LAVA THERAPEUTICS

Innovations from the therapeutics antibody space: obligate bispecific antibodies & T cell engagers

Paul W.H.I. Parren

The Antibody Society, Webinar

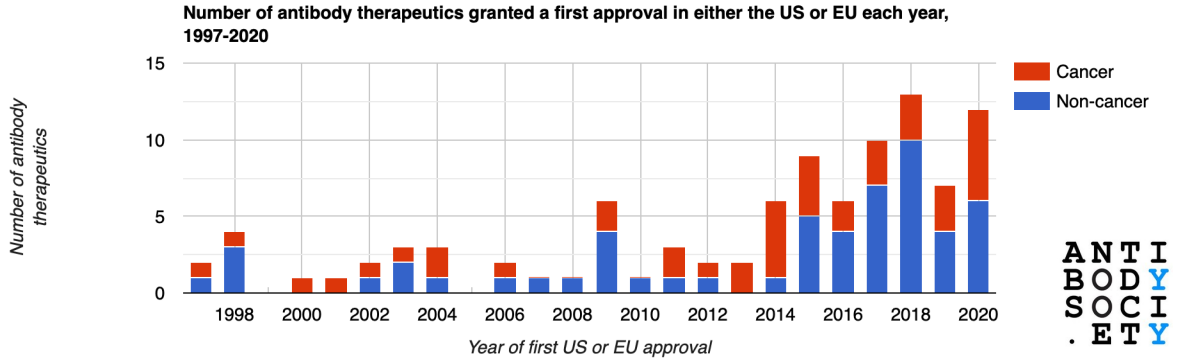
21 October 2021

The antibody landscape

NEWS · 05 MAY 2021

FDA approves 100th monoclonal antibody product

Thirty-five years on from the FDA's approval of a first monoclonal antibody, these biologics account for nearly a fifth of the agency's new drug approvals each year.



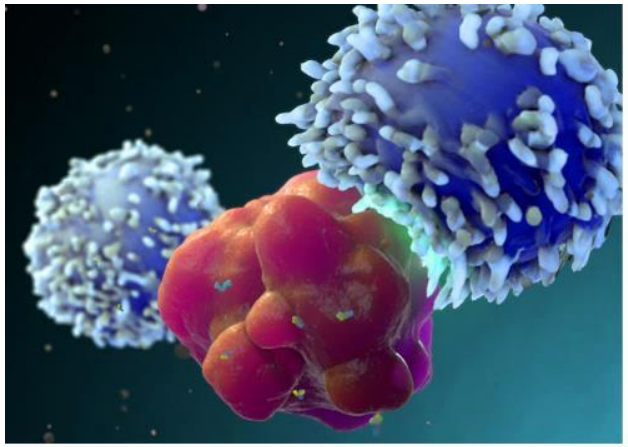
One hundred approvals in, in other words, the field is only just getting started. "The next 100 will be a lot faster than the first 100," says Parren.

Asher Mullard, Nature Reviews Drug Discovery, online May 2021,
https://www.nature.com/articles/d41573-021-00079-7

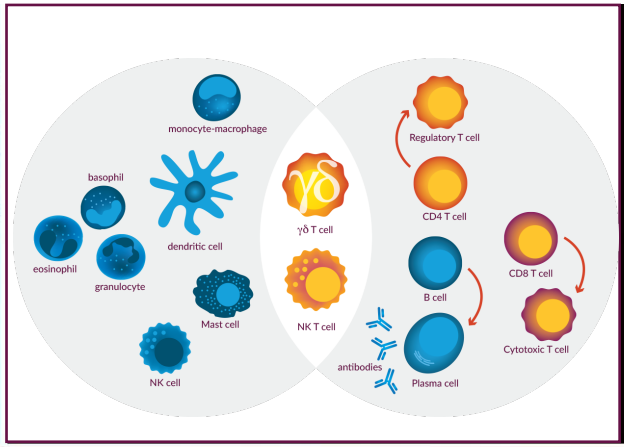
Updated October 2021: (±950 Abs in clinical trials; 110 approved/marketed in EU/US (Janice Reichert, The Antibody Society)
https://www.antibodysociety.org/resources/approved-antibodies/

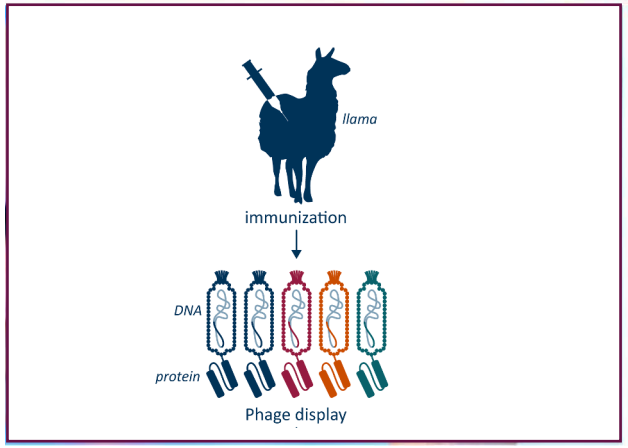
Harnasing the potency of the immune system
from basic immunological principles to innovative therapeutics

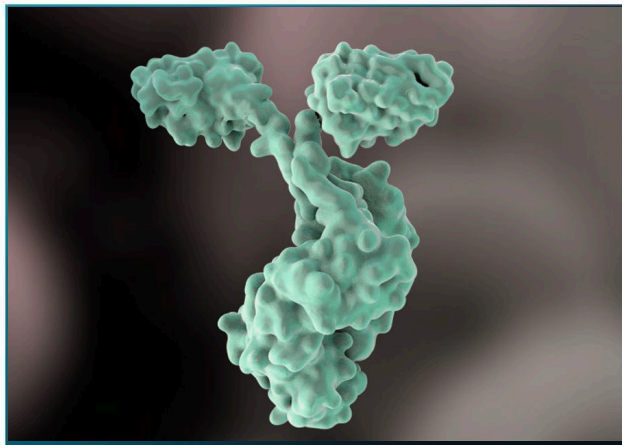
Inspired by the power of our immune system….



curious to investigate basic immunological principles…



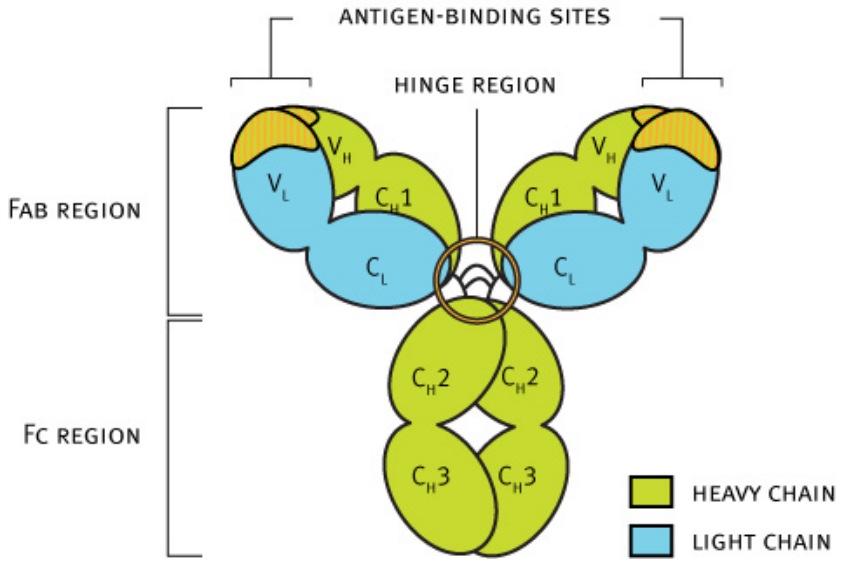


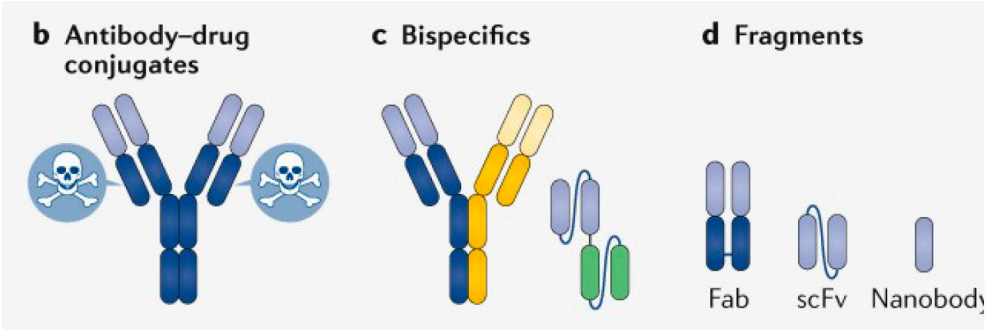


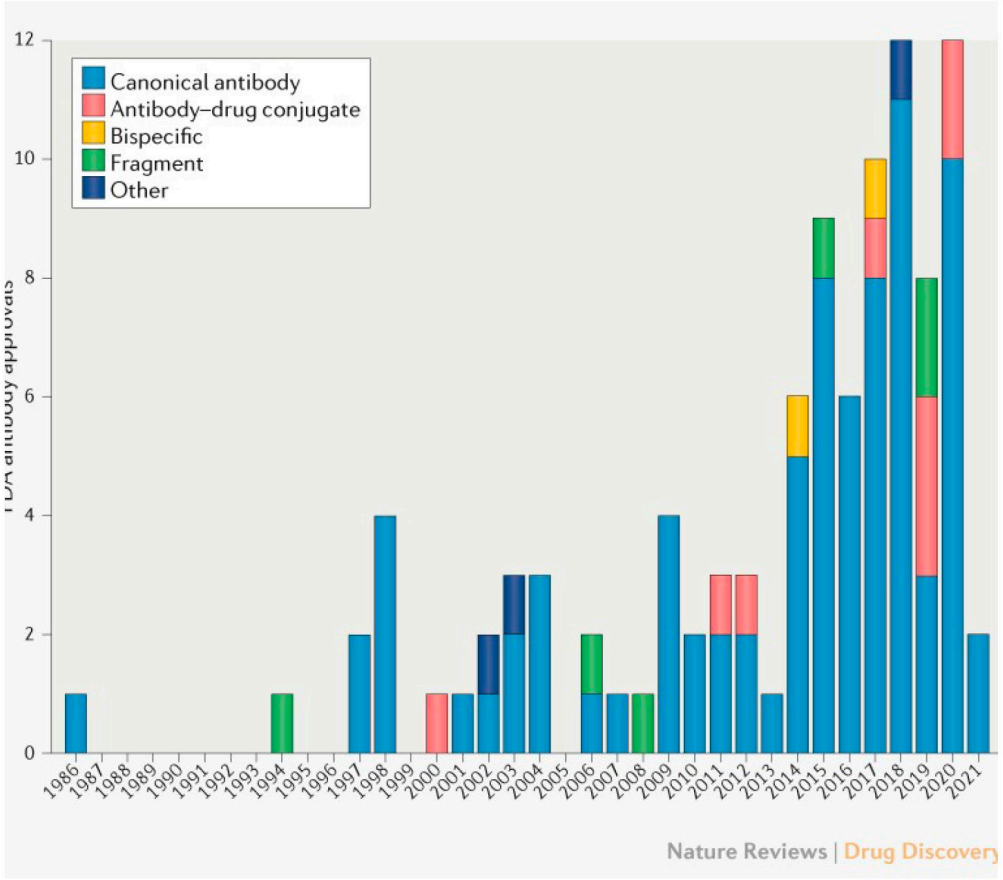
…and translate those to practical applications,…

…innovative technologies and therapeutic antibody products.

The antibody landscape - shifting gears - from canonical antibodies to novel potentiated formats







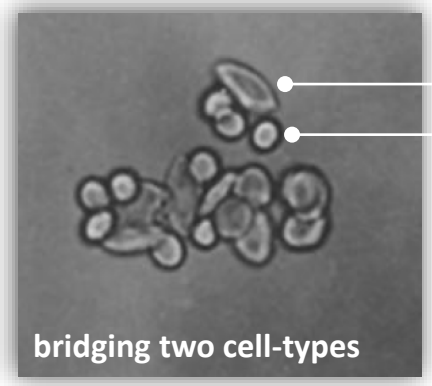
Asher Mullard, Nature Reviews Drug Discovery, online May 2021

A short history of bispecific antibodies

1960 Nisonoff *et al*
"… to attempt to prepare antibody of mixed specificity."
First mention of concept

1964 Fudenberg *et al*
First demonstration of concept

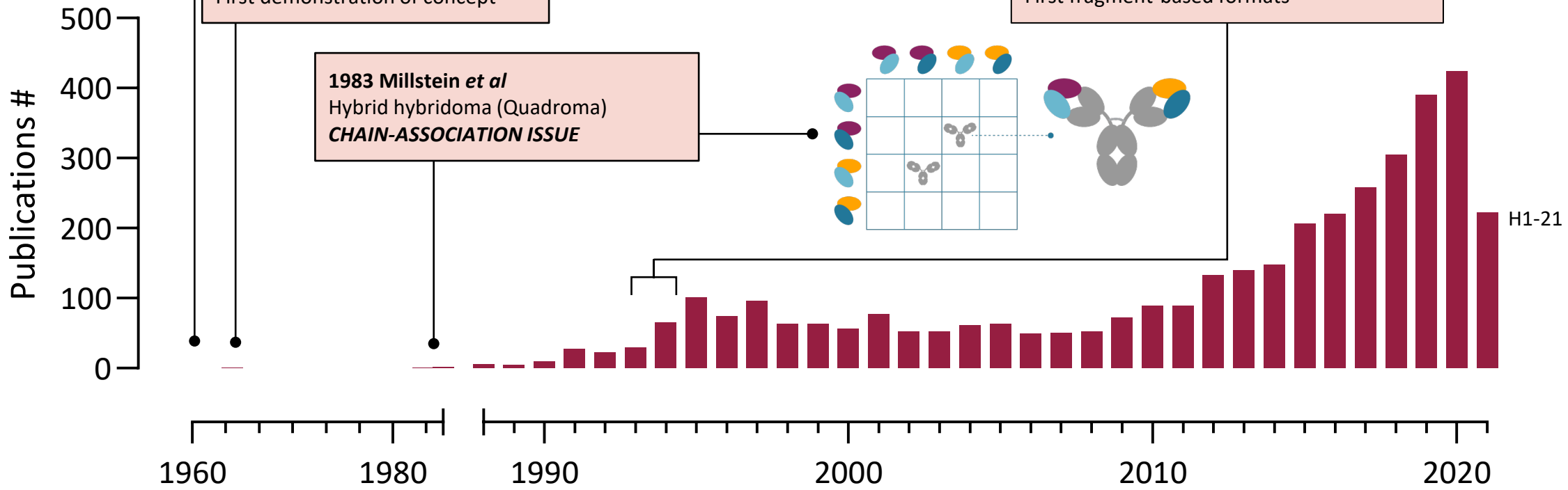
1983 Millstein *et al*
Hybrid hybridoma (Quadroma)
CHAIN-ASSOCIATION ISSUE



F(ab')$_2$

diabody tandem scFv

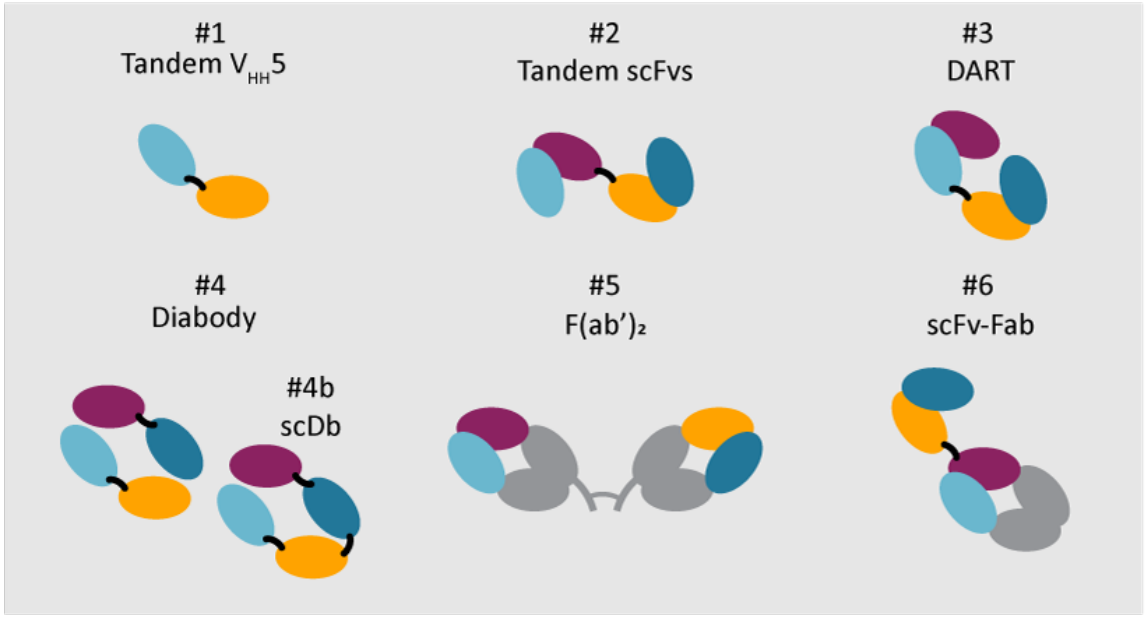
1993 Holliger *et al*
1994 Mallender *et al* & Gruber *et al*
First fragment-based formats



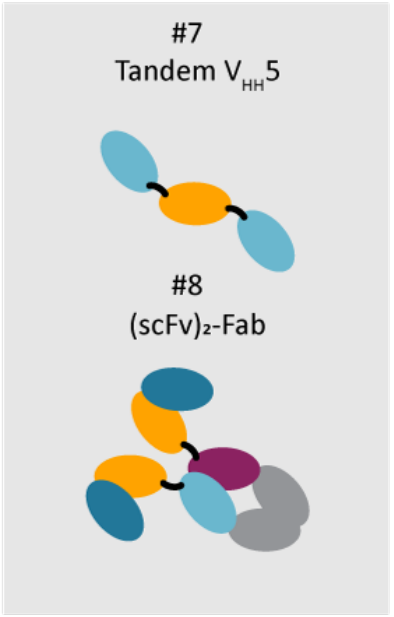
Updated September 2021

Fragment-based Formats - the minimalistic approach

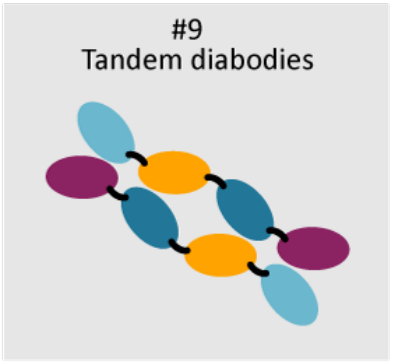
1+1 fragment-based



1+2 fragment-based



2+2 fragment-based



Features

- Modular antigen-binding units, engineered together
- No Fc-domain
- Short plasma half-life

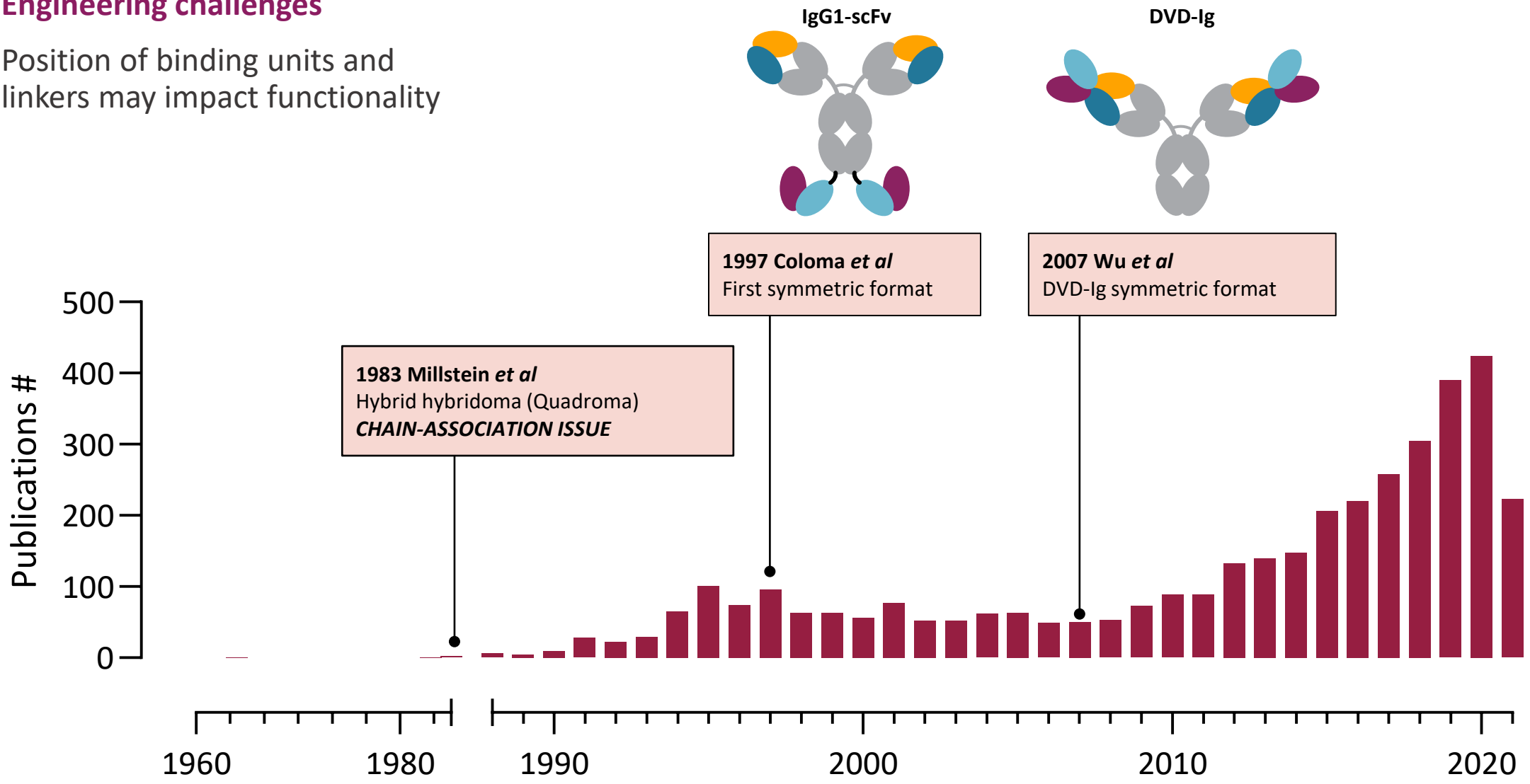
#1 & #7	Nanobody
#2	BiTE (bispecific T-cell engager)
#3	DART (dual-affinity re-targeting)
#6 & #8	iTab (immunotherapy antibody)
#9	TandAb (tandem diabody)

Formats in the clinic: cut-off 1 Mar 2019

A short history of bispecific antibodies

Engineering challenges

Position of binding units and linkers may impact functionality



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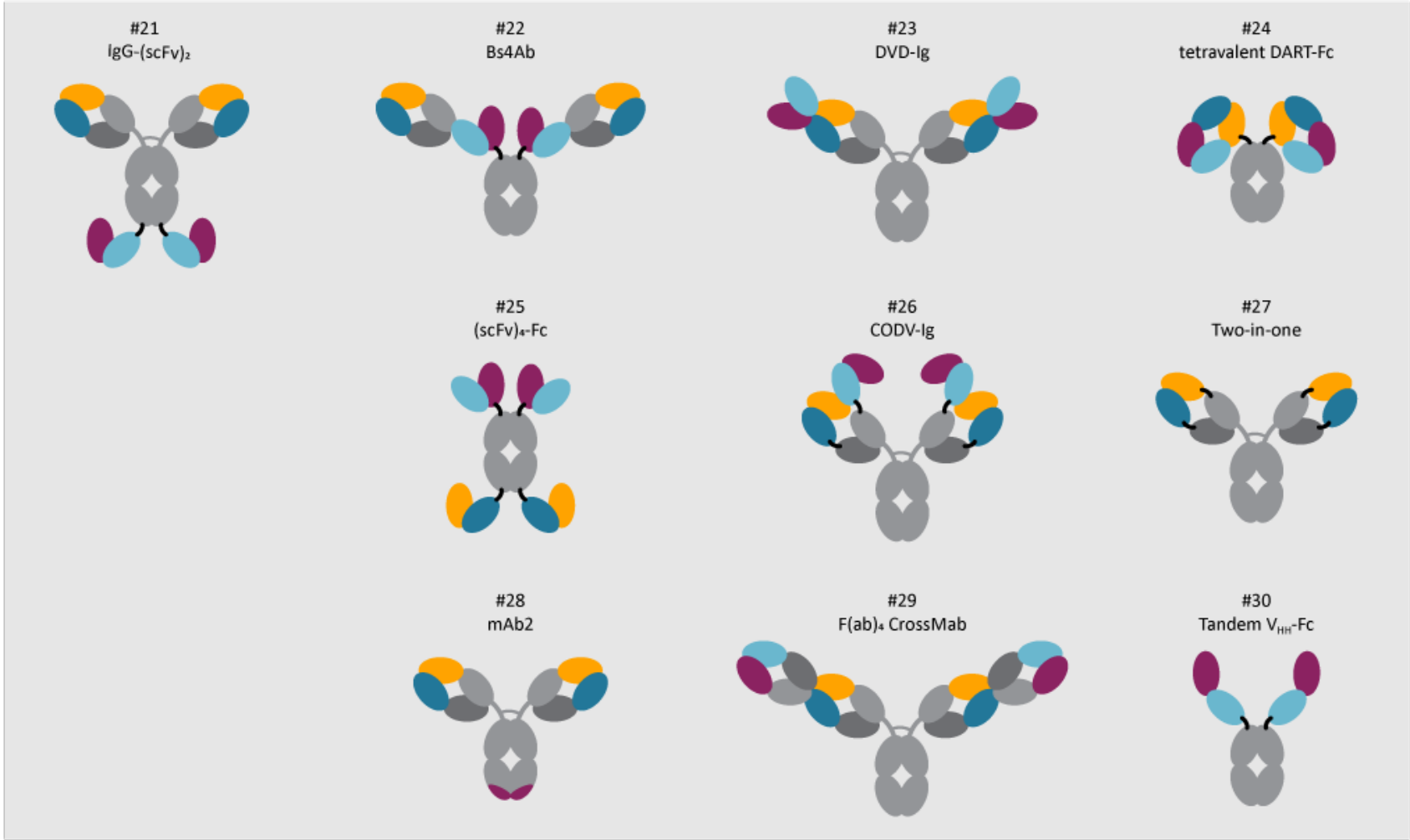
Symmetric Formats - Appended IgG / IgG-like formats

2 + 2 symmetric



Features

- Highly engineered
- Tetravalent (2+2)
- Fc-domain
- Often relatively large molecules
- Extended plasma half-life

#23 DVD (dual variable domain)
#24 DART (dual-affinity re-targeting)
#25 Adaptir
#26 CODV (cross-over dual variable)
#27 DAF (dual-action Fab)
#29 CrossMab

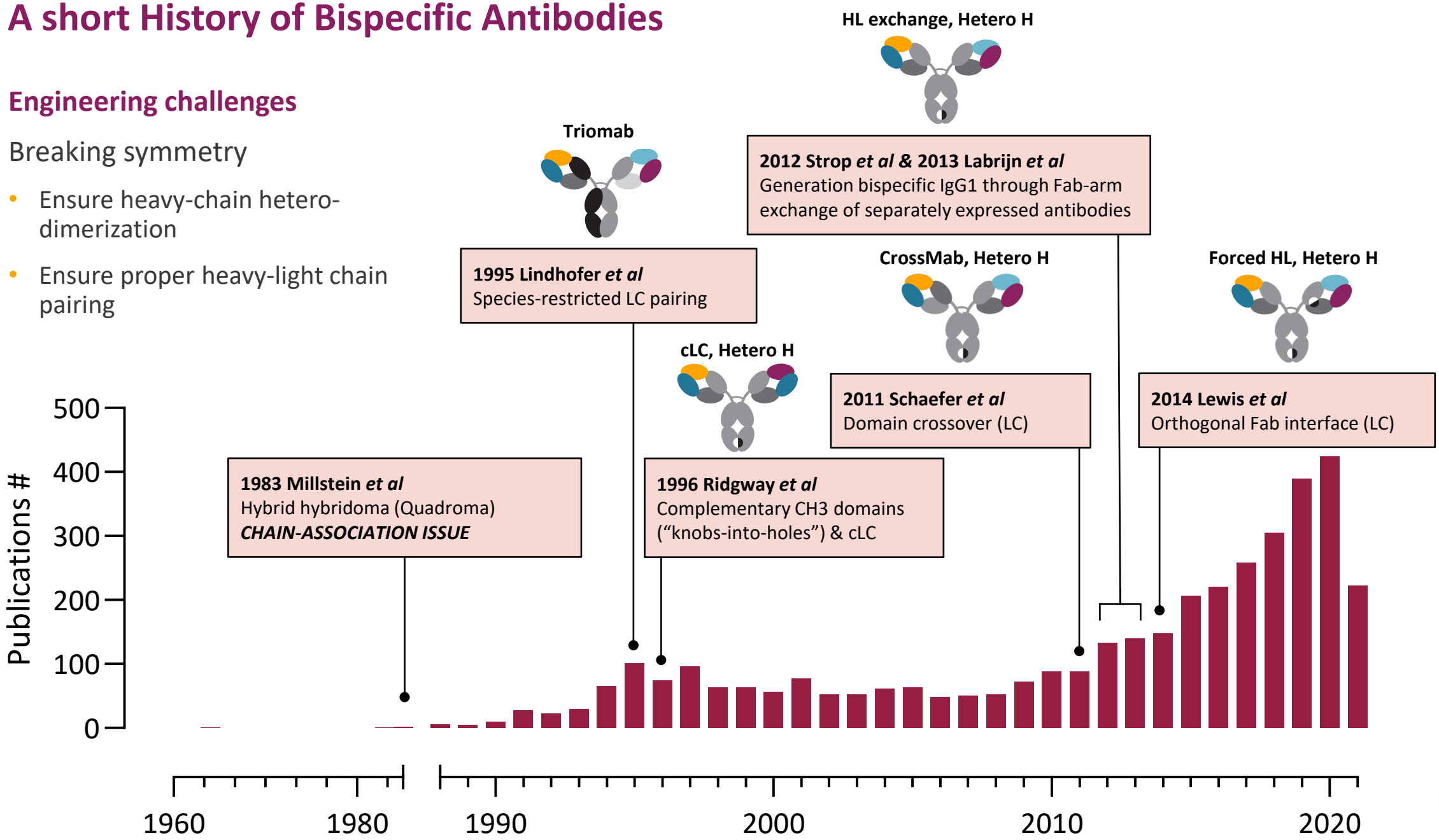
Formats in the clinic: cut-off 1 Mar 2019

A short History of Bispecific Antibodies

Engineering challenges

Breaking symmetry

- Ensure heavy-chain hetero-dimerization
- Ensure proper heavy-light chain pairing



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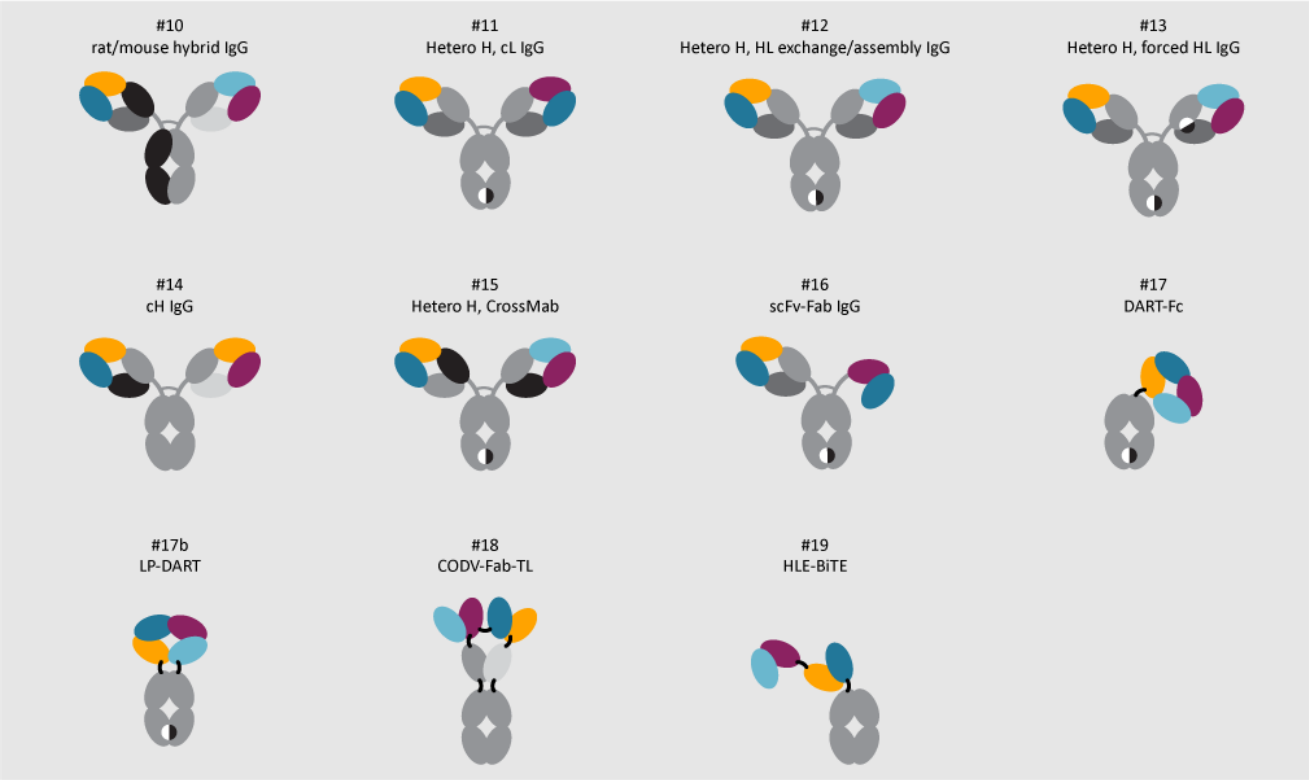
Asymmetric Formats - Preserve native IgG architecture

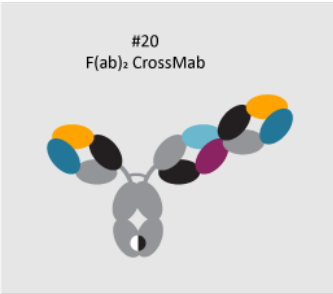
1 + 1 asymmetric



Features

- Regular IgG structure
- Monovalent for each target (except **#20**)
- Fc-domain
- Extended plasma half-life

1 + 2 asymmetric



#10 Triomab
#11 Biclonics, ART-Ig (asym. reengineering technology)
#12 DuoBody, (KiH) Knobs-into-Holes
#13 DuetMab

#14	κλ body
#15 & #20	CrossMab
#16	Xmab, YBODY, BEAT
#17(b)	DART (dual-affinity re-targeting)
#18	crossover dual variable (CODV)

Formats in the clinic: cut-off 1 Mar 2019

A short history of bispecific antibodies

Bispecific antibodies entering clinical pipeline

170+
COMPOUNDS
IN CLINICAL TRIALS

HL exchange, Hetero H

NEW NOW APPROVED RYBREVANT (amivantamab-vmjw)

amivantamab (Lung cancer)
Approved in the US in 2021

DuoBody

cLC, Hetero HC

HEMLIBRA emicizumab

Emicizumab
Approved in the US in 2017
Approved in the EU in 2018

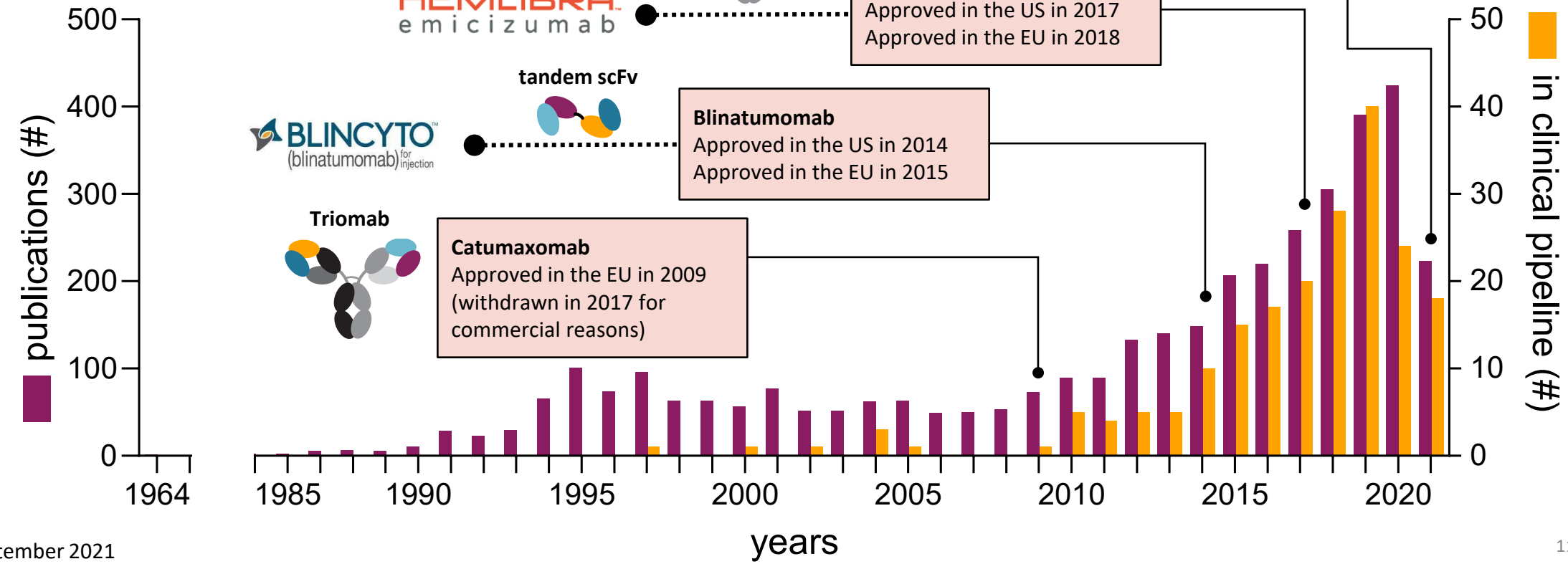
tandem scFv

BLINCYTO (blinatumomab) for injection

Blinatumomab
Approved in the US in 2014
Approved in the EU in 2015

Triomab

Catumaxomab
Approved in the EU in 2009
(withdrawn in 2017 for commercial reasons)



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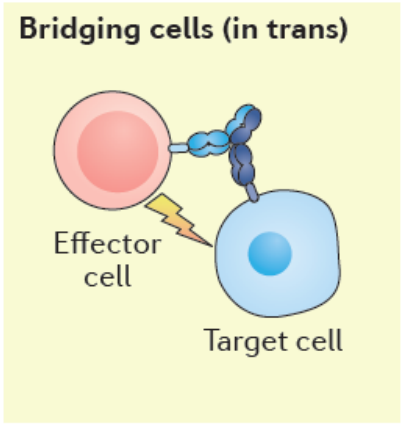
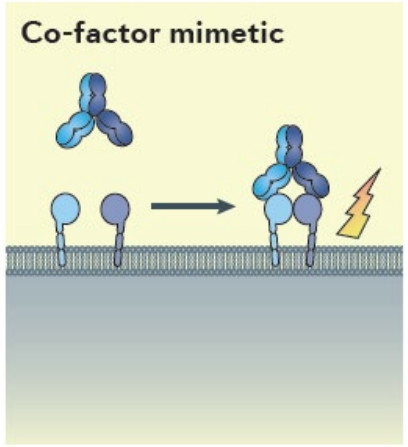
The Potential of Bispecific Antibodies ….to unlock unique mechanisms

Obligate bispecific antibody:

Bispecific antibodies that display a new activity or functionality that is dependent on the physical linkage of the two specificities

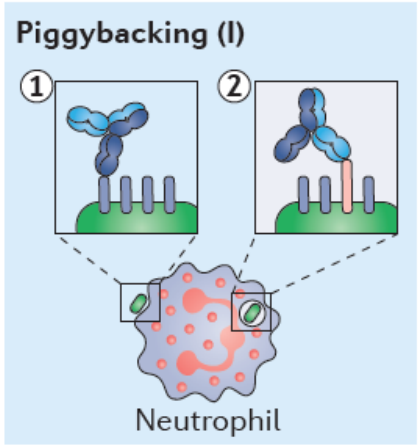
Labrijn, Janmaat, Reichert and Parren
Nature Rev Drug Discovery (18:585-608, 2019)

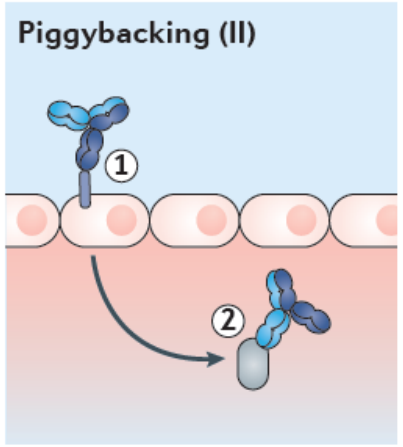




Spatial

Bispecific antibodies that require **simultaneous** binding for their functionality





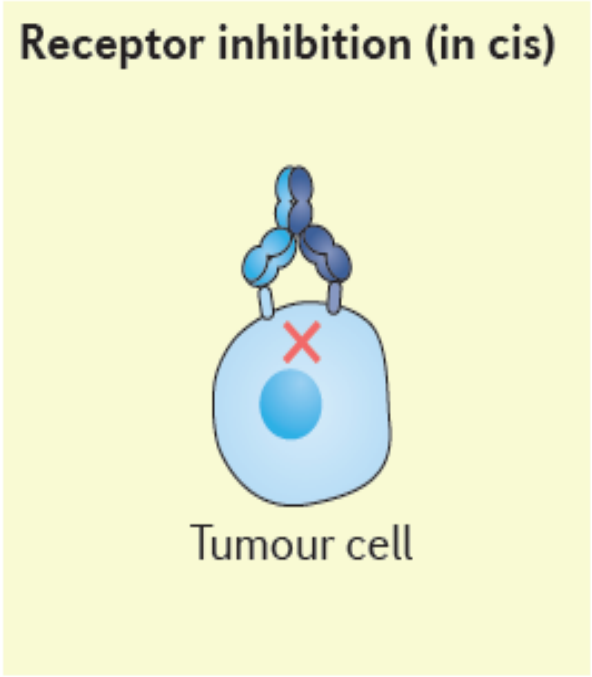
Temporal

Bispecific antibodies that require **sequential** binding for their functionality

The Potential of Bispecific Antibodies
Mechanistic classification

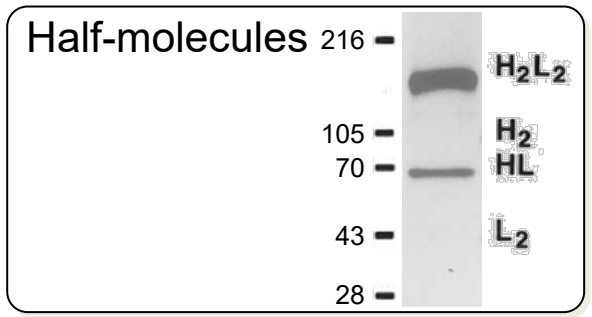
Combinatorial bispecific antibody

Bispecific antibodies that display an activity or functionality that can also be obtained by **combining separate antibodies** with the same specificities (for example, a parental or reference antibody mixture).

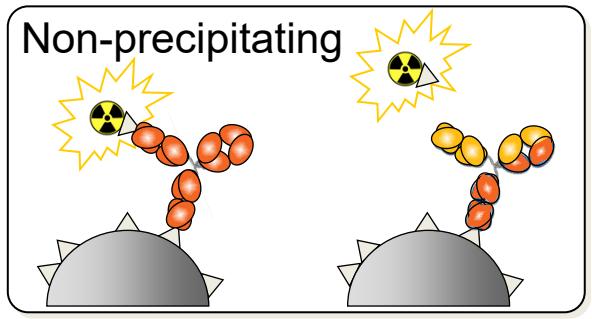


IgG4 antibodies - “peculiar” in vitro and in vivo properties -- gain bispecific properties post-production in blood

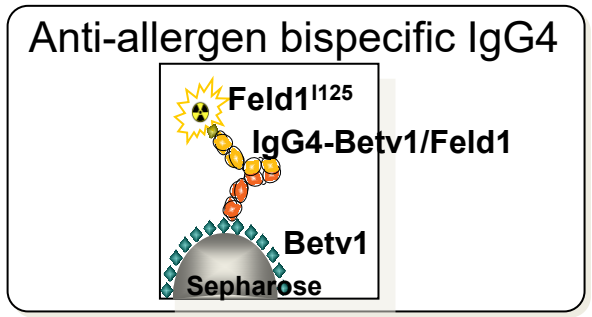
IgG4



Angal, et al, Mol Imm 1993
Schuurman, et al, Mol Imm 2001

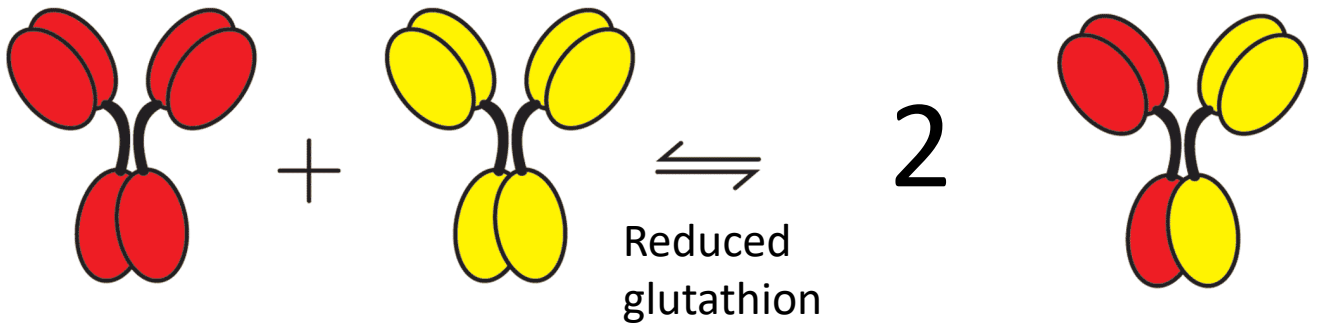


van der Zee, et al, JI 1986



van der Neut Kolfschoten et al. Science 317, 1554-1557 (2007)

IgG4 antibodies – exchange half-molecules in humans in vivo and become naturally bispecific in vivo



The process is functionally described as ‘Fab-arm exchange’

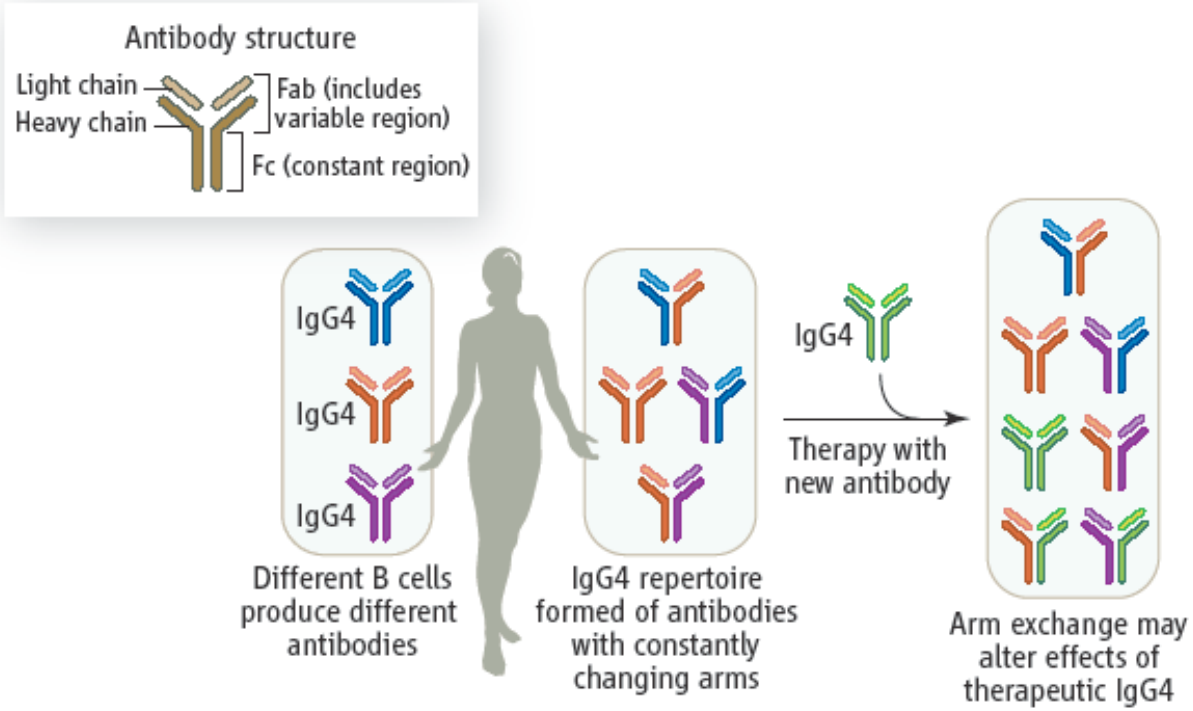
van der Neut Kolfschoten et al. (2007) Science 317:1554-1557
Labrijn et al. (2009) Nature Biotechnol 27:767-71

IMMUNOLOGY

Square-Dancing Antibodies

Dennis R. Burton and Ian A. Wilson

Antibody therapies need to take account of a subclass of immunoglobulin G that can swap subunits in vivo.



Burton and Wilson (2007) Science 317; 1507-1508
van der Neut Kolfschoten et al. (2007) Science 317:1554-1557
Labrijn et al. (2009) Nature Biotechnol 27:767-71

IMMUNOLOGY

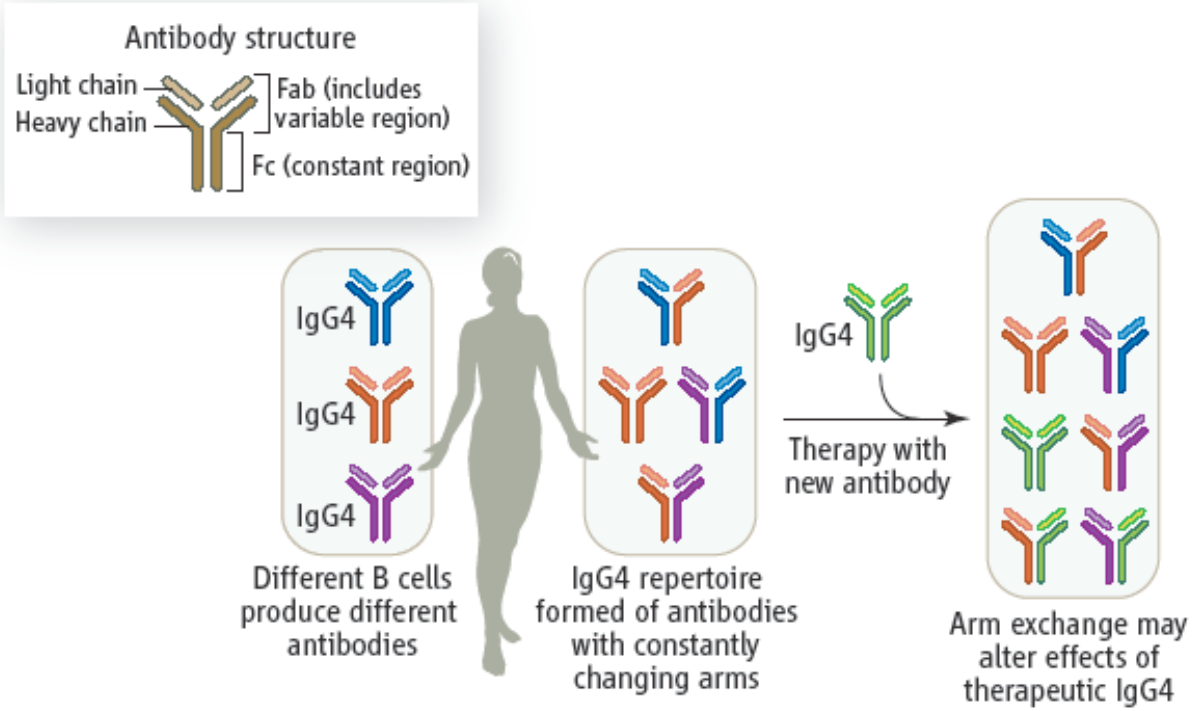
Square-Dancing Antibodies

Dennis R. Burton and Ian A. Wilson

Antibody therapies need to take account of a subclass of immunoglobulin G that can swap subunits in vivo.

IgG4 antibodies in our blood:

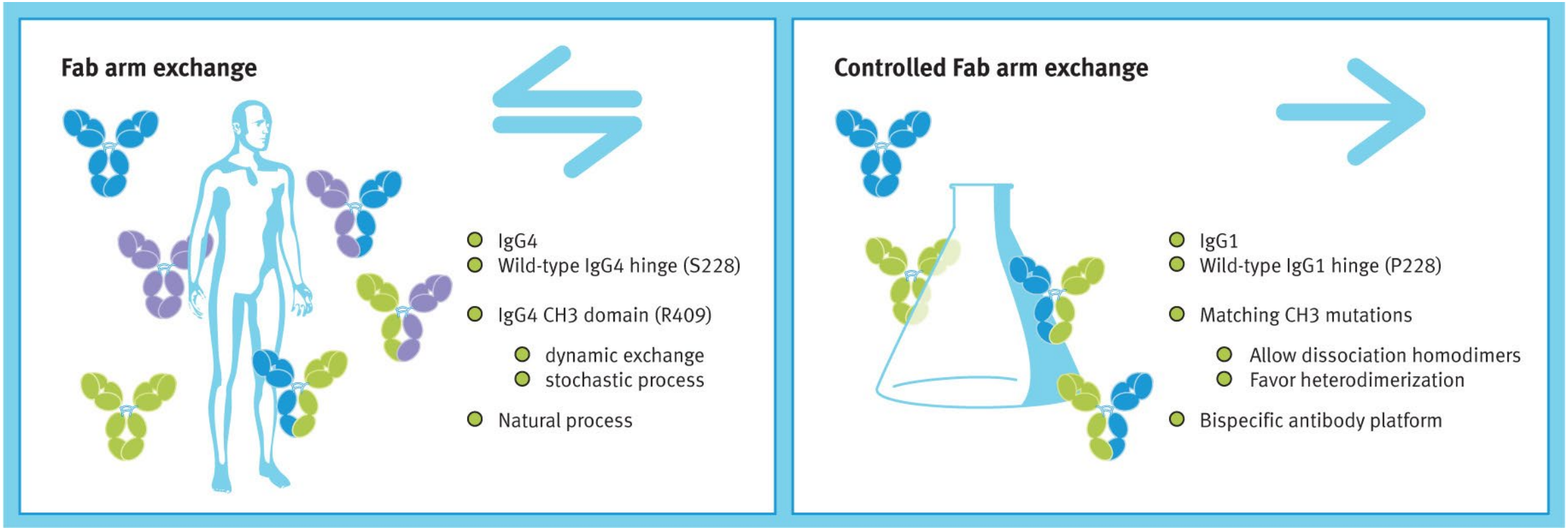
- are dynamic molecules
- acquire bispecific properties
- usually do not crosslink antigens
- do not form large immune complexes



Burton and Wilson (2007) Science 317; 1507-1508
van der Neut Kolfschoten et al. (2007) Science 317:1554-1557
Labrijn et al. (2009) Nature Biotechnol 27:767-71

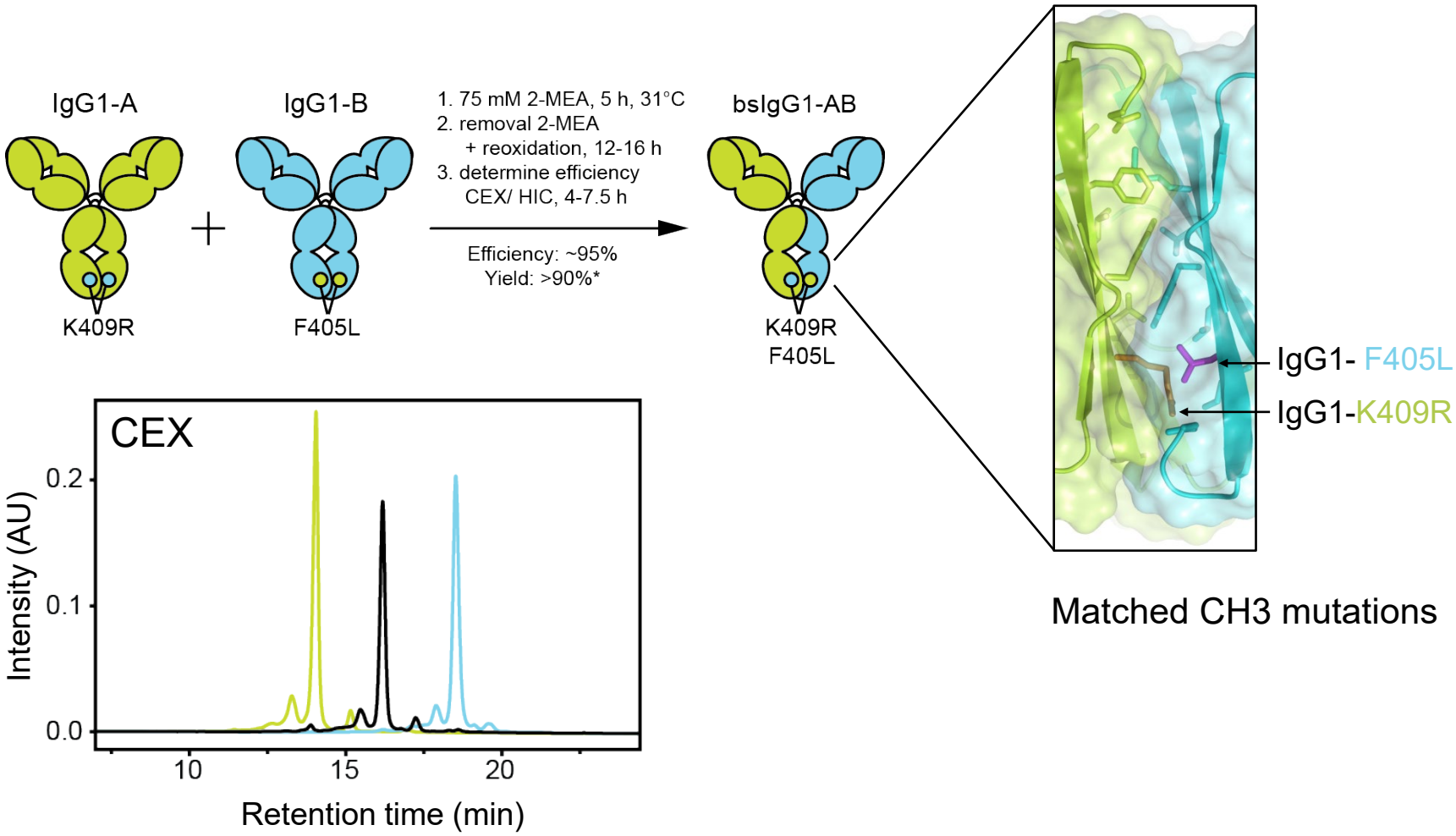
From science to a bispecific antibody platform:

Can we convert this in a manufacturing process for therapeutic antibody production?



Labrijn et al. Proc. Natl. Acad. Sci USA 10:5145-50 (2013)
Labrijn et al. Nature Protocols 9:2450-63 (2014)

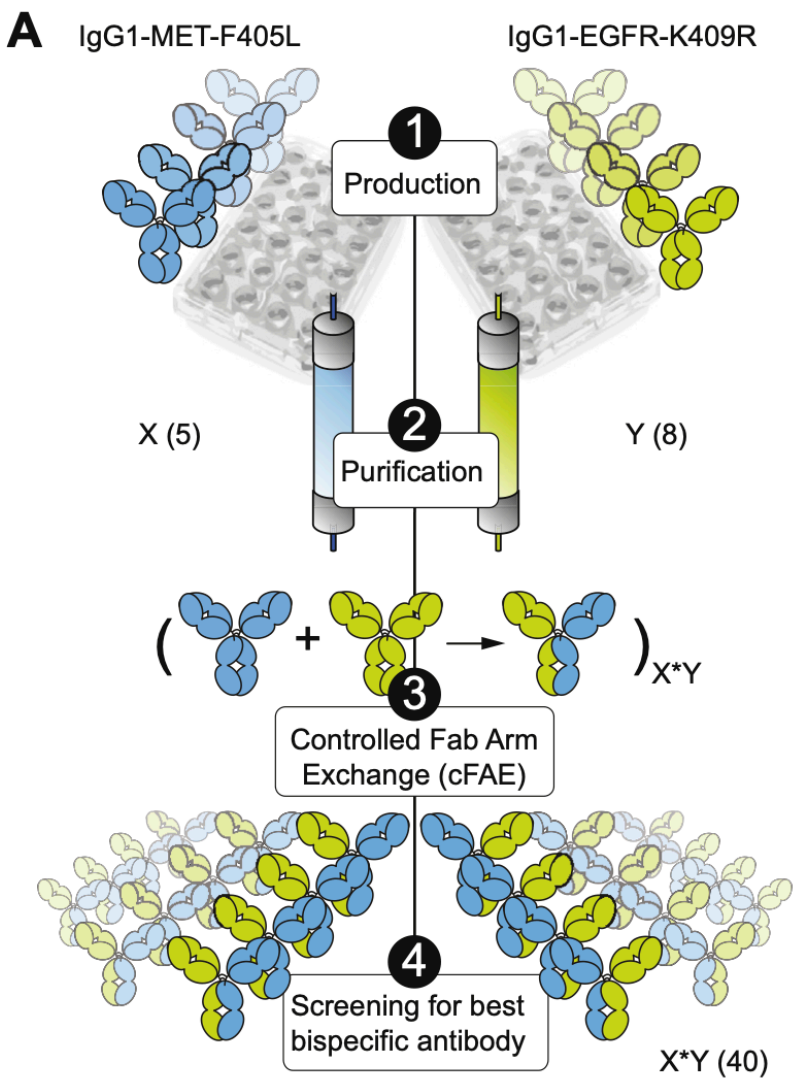
DuoBody® platform
Bispecific antibodies with high yield and stability

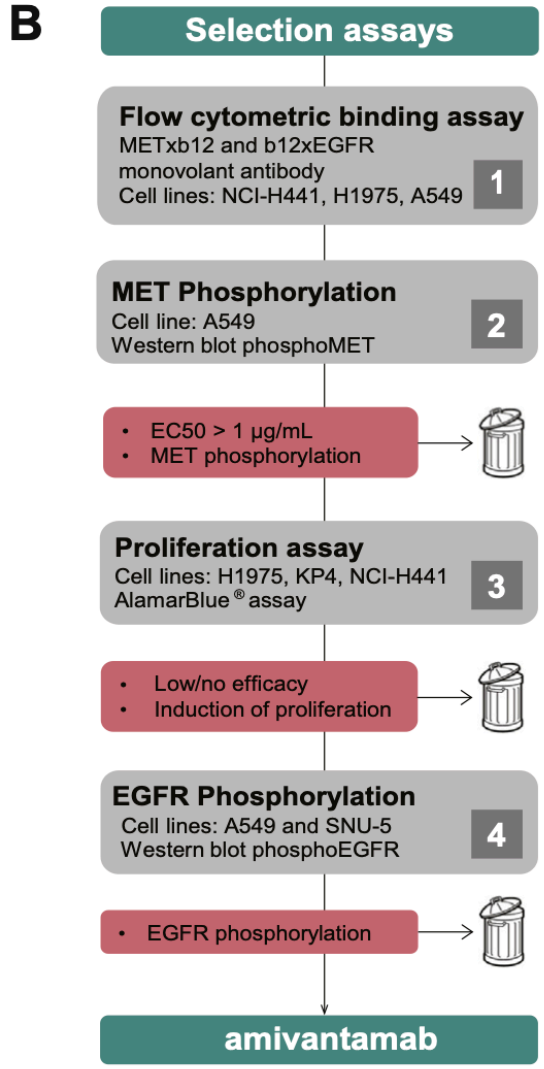


Labrijn et al. Proc. Natl. Acad. Sci USA (2013) 110: 5145-50.

DuoBody platform - bispecific antibody discovery for cancer

Generation and screening for optimal EGFR x cMet antibodies





JBC RESEARCH ARTICLE

Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET

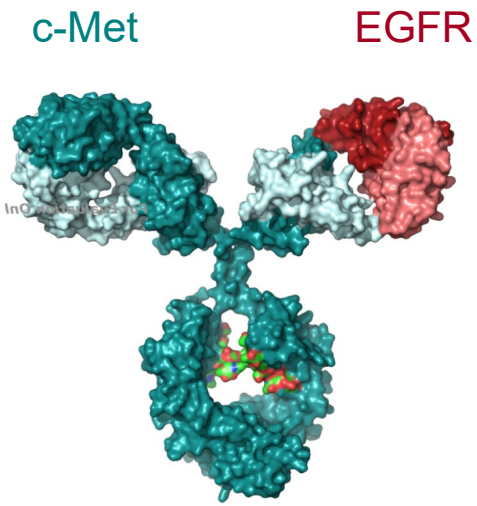
Received for publication, October 26, 2020, and in revised form, March 4, 2021 Published, Papers in Press, April 8, 2021,
https://doi.org/10.1016/j.jbc.2021.100641

Joost Neijssen[1,‡], **Rosa M. F. Cardoso**[2,‡], **Kristen M. Chevalier**[2], **Luus Wiegman**[1], **Thomas Valerius**[3], **G. Mark Anderson**[2], **Sheri L. Moores**[2], **Janine Schuurman**[1], **Paul W. H. I. Parren**[1], **William R. Strohl**[2], and **Mark L. Chiu**[2,*]

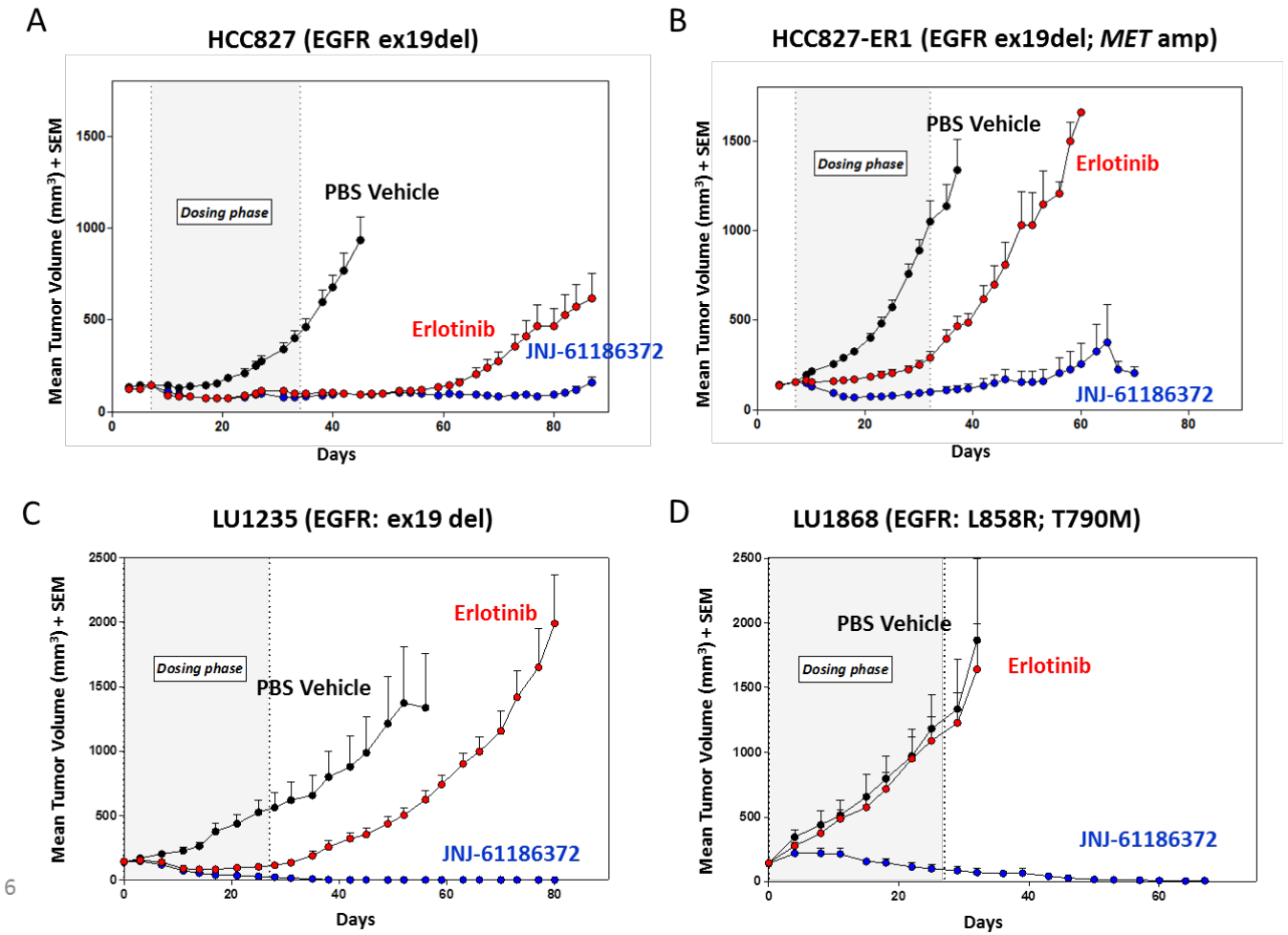
From the [1]Genmab, Utrecht, The Netherlands; [2]Janssen Research & Development, Spring House, Pennsylvania, USA; [3]Section for Stem Cell Transplantation and Immunotherapy, Department of Medicine II, Christian Albrechts University and University Hospital Schleswig-Holstein, Kiel, Germany

J. Biol. Chem. (2021) 296 100641

EGFR x cMet bispecific antibody
Highly effective in EGFR mutant models +/- cMet amplification



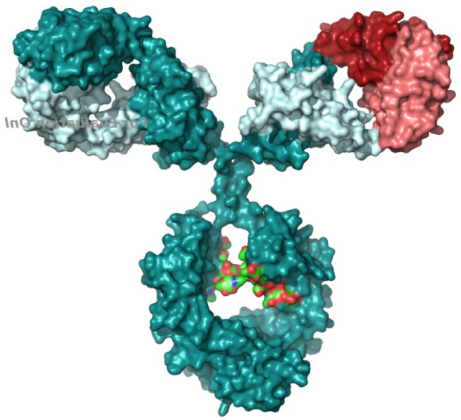
amivantamab



Jarantow et al. *J Biol. Chem. 290:24689-704* (2015)
Moores et al. *Cancer Research, 76:3942-3953* (2016)
Neijssen et al. *J. Biol. Chem. 296:100641* (2021)

Amivantamab, first DuoBody approved May 2021

c-Met EGFR



amivantamab

FDA grants accelerated approval to amivantamab-vmjw for metastatic non-small cell lung cancer

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On May 21, 2021, the Food and Drug Administration granted accelerated approval to amivantamab-vmjw (Rybrevant, Janssen Biotech, Inc.), a bispecific antibody directed against epidermal growth factor (EGF) and MET receptors, for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

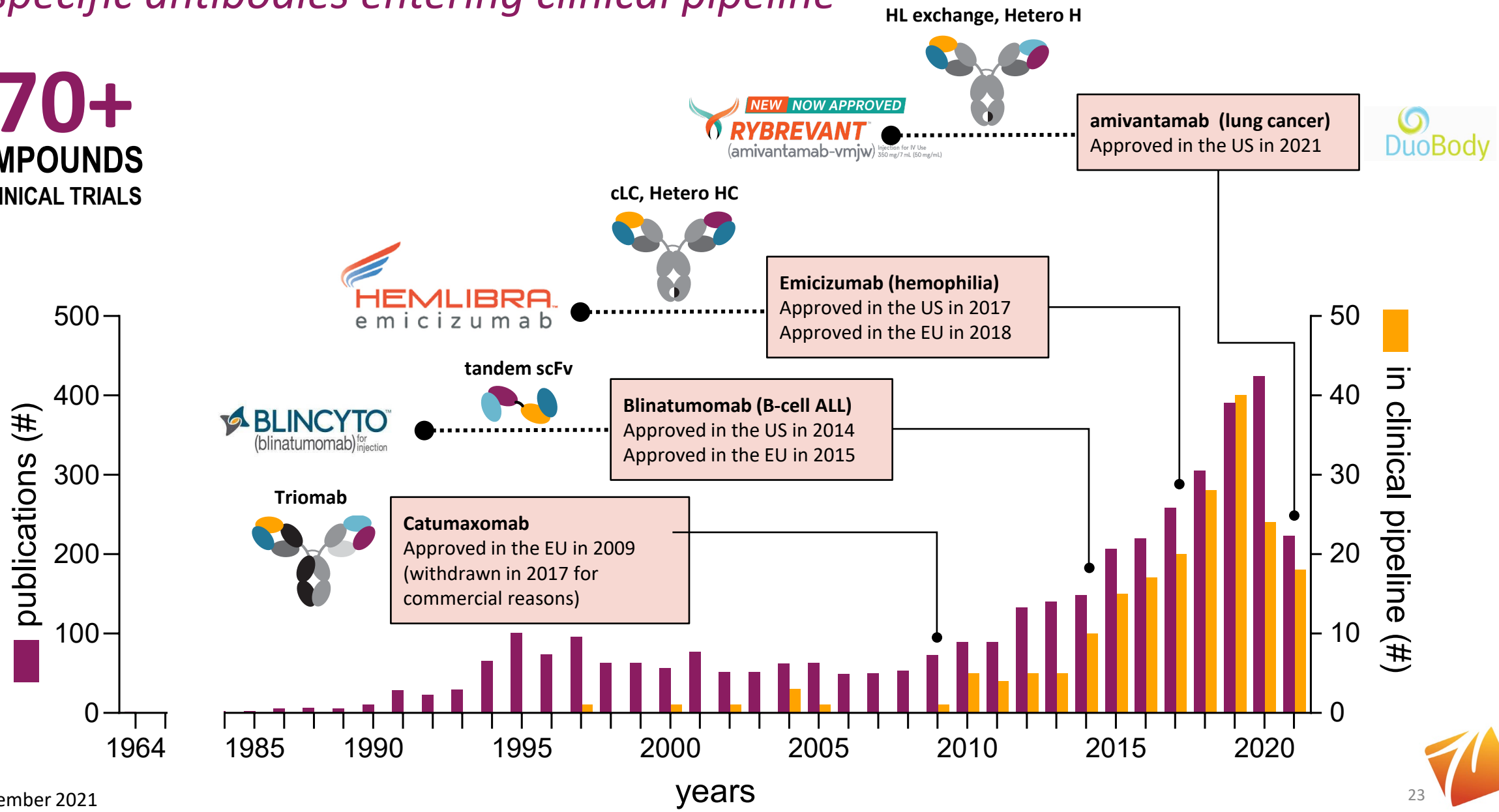
janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Jarantow et al. *J Biol. Chem. 290:24689-704* (2015)
Moores et al. *Cancer Research, 76:3942-3953* (2016)
Neijssen et al. *J. Biol. Chem. 296:100641* (2021)

A short history of bispecific antibodies

Bispecific antibodies entering clinical pipeline

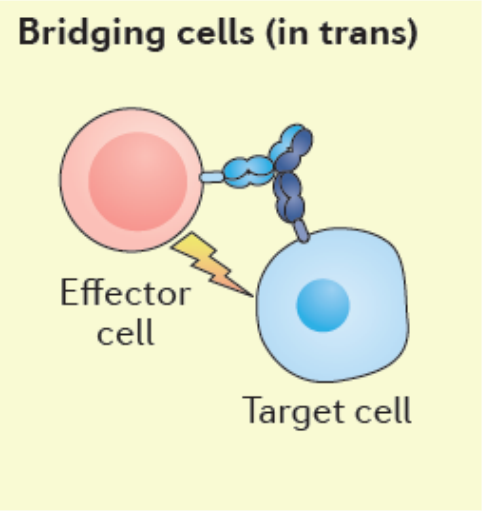
170+
COMPOUNDS
IN CLINICAL TRIALS



Updated September 2021

T-cell based bispecific antibody therapy - A promise to be realized

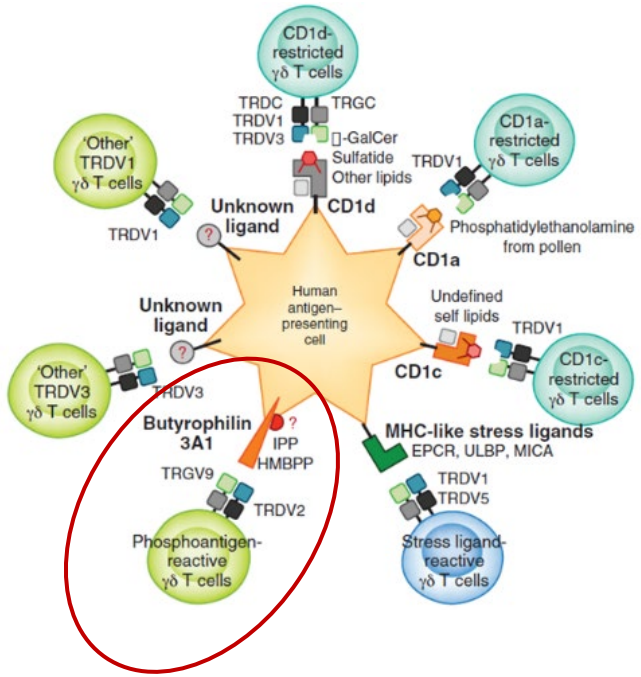
- High expectations for bispecific antibody targeted T cell therapies
- To date 2 bispecific T cell engagers bsTCE) were approved and many in the pipeline
  - Removab (catumaxomab); CD3-based bsTCE targeting EPCAM (withdrawn 2017)
  - Blincyto (blinatumomab); CD3-based bsTCE targeting CD19 (approved Dec-2014)
  - >75 bispecific T cell engagers currently in clinical development[1]
- The therapeutic window of CD3-bsTCEs is often limited
  - Unfavorable toxicity profiles driven by Cytokine Release Syndrome
  - On-target/off-tumor-related toxicities
  - Sporadic efficacy in solid tumor indications
  - Stimulation of immunosuppressive T cells
- LAVA's approach for next generation bispecific T cell engagers
  - Recruiting of Vγ9Vδ2 T cells, a T cell subset with unique advantages overcoming limitations
  - Obligate bispecific agonists which activate conditionally upon crosslinking[2]
  - Provide efficacious, safe and cost-effective opportunities for cancer treatments



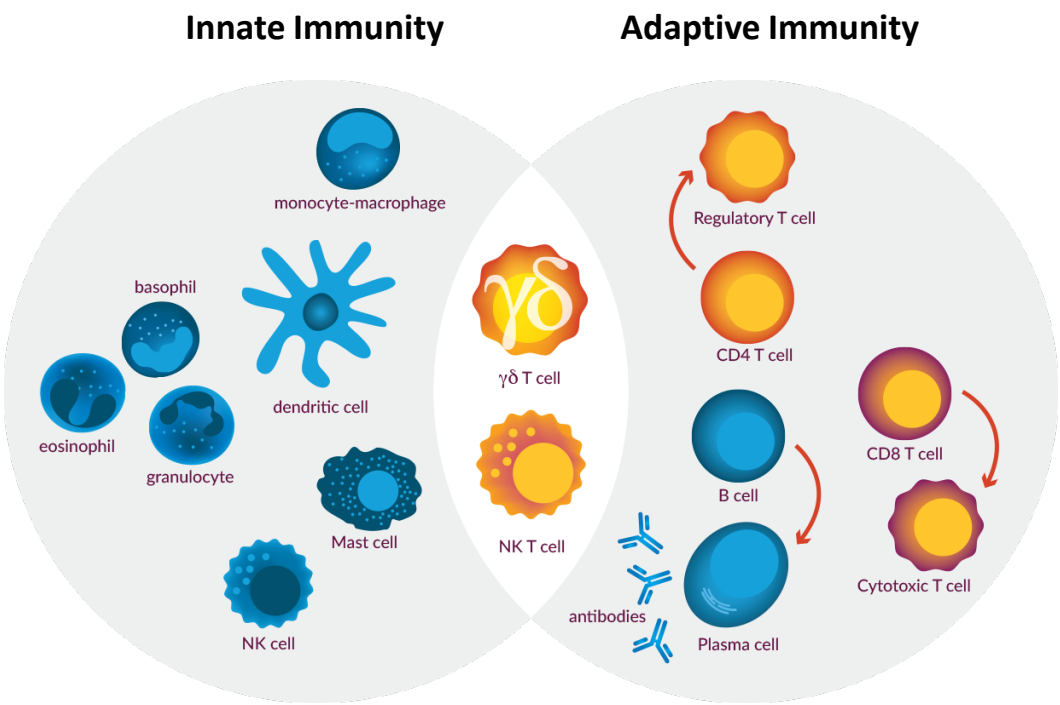
[1] Updated September 2021

[2] Labrijn, Janmaat, Reichert and Parren. Nature Rev Drug Discovery 18:585-608, 2019.

γδ T cells in immunosurveillance against cancer



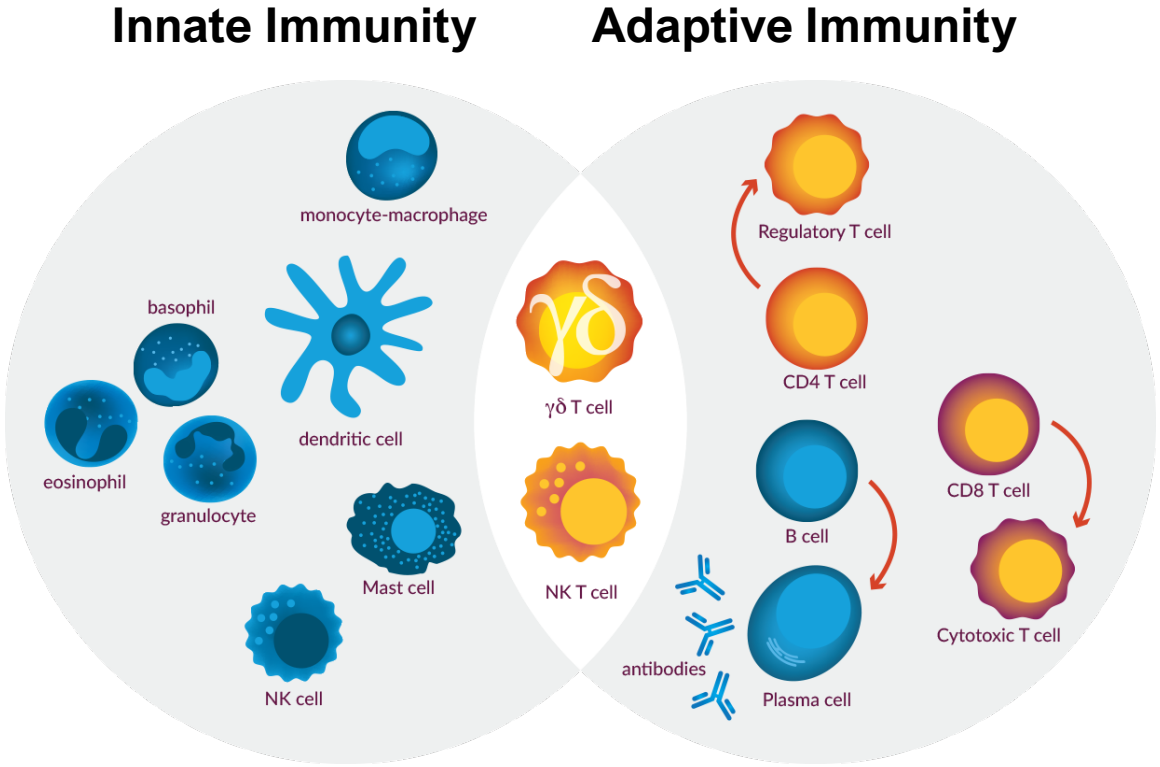
Vγ9Vδ2 T cells



Vγ9Vδ2 T cells are a natural first line of defense against cancer, with potential to elicit deep and durable clinical responses

Adapted from Dranoff G, Nature Rev Cancer 2004; 4: 11-22
Kabelitz D et al., Cell Mol Immunol 2020; 17: 925-939

γδ T Cells are Uniquely Positioned to Leverage Innate & Adaptive Immunity



Vγ9Vδ2 T Cells:

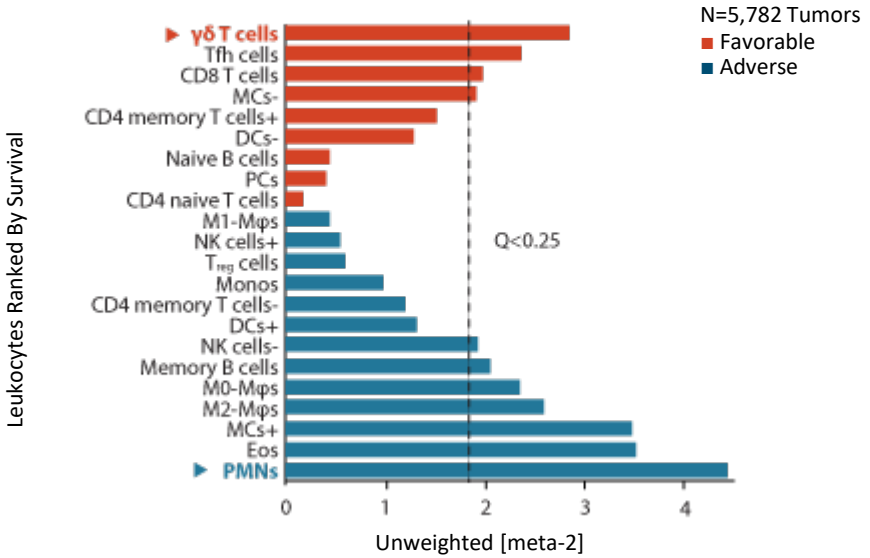
- Important immunosurveillance function
- Natural ability to recognize and kill tumor cells
- Homogeneous, highly cytotoxic effector T cell population
- Infiltrate tumors independent of mutational load
- Most prevalent gamma delta T cell clonotype in blood
- Bridge innate and adaptive immune responses
- Antigen presenting capability, potentially triggering deep and durable responses

Vγ9Vδ2 T cells are a natural first line of defense against cancer, with potential to elicit deep and durable clinical responses

Adapted from Dranoff G, Nature Rev Cancer 2004; 4: 11-22
Kabelitz D et al., Cell Mol Immunol 2020; 17: 925-939

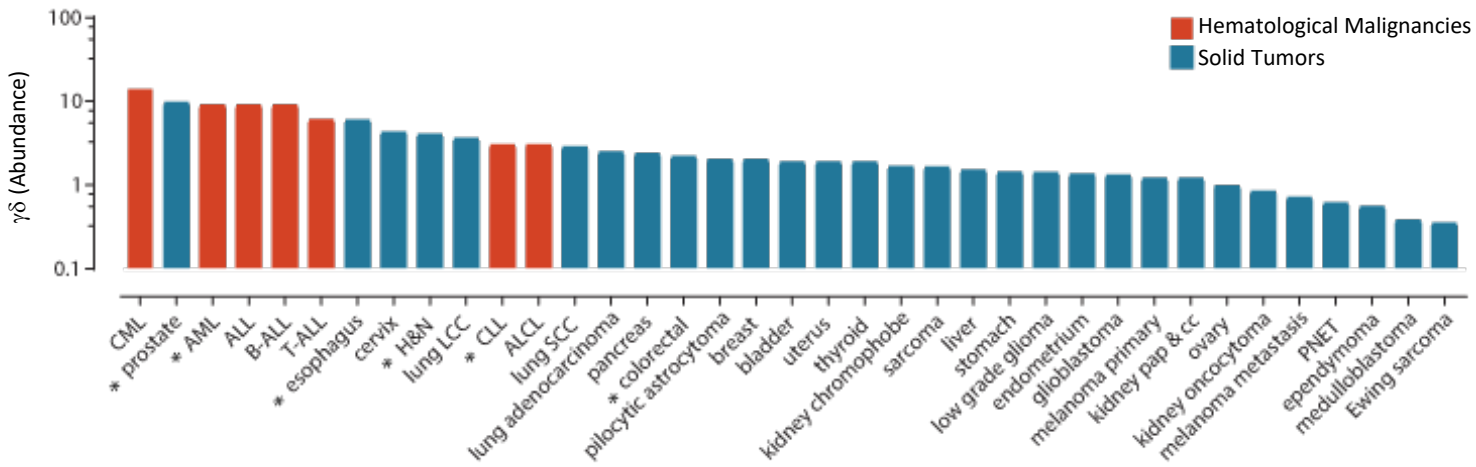
γδ T Cells Present in Many Cancers & Correlate With Favorable Prognosis

Global Prognostics Associations for 22 Leukocyte Types Across 25 Cancers



Adapted from Gentles A et al, Nature Medicine 2015; 21:938-945

Abundance of Tumor-Infiltrating Vγ9Vδ2 T Cells



* *In vivo/ex vivo* data generated using Lava's γδ–bsTCEs

Adapted from Tosolini M et al. Oncoimmunology 2017; 6, e1284723

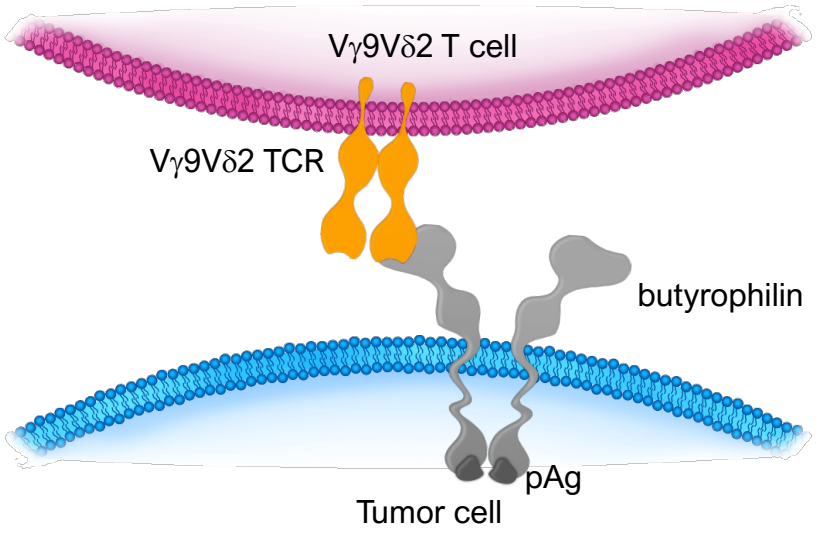
γδ T cells indicate highest correlation with favorable outcome among all leukocyte subsets analyzed

Vγ9Vδ2 T cells are present across a wide array of hematological and solid malignancies

LAVA Therapeutics' off-the-Shelf Gammabody™ Platform

Natural Activation Mechanism

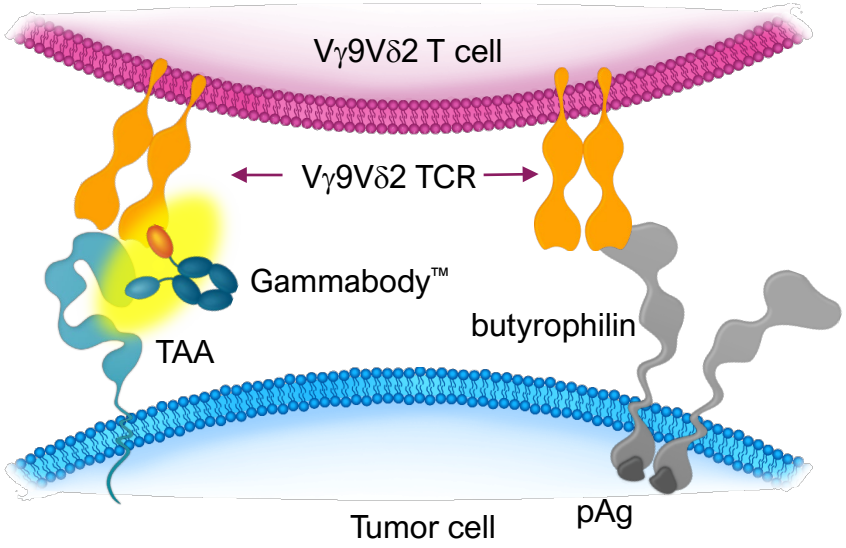
1 Vγ9Vδ2 T cells recognize stress signals – TCR interacts with pAg-butyrophilin complex



Gammabody™ Provides Tumor Recognition to Trigger Vγ9Vδ2 T Cell-Mediated Immunity

1 Conditionally activate Vγ9Vδ2 T cells upon crosslinking with tumor associated antigen (TAA)

2 Retains recognition of natural stress signals



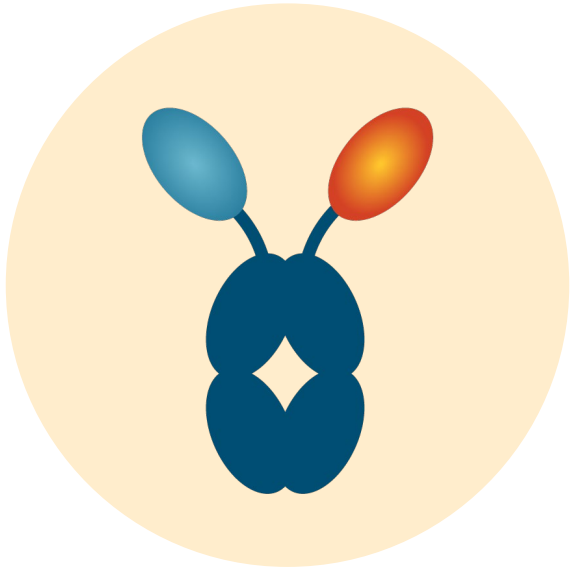
LAVA's bispecific antibodies arm and activate Vγ9Vδ2 T cells while retaining stress signal recognition to induce both direct tumor cell killing and orchestrate an immunological cascade of anti-cancer responses

Two bispecific Vγ9Vδ2-T cell engaging formats

Proof-of-concept with e.g. EGFR, CD1d, PSMA, CD40, CD20

Bispecific single domain antibody

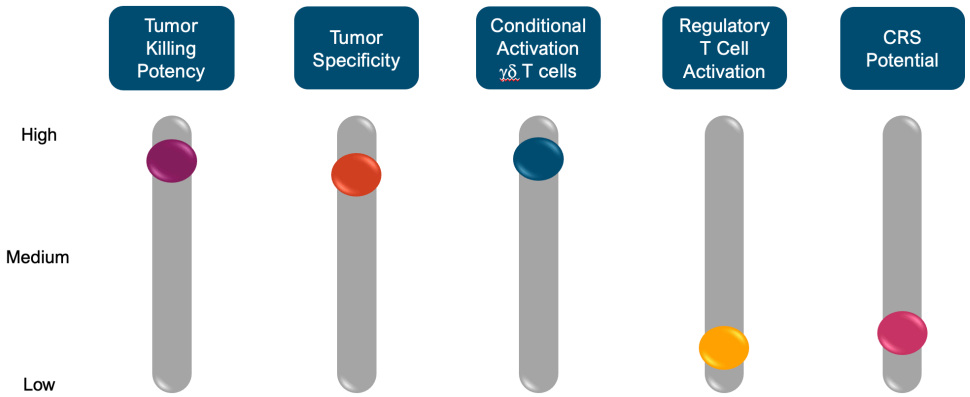
- High affinity binding and high potency
- Short *in vivo* half-life, prolonged functional half-life
- Smaller molecule than regular IgG1 (~30kD)
- Used for lead hematological program (LAVA-051)



Bispecific single domain antibody with inert Fc domain

- High affinity binding and high potency
- *In vivo* half-life similar to regular IgG1
- Smaller molecule than regular IgG1 (~ 80kD)
- Validated mutations to silence Fc effector function
- Used for lead solid tumor program (LAVA-1207)

The high tumor selectivity and potency of LAVA's γδ-bsTCEs and low risk of CRS may provide a broad therapeutic window



Gammabody efficacy characteristics

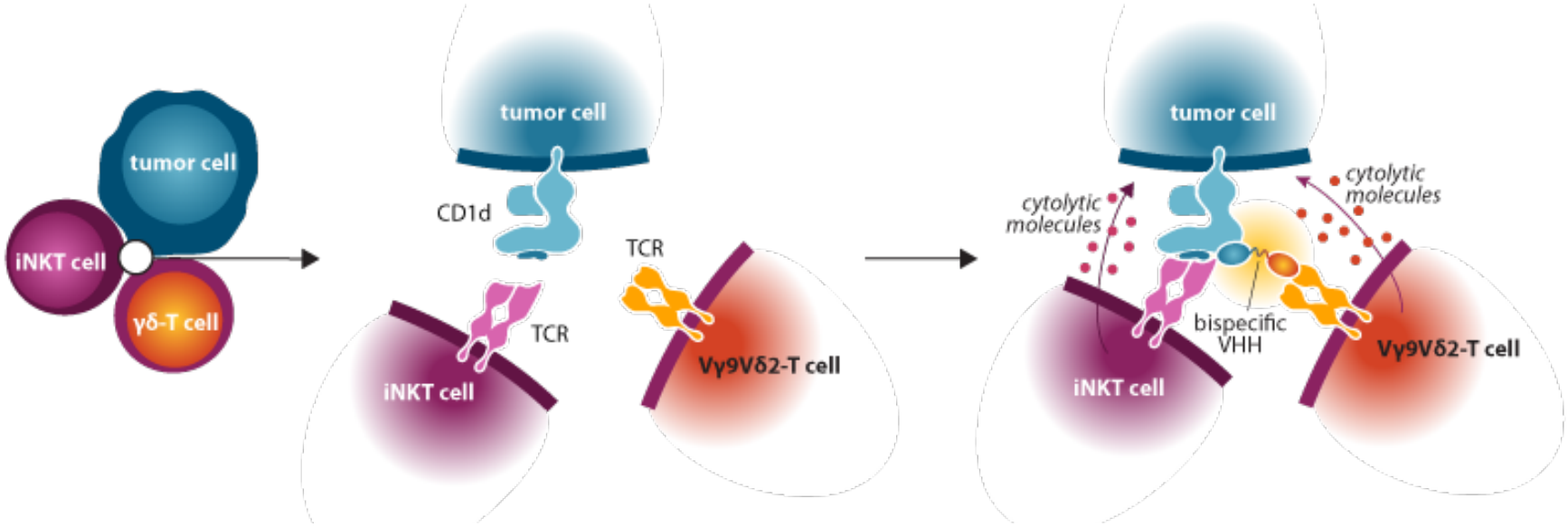
- Potent killing of cancer cells (EC50s in the low picomolar range)
- No co-activation of immune-suppressive Tregs which dampen antitumor efficacy of cytotoxic T cells
- Antigen presenting capability and cytokine release drive innate and adaptive immune responses, potentially resulting in potent and durable responses
- Potential activity in hematologic malignancies and solid tumors, including immunologically "cold" tumors
- Induction of Vγ9Vδ2 T cell activation can result in an increased number of anti-tumor Vγ9Vδ2 T cells

Potential Gammabody safety characteristics

- Conditional activation gives high precision
- Greatly reduced potential for cytokine release syndrome (CRS); no evidence of CRS in NHP studies

Gammabody LAVA-051: A bispecific iNKT and Vγ9Vδ2-T cell engager targeting CD1d induces potent anti-tumor activity

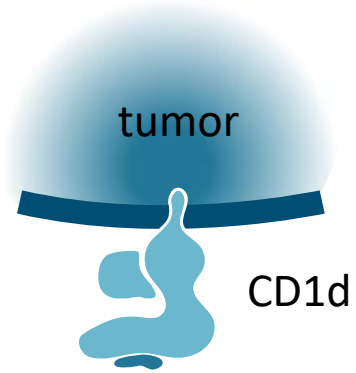
Lameris et al., Nature Cancer 1: 1054–1065, 2020

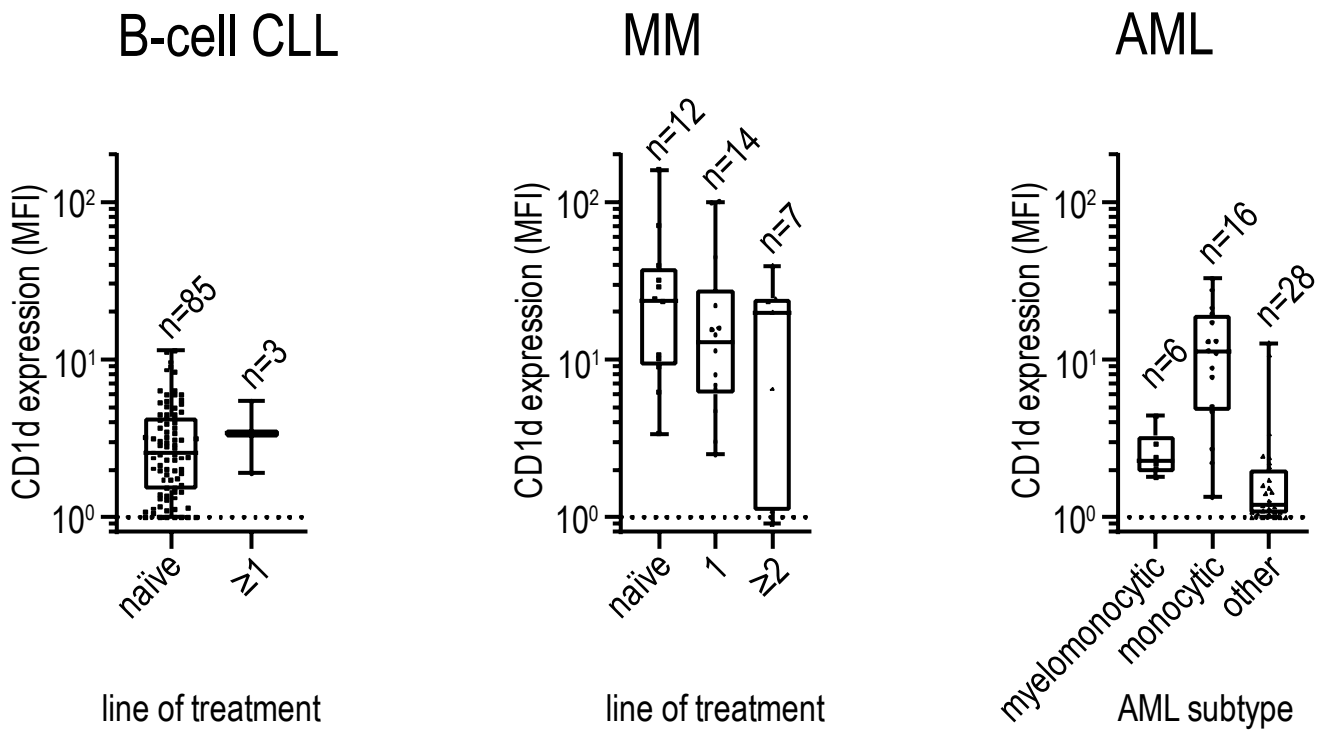


- CD1d is a MHC class I-related glycoprotein expressed on the surface of various human antigen presenting cells
- iNKT cells (a.k.a. type 1 NKT cells)
  - Inherent anti-tumor activity
  - Respond to (glyco)lipid antigens presented by CD1d

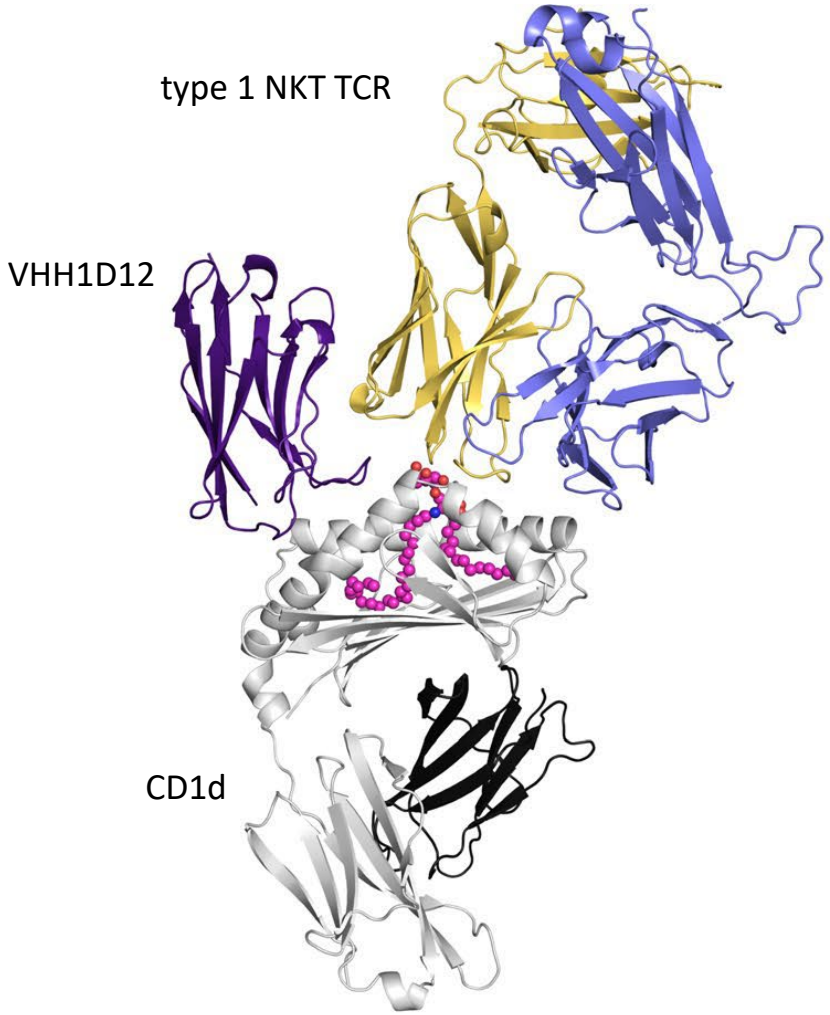
CD1d is also a tumor-associated target

- CD1d is overexpressed on CLL and MM cells in the majority of patients
- Expression on AML cells is most pronounced on (myelo)monocytic subtypes
- Expression independent of prior lines of treatment



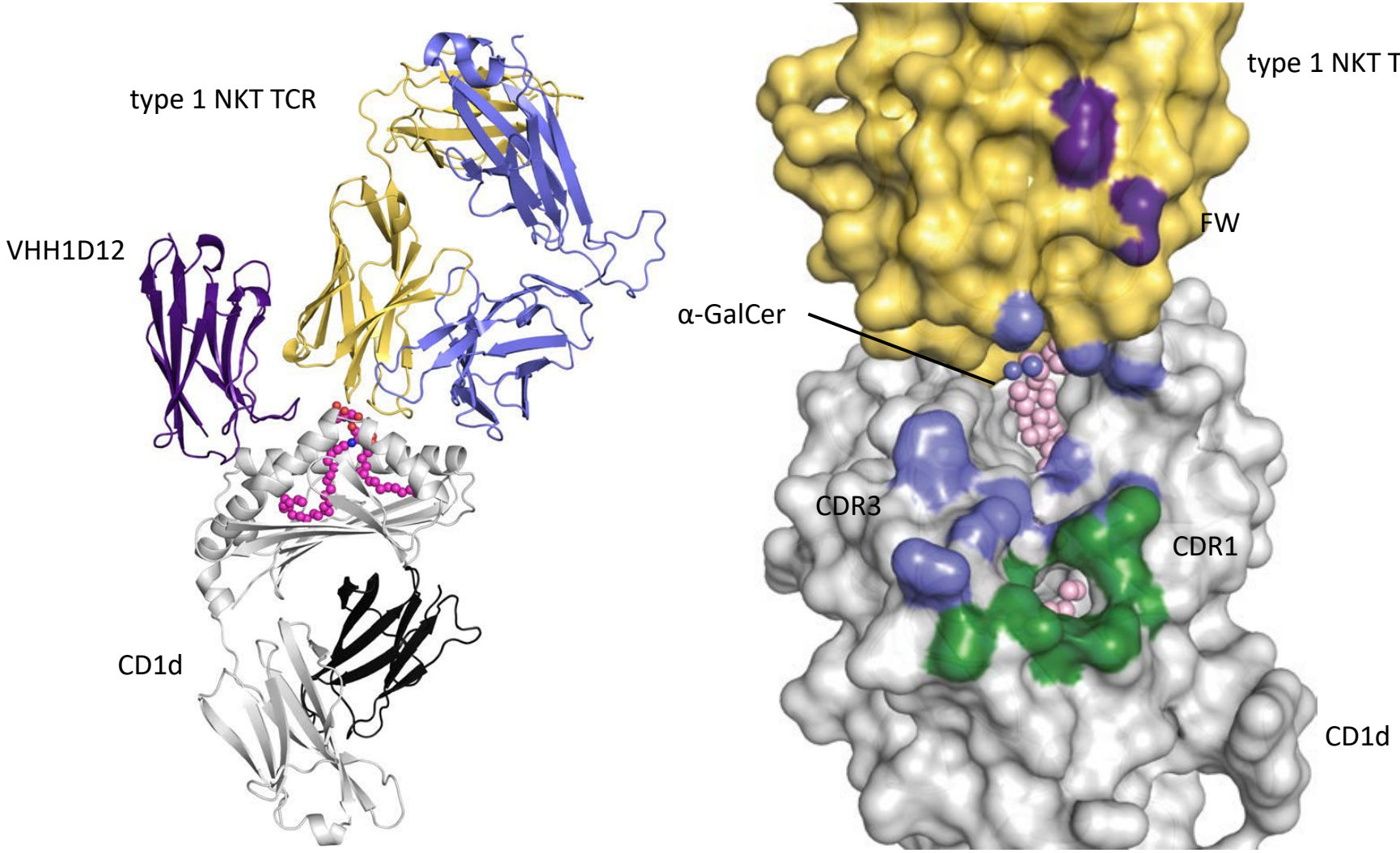


CD1d-binding arm of Gammabody LAVA-051 has intrinsic bispecific properties



Lameris et al., Nature Cancer 1: 1054–1065, 2020

CD1d-binding arm of Gammabody LAVA-051 has intrinsic bispecific properties



Lameris et al., Nature Cancer 1: 1054–1065, 2020

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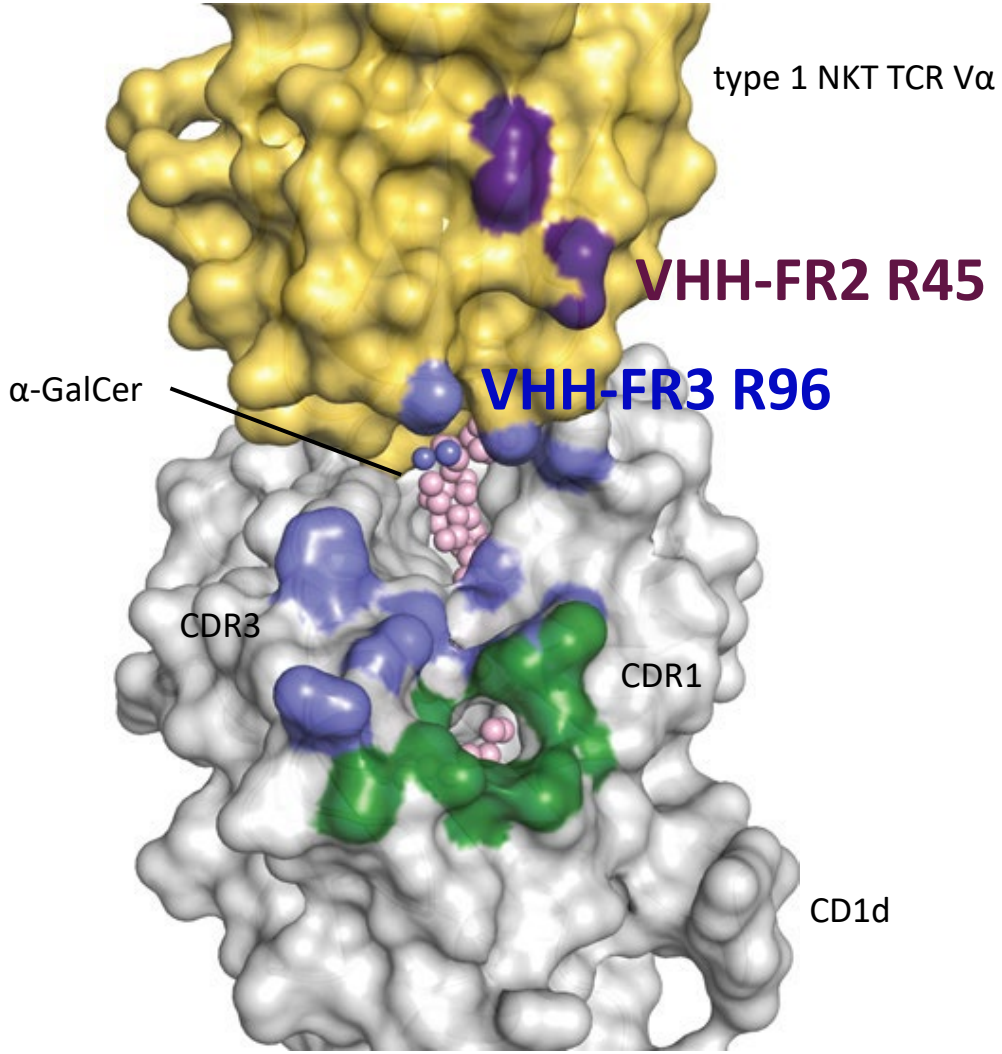
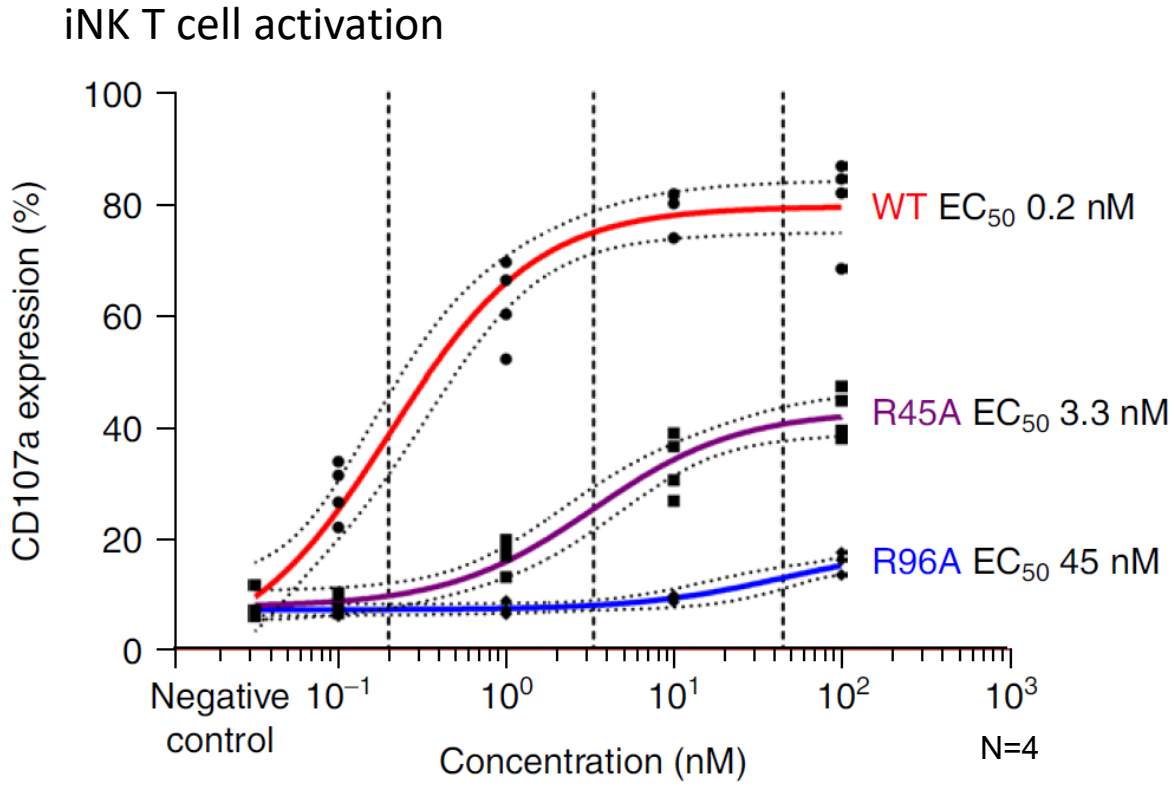
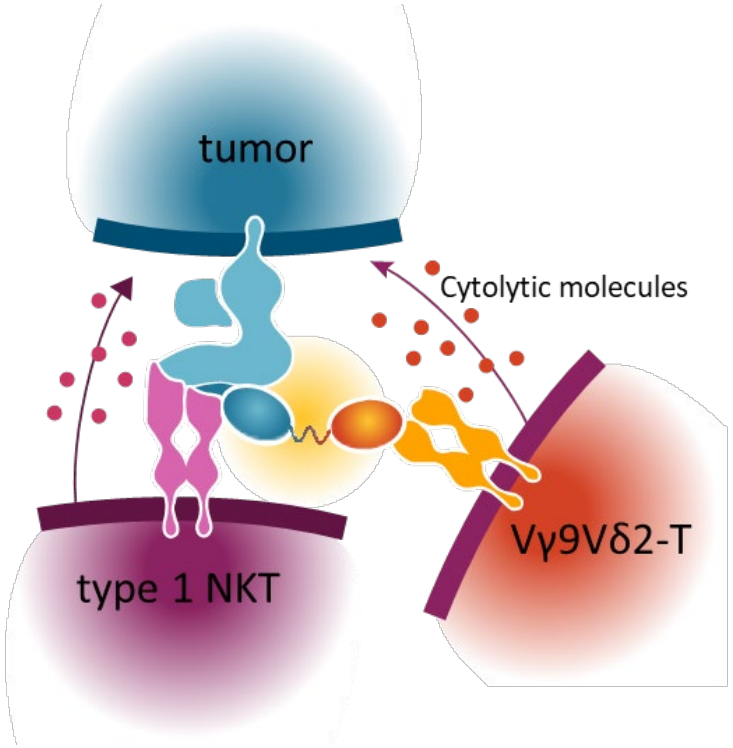
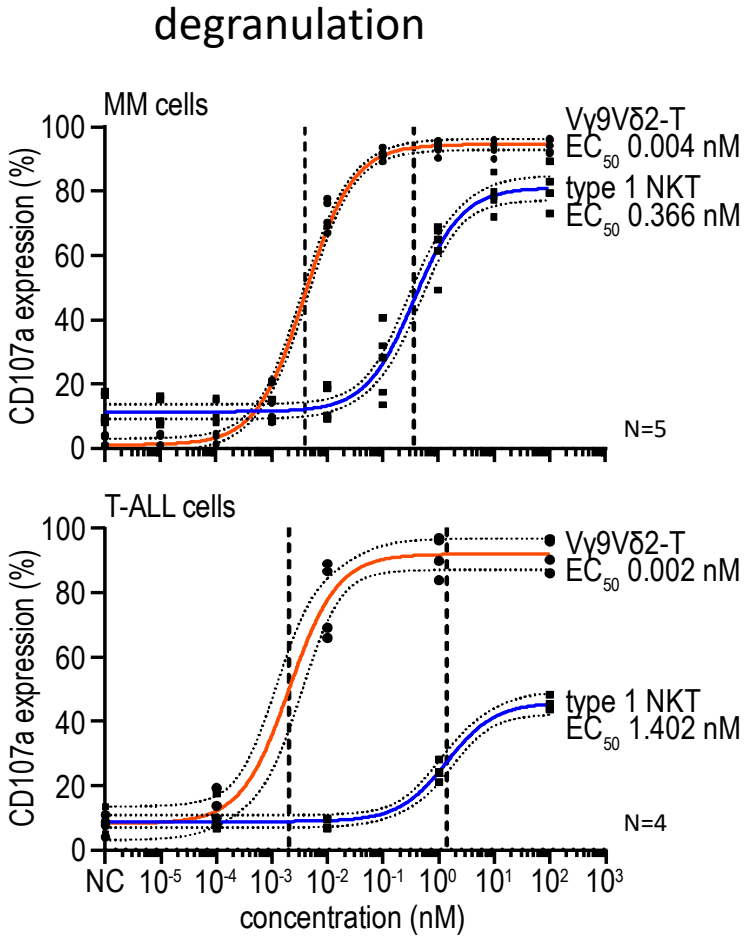


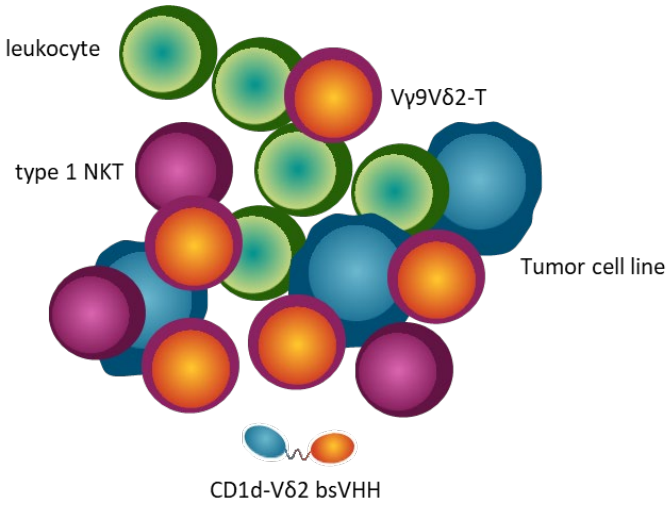


Gammabody LAVA-051 activates both type 1 NKT cells and Vγ9Vδ2-T cells



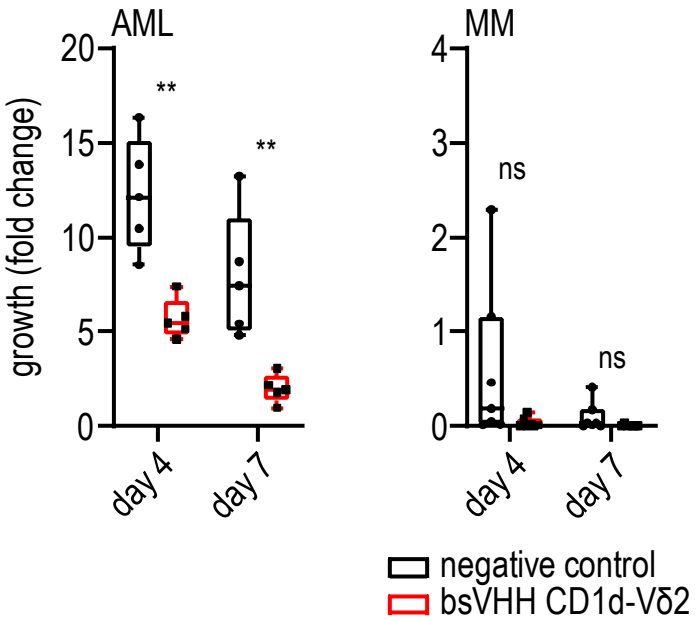


Gammabody LAVA-051 controls tumor cell growth and triggers expansion of type 1 NKT and Vγ9Vδ2-T cells

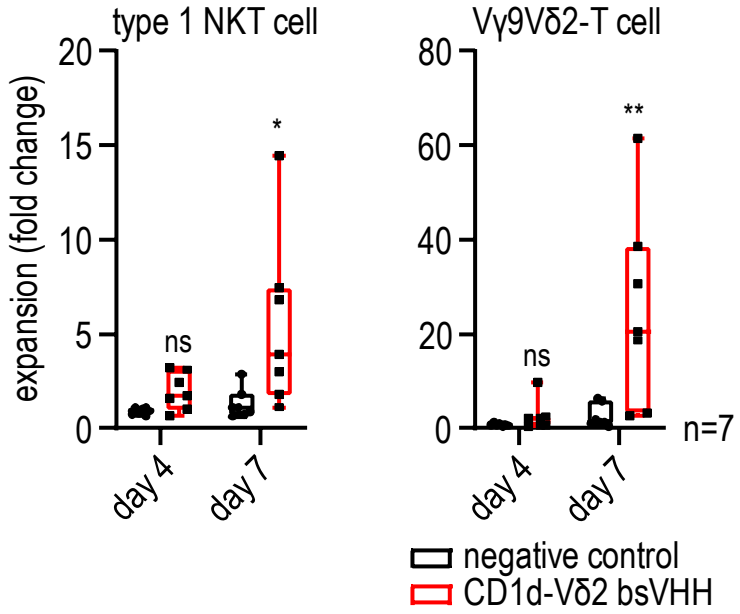


Effector cells: PBMC
Target: tumor cell line

Anti-tumor activity



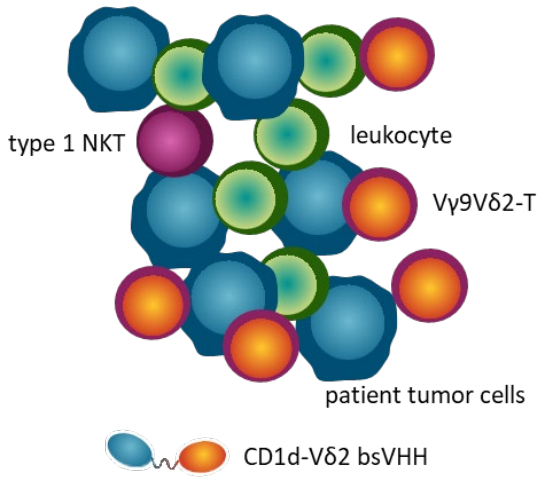
effector cell expansion



AML: Molm-13
MM: MM.1s

*p<0.05, **p<0.01

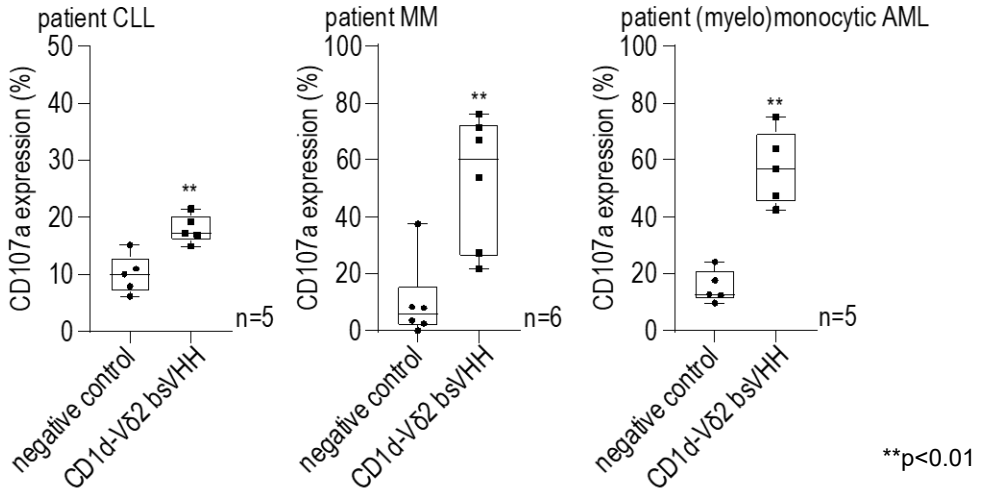
Anti-tumor activity of Gammabody LAVA-051 against patient CLL, MM and AML cells



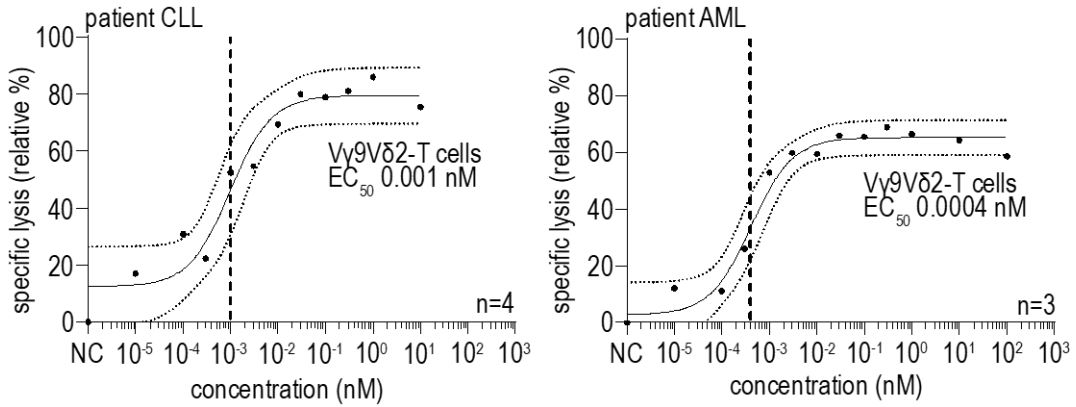
Patient PBMC or bone marrow cells

Vγ9Vδ2 T cells with patient PBMC/BM (E:T 1:1)

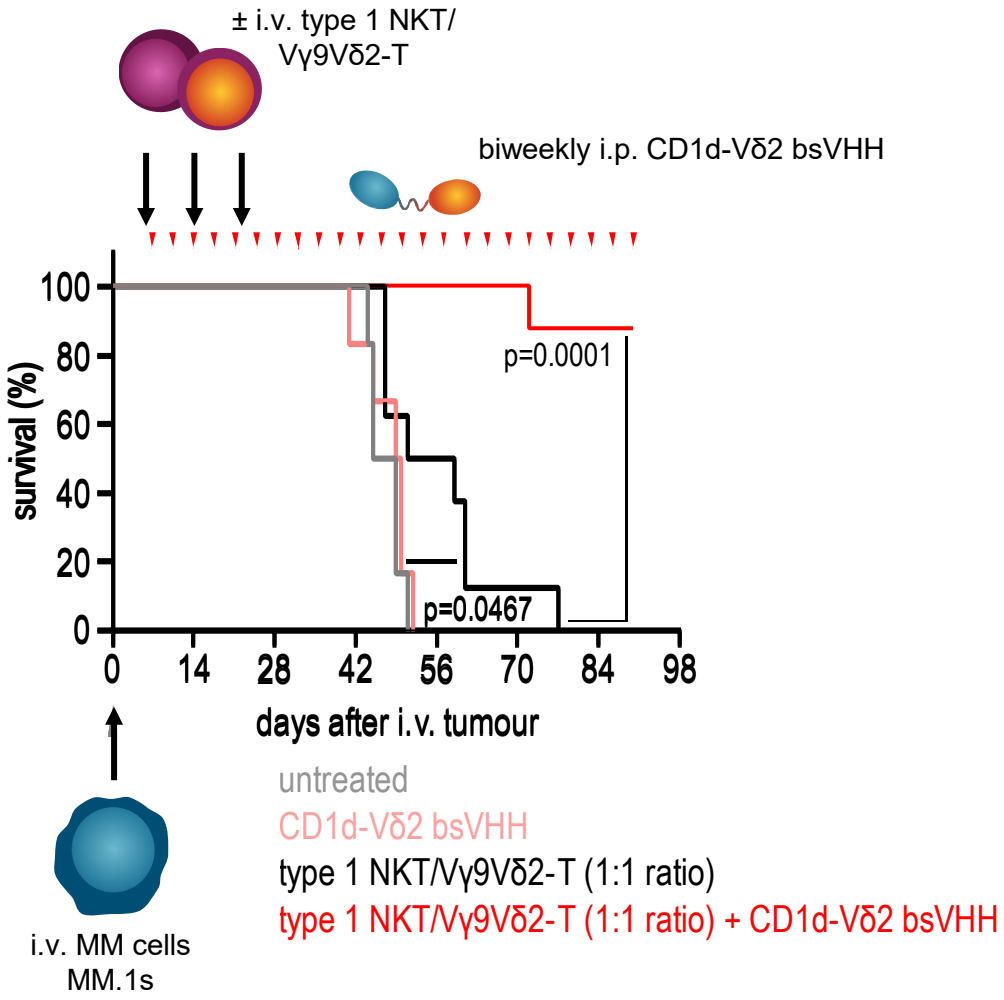
autologous Vγ9Vδ2-T cell degranulation



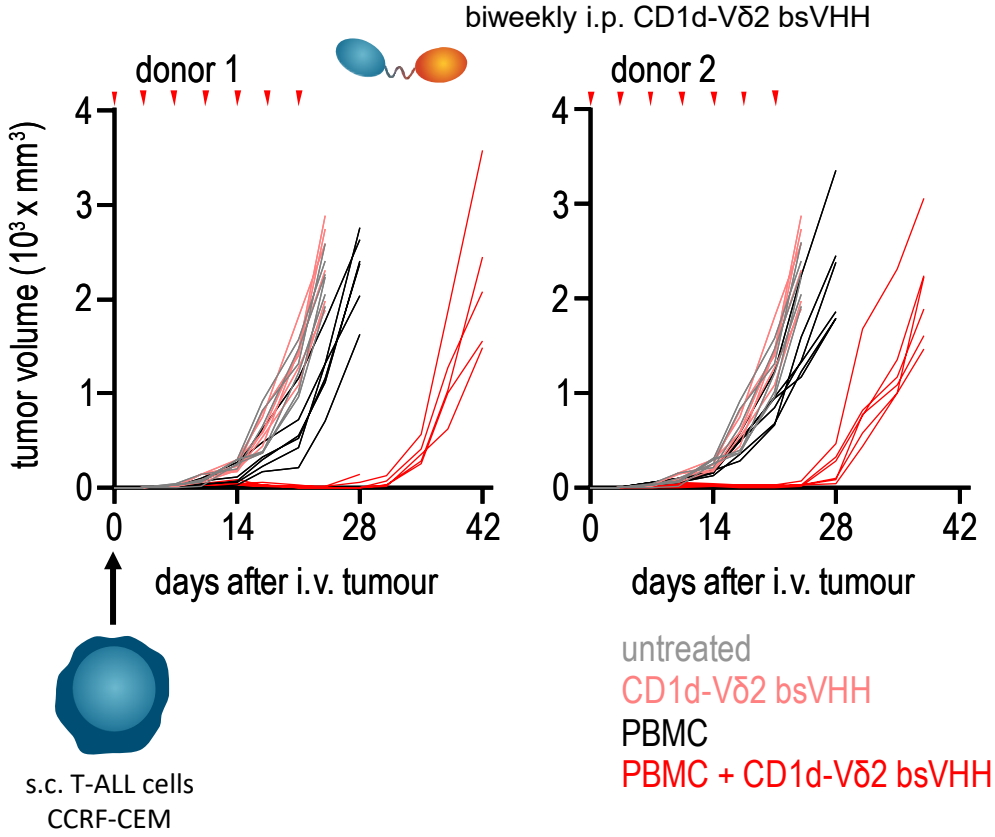
cytotoxicity



Gammabody LAVA-051 induces type 1 NKT cell and Vγ9Vδ2-T cell antitumor activity *in vivo* and increases survival

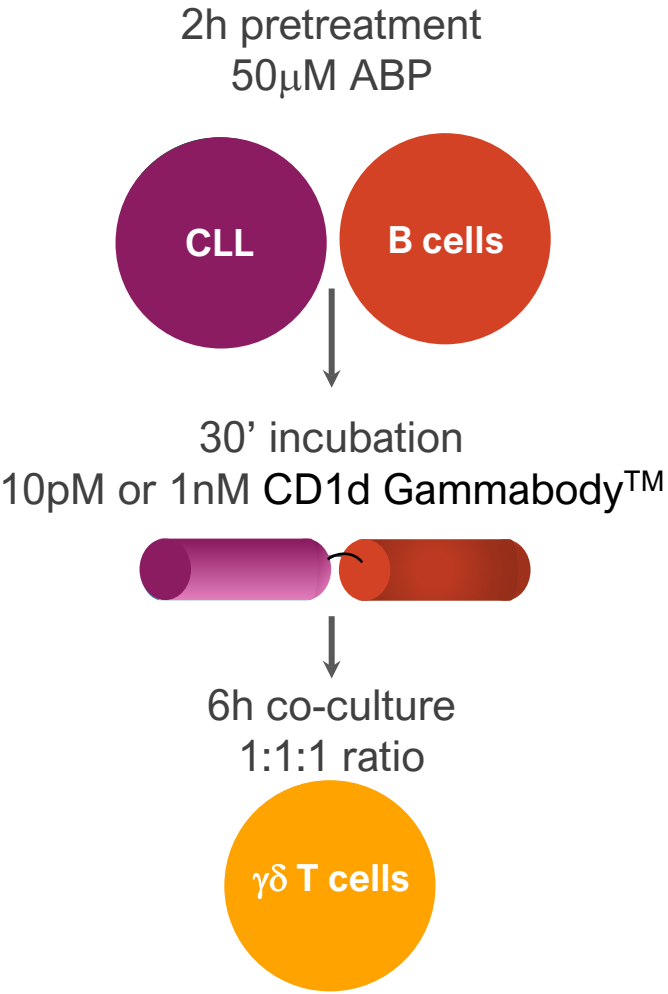


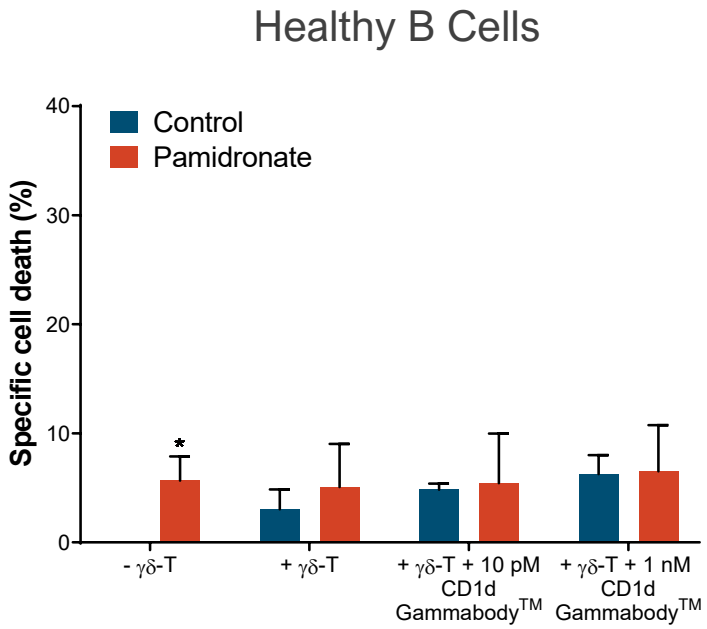
Intravenous Multiple Myeloma model

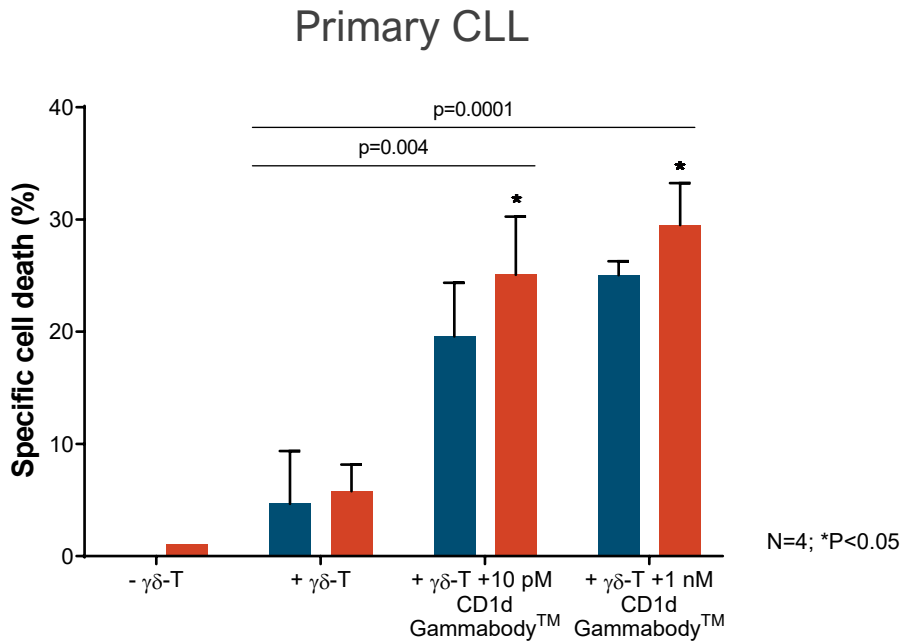


Subcutaneous T-ALL model

Selectively Kills Cancer Cells & Spares Healthy Cells



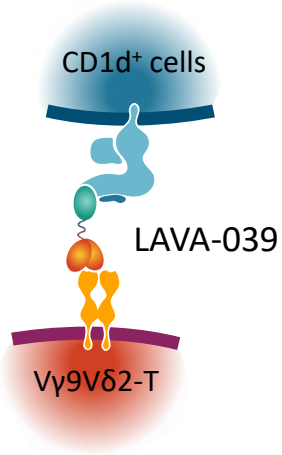




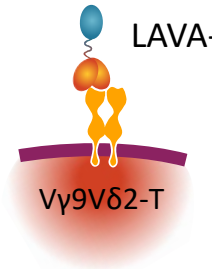
Preferential killing of cancer versus healthy cells demonstrated *in vitro* and *ex vivo*; which may allow for targeting of broadly expressed tumor associated antigens

De Weerdt I et al., Clin Cancer Res 2021; 27: 1744-1755

Cross-reactive surrogate Gammabody against CD1d (LAVA-039) for NHP studies

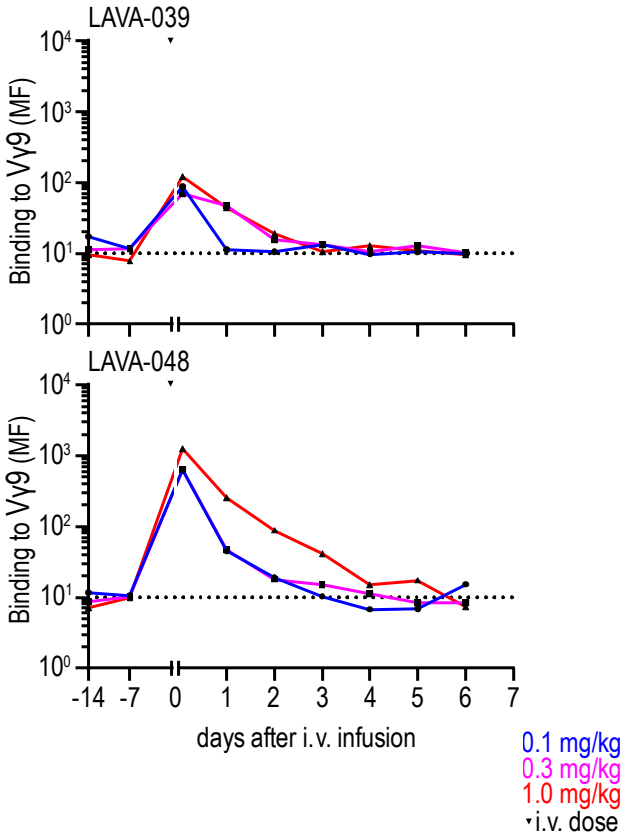


Surrogate Gammabody to CD1d

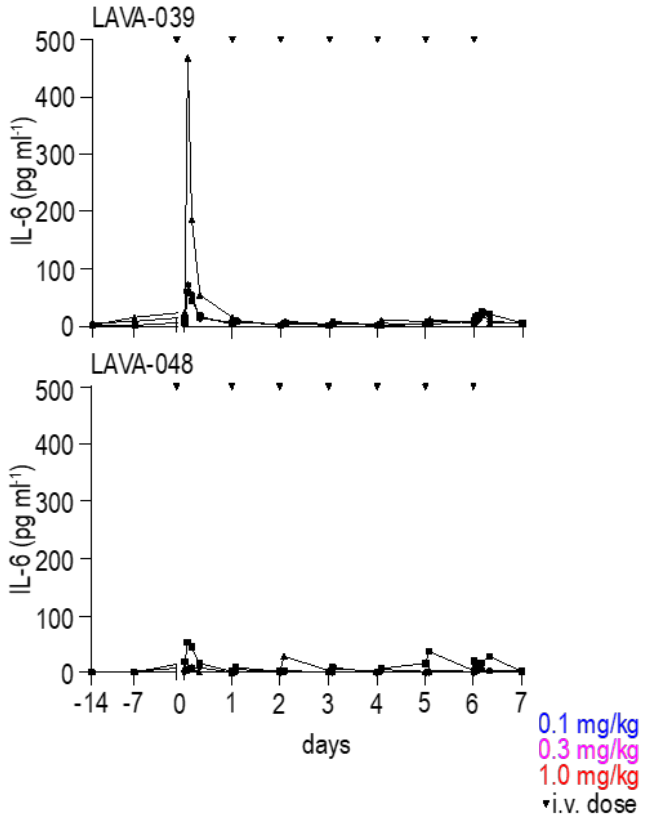


Control Gammabody

binding to NHP Vγ9Vδ2-T cells



limited and transient IL-6 release



Binding of surrogate molecules to Vγ9Vδ2-T cells over time (single dose administrations, up to 1 mg /kg i.v.), analysed by flow cytometry (MF, median fluorescence)

Platform safety supported by non-human primate studies with fully cross-reactive CD1d and EGFR gamma-delta bsTCEs

Dosing Schedules

CD1d

- Surrogate CD1d gamma-delta bsTCE safely dosed to 10 mg/kg (4 hr infusion, 4 doses, every 2 days) and twice weekly at 1 mg/kg for 1 month

EGFR

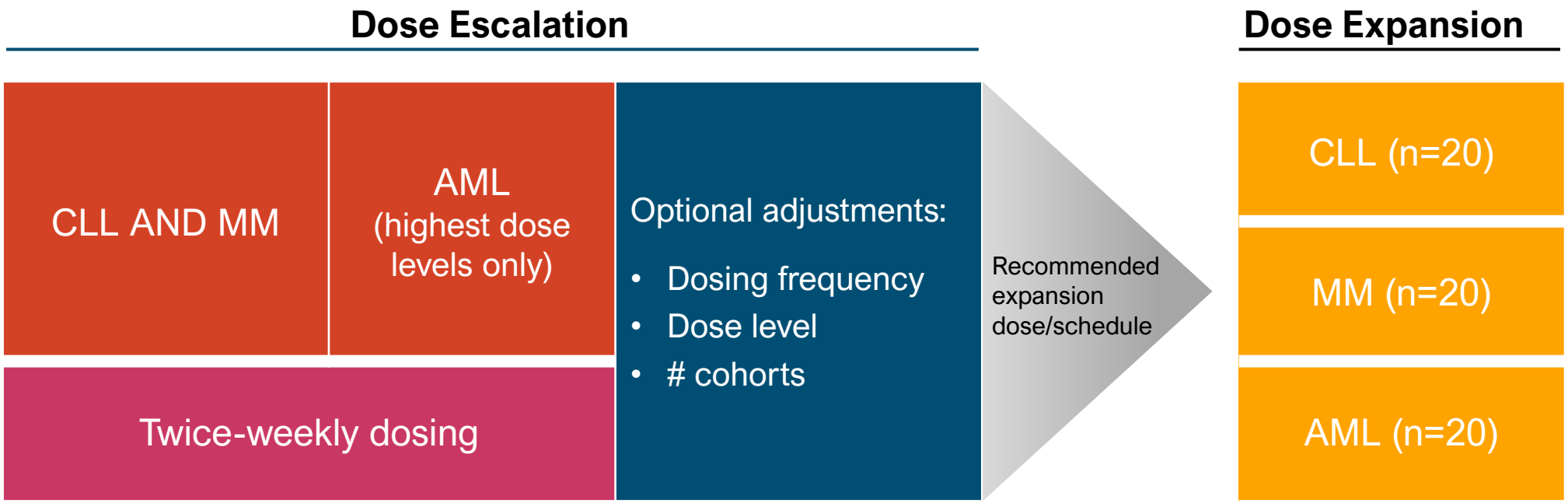
- Surrogate EGFR gamma-delta bsTCE safely dosed to 10 mg/kg (4 hr infusion, 4 doses, every 2 days)*

- Mild to no clinical signs of toxicity;
- Low first-dose cytokine spike, no CRS
- No clinical chemistry abnormalities
- No histopathological abnormalities
- Gamma-delta bsTCEs detectable on PB and LN gamma-delta T cells

NHP data support the benign safety profile of LAVA's gamma-delta bsTCEs *in vivo*

* Previousy Lutterbuese et al., PNAS 2010 reported high toxicity of a CD3-based TCE against EGFR at doses >31 μg/kg continuous infusion

LAVA-051 Phase 1/2a Initiated in Hematological Malignancies



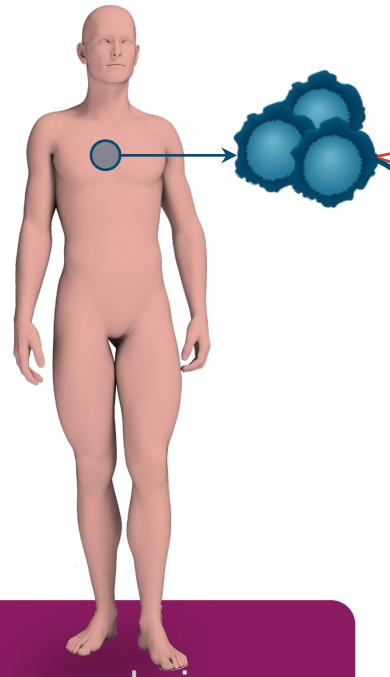
Goal: Determine recommended dose and schedule based on maximum tolerated dose (MTD) or optimal biological dose

n= estimated number of patients per indication

Goal: Determine preliminary level of activity per disease

Data from Phase 1 expected in 1H 2022;
Phase 2a dose expansion expected in 2H 2022

LAVA-051 Phase 1/2a: Extensive Biomarker Analysis



Biomarker analysis to validate whether LAVA's Gammabody™ platform performs in humans as predicted based on preclinical data

Pharmacodynamics	Cytokines (IL-1β, IL-2, IL-6, IL-8, TNF-α, IFN-γ, GM-CSF)	
	a.	Binding of LAVA-051: Vγ9Vδ2-T cells | CD1d positive tumor cells
	b.	Activation status & frequency: Vγ9Vδ2-T cells | iNKT cells
	c.	Induction of activation of Vγ9Vδ2-T cells *ex vivo* when exposed to CD1d (functional assay)
	d.	Immune-monitoring (frequency and activation status of B cells, T cell subsets, NK cells, monocytes, dendritic cells)
Disease assessments	Tumor-defining markers/CD1d/BTN3A	- MM (peripheral blood, urine, CT scan, bone marrow biopsy) - CLL (peripheral blood, CT scan, bone marrow biopsy) - AML (peripheral blood, bone marrow biopsy)
Safety	Chemistry / hematology / urine	
Pharmacokinetics		
Anti-Drug Antibodies		

LAVA Therapeutics

2010

Idea to engage Vγ9Vδ2-T cells for cancer therapy - Hans van der Vliet lab at VUmc, Amsterdam

2015

First patent application on Vγ9Vδ2-T cell engagers

2016

BioX Biosciences BV the biobusiness generator

LUPUS VENTURES BV

Seed funding $1M

LAVA Therapeutics founded

2018

2019

Opening US office

Opening Lab in Utrecht

Financing €87M

novo holdings Investors in life science

Gilde HEALTHCARE

VERSANT ventures

Redmile Group

MRL VENTURES FUND

SANOFI VENTURES

YSIOS CAPITAL

BB Pureos Bioventures

2020

J.P.Morgan

SVBLEERINK

Kempen

Jefferies

IPO on Nasdaq
Financing $107M

2021

Opened first clinical trial

https://www.lavatherapeutics.com/

Acknowledgements

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Myrthe Veth*
Tanja de Gruijl

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