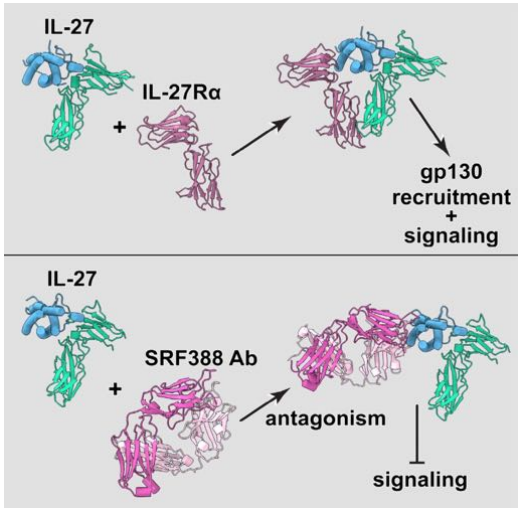
INTRODUCTION

Interleukin-12 (IL-12) family cytokines (IL-12, IL-23, and IL-27, and the more recently reported IL-35 and IL-39) are distinguished by the pairing of their helical IL-6-like cytokine subunits (α-subunit) with soluble receptor chains (β-subunit), and the subsequent sharing of signaling receptors that regulate innate and adaptive immune responses in T cell populations (Hasegawa et al., 2016; Wojno et al., 2019). IL-27 is produced by activated antigen-presenting cells, such as dendritic cells and activated macrophages, and has emerged as perhaps the most unique member of the IL-12 family. IL-27 comprises a heterodimeric assembly of a p28 helical cytokine subunit with the compact soluble receptor Epstein-Barr virus-induced gene 3 (EBI3), respectively serving as the α- and β-cytokine subunits of a non-covalently linked heterodimeric cytokine. IL-27 signals through its specific cognate receptor IL-27Rα (also known as WSX-1 or TCCR) and the shared receptor gp130 (Pflanz et al., 2002, 2004) to drive Signal Transducer and Activator of Transcription (STAT) 1 and 3 signaling pathways (Pflanz et al., 2004; Wojno et al., 2019). The predicted structural homology of IL-27 with the archetypical IL-12 and IL-23 composite cytokines (that share a common p40 soluble receptor β-subunit), and the similarity of the p28 cytokine α-subunit with IL-6, imparted a pro-inflammatory skew to its ability to promote the production of interferon-γ (IFN-γ) by natural killer (NK) and T cells via Th1 responses. However, the currently understood functional landscape of IL-27 calls for a much broader influence on the inflammation spectrum due to its ability to modify CD4+ and CD8+ T cell effector functions, to promote T regulatory cell responses, and to orchestrate a suppressive transcriptional network (Andrews et al., 2016; Yoshida and Hunter, 2015). For instance, IL-27 is a potent inducer of the anti-inflammatory cytokine IL-10 (Awasthi et al., 2007; Fitzgerald et al., 2007; Stumhofer et al., 2007), which suppresses the development of Th17 cells



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

PDB code: 7ZXK



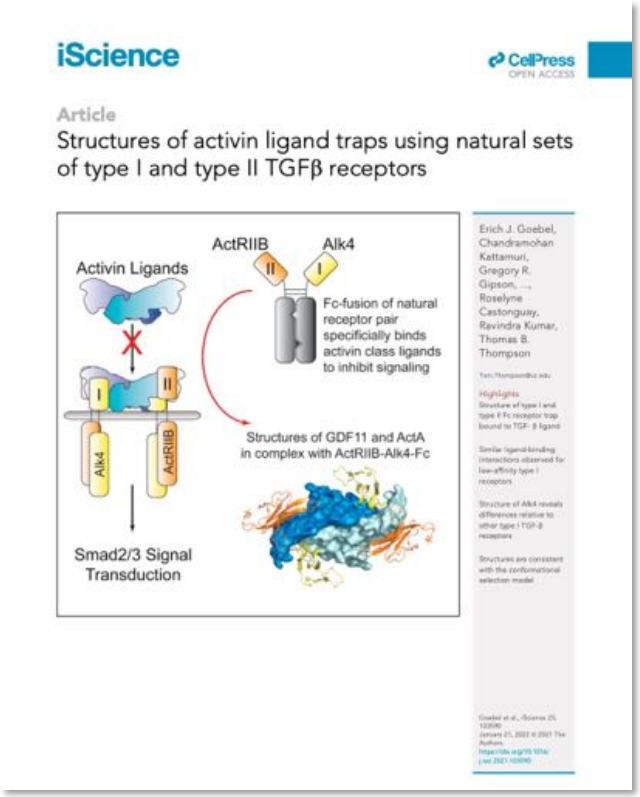
- IL-27Ra interacts both with the p28 and EBI3 subunits of IL- 27
- SRF388 and IL-27Ra occupy mutually exclusive binding sites on IL-27
- IL-27 mediates receptor assemblies distinct from IL-12 and IL-23

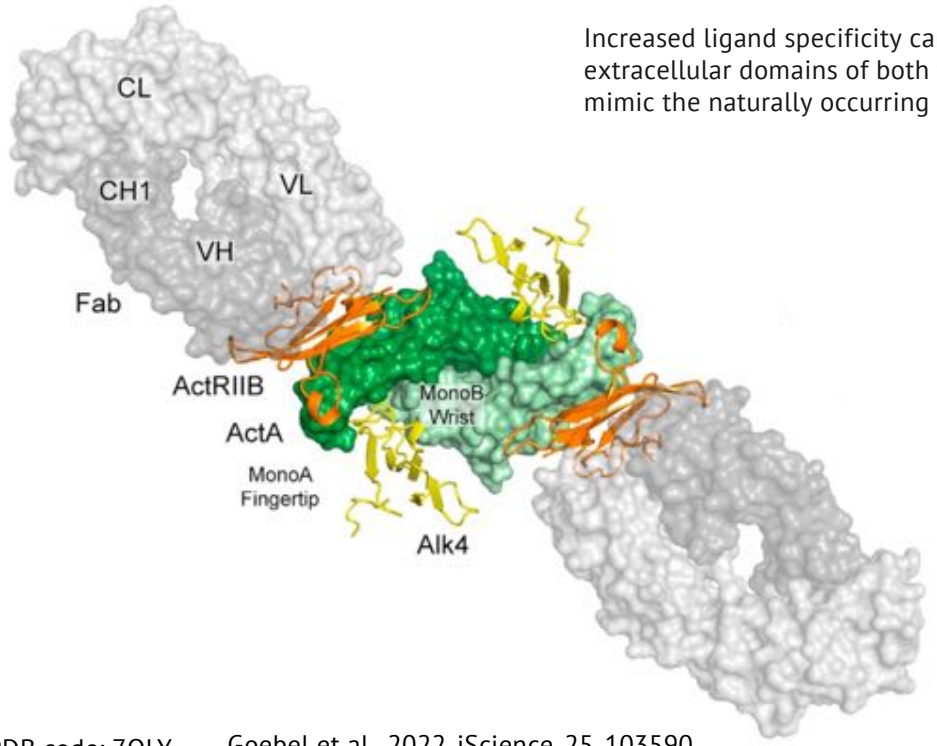
Skladanowska et al., 2022, Cell Reports, 41, 111490.

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

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Article Contents

Abstract

Supplementary data

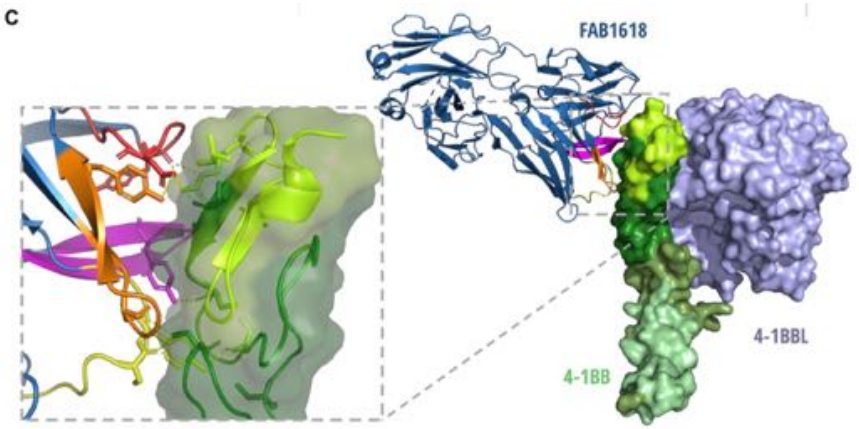
RESEARCH ARTICLE | NOVEMBER 07 2022

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

Split-Screen Views PDF Share Tools Versions

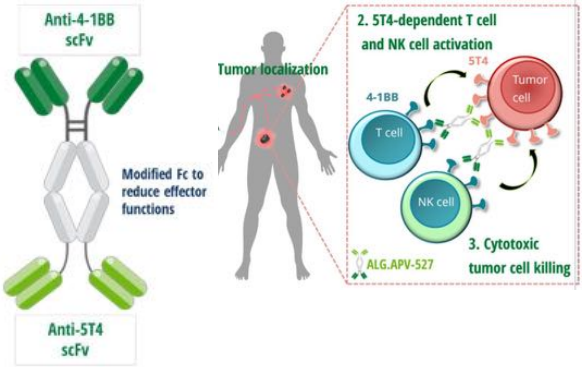
Abstract

4-1BB (CD137) is an activation-induced co-stimulatory receptor that regulates immune responses of activated CD8 T and NK cells, by enhancing proliferation, survival, cytolytic activity and IFN□ production. The ability to induce potent anti-tumor activity by stimulating 4-1BB on tumor-specific cytotoxic T cells makes 4-1BB an attractive target for designing novel immuno-oncology therapeutics. To minimize systemic immune toxicities and enhance activity at the tumor site, we have developed a novel bispecific antibody that stimulates 4-1BB function when co-engaged with the tumor-associated antigen 5T4. ALG.APV-527 was built based on the ADAPTIR™ bispecific platform with optimized binding domains to 4-1BB and 5T4 originating from the ALLIGATOR-GOLD® human single chain variable fragment library. The epitope of ALG.APV-527 was determined to be located at domain 1 and 2 on 4-1BB using X-ray crystallography. As demonstrated in reporter and primary cell assays in vitro, ALG.APV-527 triggers dose-dependent 4-1BB activity mediated only by 5T4 crosslinking. In vivo, ALG.APV-527 demonstrates robust anti-tumor responses, by inhibiting growth of established tumors expressing human 5T4 followed by a long-lasting memory immune response. ALG.APV-527 has an antibody-like half-life in cynomolgus macaques and was well tolerated at 50.5 mg/kg. ALG.APV-527 is uniquely designed for 5T4-conditional 4-1BB-mediated anti-tumor activity with potential to minimize systemic immune activation and hepatotoxicity while providing efficacious tumor-specific responses in a range of 5T4-expressing tumor indications as demonstrated by robust activity in preclinical in vitro and in vivo models. Based on the combined preclinical dataset, ALG.APV-527 has potential as a promising anti-cancer therapeutic for the treatment of 5T4-expressing tumors.



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

PDB code: 7YXU



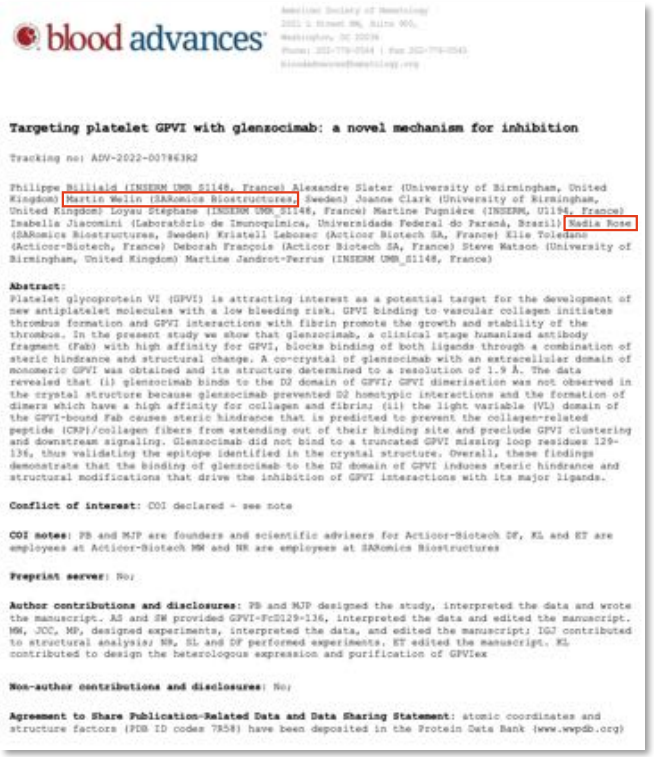
- ALG.APV-527 directs the stimulation of T cells and NK cells to 5T4+ tumors and is designed to minimize the toxicity observed with other 4-1BB therapeutics
- Binding sites of ALG.APV-527 and the 4-1BBL on 4-1BB are distinct

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

Tracking no: ADV-2022-007863R2

Philippe Billiald (INSERM UMR S1148, France) Alexandre Slater (University of Birmingham, United Kingdom) Martin Wellin (SARomics Biostructures, Sweden) Joanne Clark (University of Birmingham, United Kingdom) Loyau Stephane (INSERM UMR_S1148, France) Martine Pugnière (INSERM, U1194, France) Isabelia Jiacomini (Laboratório de Imunopulmica, Universidade Federal do Paraná, Brazil) Nadia Rose (SARomics Biostructures, Sweden) Kristell Leboeuf (Acticor Biotech SA, France) Kile Toledano (Acticor-Biotech, France) Deborah François (Acticor Biotech SA, France) Steve Watson (University of Birmingham, United Kingdom) Martine Jandrot-Perrus (INSERM UMR_S1148, France)

Abstract:
Platelet glycoprotein VI (GPVI) is attracting interest as a potential target for the development of new antiplatelet molecules with a low bleeding risk. GPVI binding to vascular collagen initiates thrombus formation and GPVI interactions with fibrin promote the growth and stability of the thrombus. In the present study we show that glenzocimab, a clinical stage humanised antibody fragment (Fab) with high affinity for GPVI, blocks binding of both ligands through a combination of steric hindrance and structural change. A co-crystal of glenzocimab with an extracellular domain of monomeric GPVI was obtained and its structure determined to a resolution of 1.9 Å. The data revealed that (i) glenzocimab binds to the D2 domain of GPVI; GPVI dimerisation was not observed in the crystal structure because glenzocimab prevented D2 homotypic interactions and the formation of dimers which have a high affinity for collagen and fibrin; (ii) the light variable (VL) domain of the GPVI-bound Fab causes steric hindrance that is predicted to prevent the collagen-related peptide (CRP)/collagen fibers from extending out of their binding site and preclude GPVI clustering and downstream signaling. Glenzocimab did not bind to a truncated GPVI missing loop residues 129-136, thus validating the epitope identified in the crystal structure. Overall, these findings demonstrate that the binding of glenzocimab to the D2 domain of GPVI induces steric hindrance and structural modifications that drive the inhibition of GPVI interactions with its major ligands.

Conflict of interest: COI declared - see note

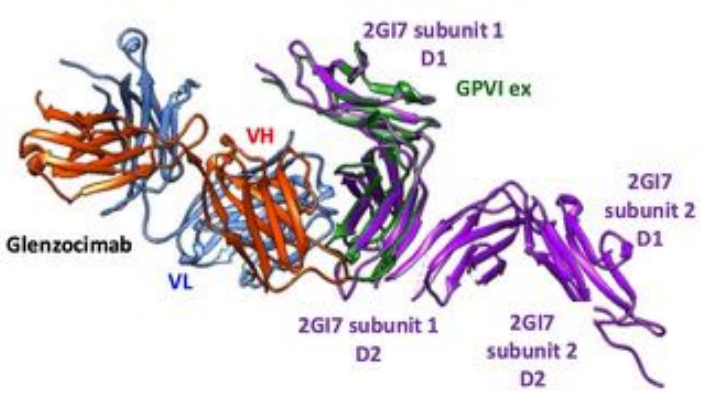
COI notes: PB and MJP are founders and scientific advisers for Acticor-Biotech SF, KL and ET are employees at Acticor-Biotech MM and NR are employees at SARomics Biostructures

Preprint server: No;

Author contributions and disclosures: PB and MJP designed the study, interpreted the data and wrote the manuscript. AS and SW provided GPVI-Fc(129-136, interpreted the data and edited the manuscript. MM, JCC, MP, designed experiments, interpreted the data, and edited the manuscript; IGJ contributed to structural analysis; NR, SL and SF performed experiments, ET edited the manuscript. KL contributed to design the heterologous expression and purification of GPVIex

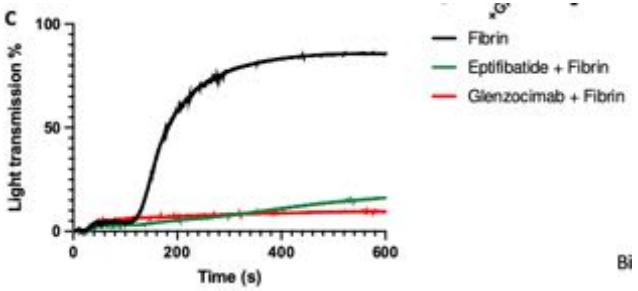
Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: atomic coordinates and structure factors (PDB ID codes 7R58) have been deposited in the Protein Data Bank (www.wwpdb.org)



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

nature COMMUNICATIONS

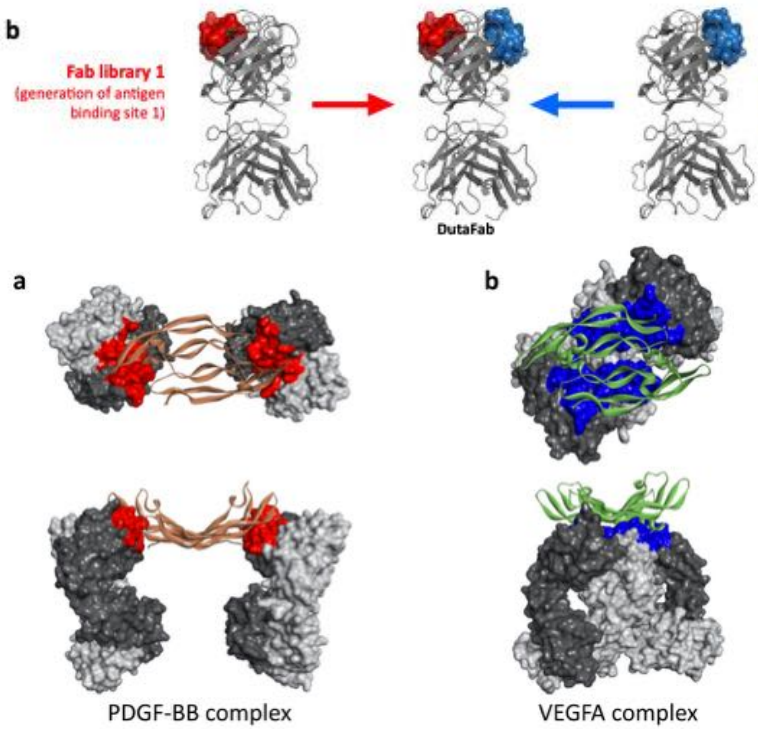
ARTICLE

OPEN

DutaFabs are engineered therapeutic Fab fragments that can bind two targets simultaneously

Roland Beckmann, Kristian Jensen, Sebastian Fenn, Janina Speck, Katrin Krause, Anastasia Meier, Melanie Röth, Sascha Fauser, Raymond Kimbung, Derek T. Logan, Martin Steegmaier & Hubert Kettenberger

We report the development of a platform of dual targeting Fab (DutaFab) molecules, which comprise two spatially separated and independent binding sites within the human antibody CDR loops: the so-called H-side paratope encompassing HCDR1, HCDR3 and LCDR2, and the L-side paratope encompassing LCDR1, LCDR3 and HCDR2. Both paratopes can be independently selected and combined into the desired bispecific DutaFabs in a modular manner. X-ray crystal structures illustrate that DutaFabs are able to bind two target molecules simultaneously at the same Fv region comprising a VH-VL heterodimer. In the present study, this platform is applied to generate DutaFabs specific for VEGFA and PDGF-BB, which show high affinities, physico-chemical stability and solubility, as well as superior efficacy over anti-VEGF monotherapy in vivo. These molecules exemplify the usefulness of DutaFabs as a distinct class of antibody therapeutics, which is currently being evaluated in patients.



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

Published in Nature Communications!

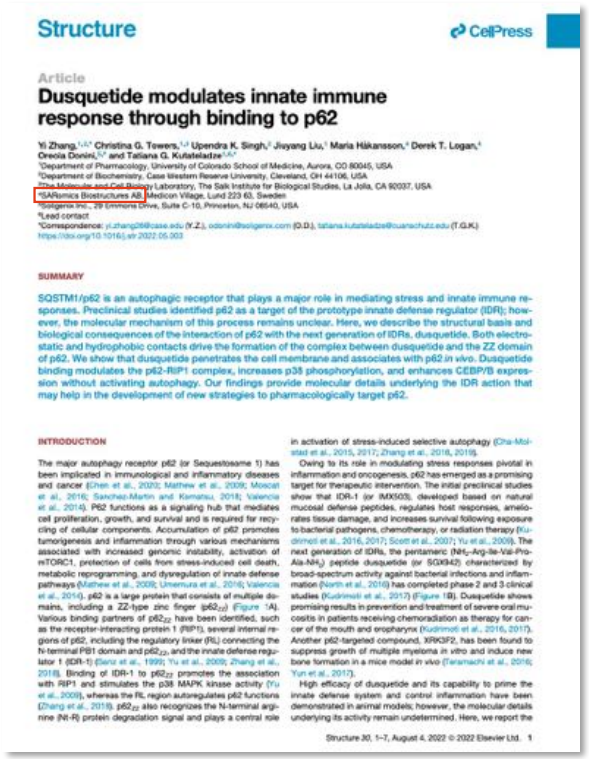
PDB code: 6T9E 6T9D

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

Article

Dusquetide modulates innate immune response through binding to p62

Yi Zhang,[1,6,*] Christina G. Towers,[1,2] Upendra K. Singh,[3] Jiuyang Liu,[1] Maria Håkansson,[4] Derek T. Logan,[4] Oreola Donini,[3,*] and Tatiana G. Kutateladze[1,5,*]

[1]Department of Pharmacology, University of Colorado School of Medicine, Aurora, CO 80045, USA

[2]Department of Biochemistry, Case Western Reserve University, Cleveland, OH 44106, USA

[3]The Molecular and Cell Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA

[4]SARomics Biostructures AB, Medicon Village, Lund 223 63, Sweden

[5]Soligenix Inc., 29 Emmons Drive, Suite C-10, Princeton, NJ 08540, USA

[6]Lead contact

[*]Correspondence: yi.zhang2@case.edu (Y.Z.), odonini@soligenix.com (O.D.), tatiana.kutateladze@ouanschutz.edu (T.G.K.)

https://doi.org/10.1016/j.str.2022.05.003

SUMMARY

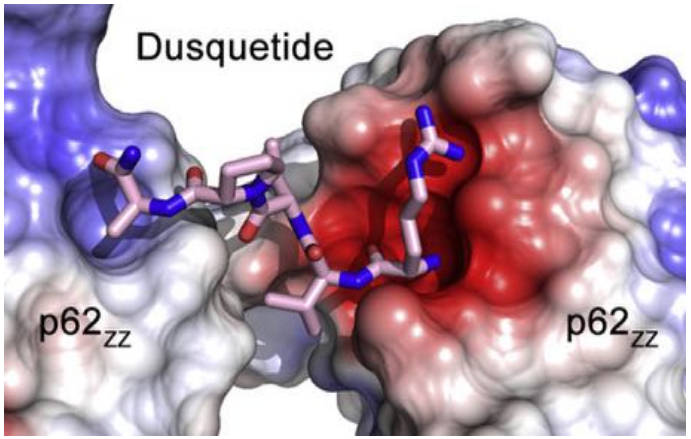
SQSTM1/p62 is an autophagic receptor that plays a major role in mediating stress and innate immune responses. Preclinical studies identified p62 as a target of the prototype innate defense regulator (IDR); however, the molecular mechanism of this process remains unclear. Here, we describe the structural basis and biological consequences of the interaction of p62 with the next generation of IDRs, dusquetide. Both electrostatic and hydrophobic contacts drive the formation of the complex between dusquetide and the ZZ domain of p62. We show that dusquetide penetrates the cell membrane and associates with p62 *in vivo*. Dusquetide binding modulates the p62-RIP1 complex, increases p38 phosphorylation, and enhances CEBP/B expression without activating autophagy. Our findings provide molecular details underlying the IDR action that may help in the development of new strategies to pharmacologically target p62.

INTRODUCTION

The major autophagy receptor p62 (or Sequestosome 1) has been implicated in immunological and inflammatory diseases and cancer (Chen et al., 2020; Mathew et al., 2009; Moscat et al., 2016; Sanchez-Martin and Komatsu, 2018; Valencia et al., 2014). P62 functions as a signaling hub that mediates cell proliferation, growth, and survival and is required for recycling of cellular components. Accumulation of p62 promotes tumorigenesis and inflammation through various mechanisms associated with increased genomic instability, activation of mTORC1, protection of cells from stress-induced cell death, metabolic reprogramming, and dysregulation of innate defense pathways (Mathew et al., 2009; Umemura et al., 2016; Valencia et al., 2014). p62 is a large protein that consists of multiple domains, including a ZZ-type zinc finger ($p62_{ZZ}$) (Figure 1A). Various binding partners of $p62_{ZZ}$ have been identified, such as the receptor-interacting protein 1 (RIP1), several internal regions of p62, including the regulatory linker (RL) connecting the N-terminal PB1 domain and $p62_{ZZ}$, and the innate defense regulator 1 (IDR-1) (Seiz et al., 1999; Yu et al., 2009; Zhang et al., 2018). Binding of IDR-1 to $p62_{ZZ}$ promotes the association with RIP1 and stimulates the p38 MAPK kinase activity (Yu et al., 2009), whereas the RL region autoregulates p62 functions (Zhang et al., 2018). $p62_{ZZ}$ also recognizes the N-terminal arginine (N-R) protein degradation signal and plays a central role in activation of stress-induced selective autophagy (Cha-Molstad et al., 2015, 2017; Zhang et al., 2018, 2019).

Owing to its role in modulating stress responses pivotal in inflammation and oncogenesis, p62 has emerged as a promising target for therapeutic intervention. The initial preclinical studies show that IDR-1 (or IMX503), developed based on natural mucosal defense peptides, regulates host responses, ameliorates tissue damage, and increases survival following exposure to bacterial pathogens, chemotherapy, or radiation therapy (Kudrimoti et al., 2016, 2017; Scott et al., 2007; Yu et al., 2009). The next generation of IDRs, the pentameric (NH_2-Arg-Ile-Val-Pro-Ala-NH_2) peptide dusquetide (or SGX942) characterized by broad-spectrum activity against bacterial infections and inflammation (North et al., 2018) has completed phase 2 and 3 clinical studies (Kudrimoti et al., 2017) (Figure 1B). Dusquetide shows promising results in prevention and treatment of severe oral mucositis in patients receiving chemoradiation as therapy for cancer of the mouth and oropharynx (Kudrimoti et al., 2016, 2017). Another p62-targeted compound, XRK3F2, has been found to suppress growth of multiple myeloma *in vitro* and induce new bone formation in a mice model *in vivo* (Teramachi et al., 2016; Yun et al., 2017).

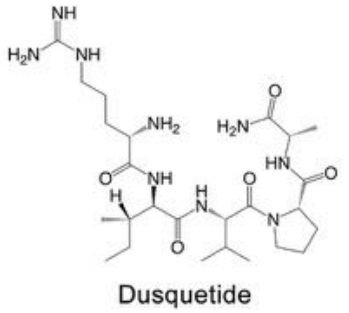
High efficacy of dusquetide and its capability to prime the innate defense system and control inflammation have been demonstrated in animal models; however, the molecular details underlying its activity remain undetermined. Here, we report the



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

Björn Walse
CEO
SARomics Biostructures AB
bjorn.walse@saromics.com
Tel: +46 46 26 10 470

www.saromics.com

Headquarters
Medicon Village • SE-223 81 Lund • Sweden

US branch
245 First Street • Cambridge MA 02142 • USA
Tel: +1 857 444 4570

Japanese distributor
Carna Biosciences. Inc.
BMA 3F • 1-5-5 Minatojima-Minamimachi • Chuo-ku
Kobe 650-0047 • Japan
Tel: +81 78 302 7091