HOVON · NVvH

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Papendal, Arnhem

Antibody therapeutic approaches for cancer – building a career at the interface of science & business

Moderator

Prof.dr. Marie Jose Kersten

speaker

Prof.dr. Jan van de Winkel

Conflict of Interest Disclosure Form

In accordance with the rules of the Health Care Inspectorate (IGZ)

Name: Jan van de Winkel

Affiliation: President and CEO, Genmab A/S

☐ I have no potential conflict of interest to report

☑ I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	
Receipt of honoraria or consultation fees:	
Participation in a company sponsored speaker's bureau:	
Stock shareholder:	Genmab A/S
Other support (please specify):	Co-founder, President and CEO
Scientific advisory board	

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This presentation contains forward looking statements. The words “believe”, “expect”, “anticipate”, “intend” and “plan” and similar expressions identify forward looking statements. All statements other than statements of historical facts included in this presentation, including, without limitation, those regarding our financial position, business strategy, plans and objectives of management for future operations (including development plans and objectives relating to our products), are forward looking statements. Such forward looking statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward looking statements. Such forward looking statements are based on numerous assumptions regarding our present and future business strategies and the environment in which we will operate in the future. The important factors that could cause our actual results, performance or achievements to differ materially from those in the forward looking statements include, among others, risks associated with product discovery and development, uncertainties related to the outcome of clinical trials, slower than expected rates of patient recruitment, unforeseen safety issues resulting from the administration of our products in patients, uncertainties related to product manufacturing, the lack of market acceptance of our products, our inability to manage growth, the competitive environment in relation to our business area and markets, our inability to attract and retain suitably qualified personnel, the unenforceability or lack of protection of our patents and proprietary rights, our relationships with affiliated entities, changes and developments in technology which may render our products obsolete, and other factors. Further, certain forward looking statements are based upon assumptions of future events which may not prove to be accurate. The forward looking statements in this document speak only as at the date of this presentation.

Brief biography
Jan van de Winkel

’73 – ’79	Gymnasium β, Venray
’79 – ’85	Biology, University Nijmegen
’85 – ’88	PhD Immunology, University Nijmegen
’88 – ’89	Postdoc Immunology, Utrecht University
’90	Visiting Scientist, USA
’91 – ’96	Asst.- full Prof., University Medical Center Utrecht
’96 – present	Prof. Immunotherapy UMCU [Part-time]
’97 – ’00	VP & Scientific Director, Medarex Europe
’99 – ’10	Co-founder & CSO, Genmab
‘10 – present	President & CEO, Genmab

Research Focus

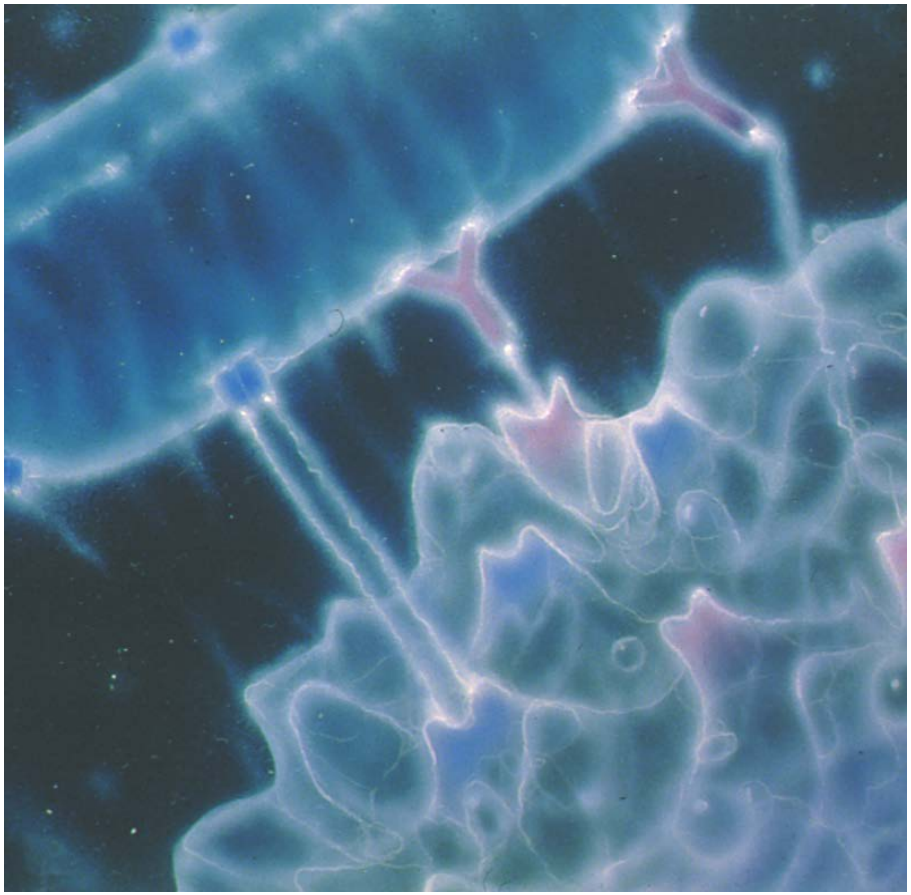
Antibodies, Fc receptors & Immunotherapy

Subject

Role antibodies & FcR in physiology and pathology, novel therapeutic concepts.

Questions

Genomic complexity, polymorphisms, signalling & cell biology, role FcR for antibody therapy, mechanisms of action therapeutic mAb.

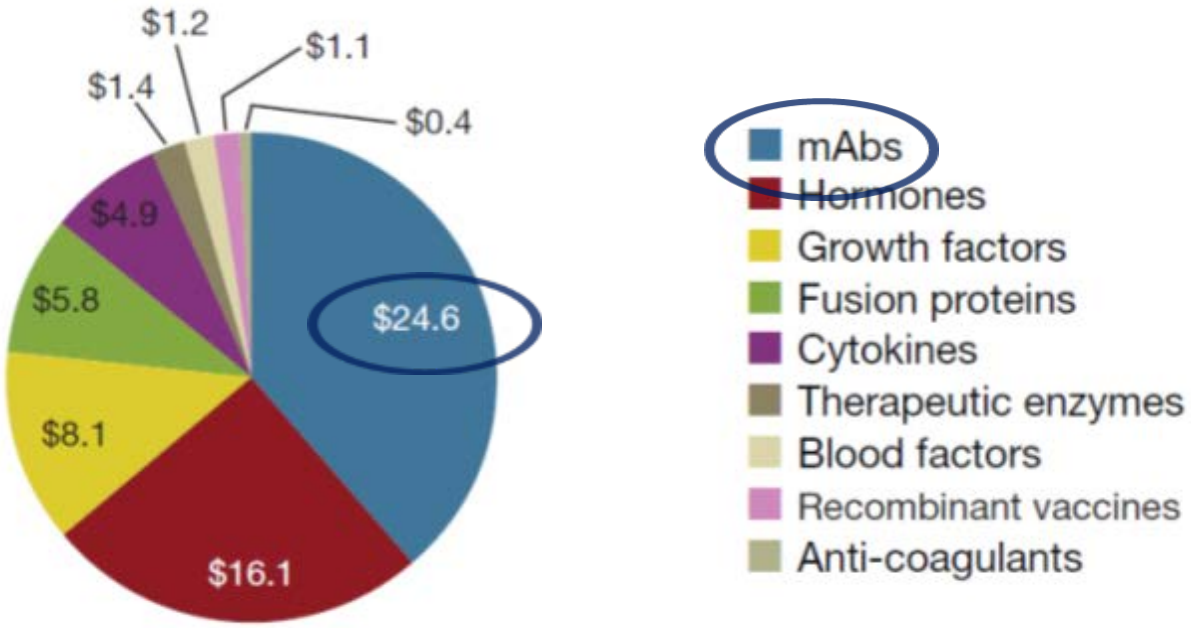


Discovery antibodies & serum therapy

1890 von Behring & Kitasato

Antibodies lead Biologics

US sales 2012 [$ billions]



- **Biotechnology**
  - Drives innovation
  - Responsible for 1/3 all molecules in development
- **Antibodies**
  - 27% of all biopharmaceutical approvals [2010 – 2014]

Nature Biotechnol. 2014; 32: 32-39
Nature Biotechnol. 2014; 32:992-1000

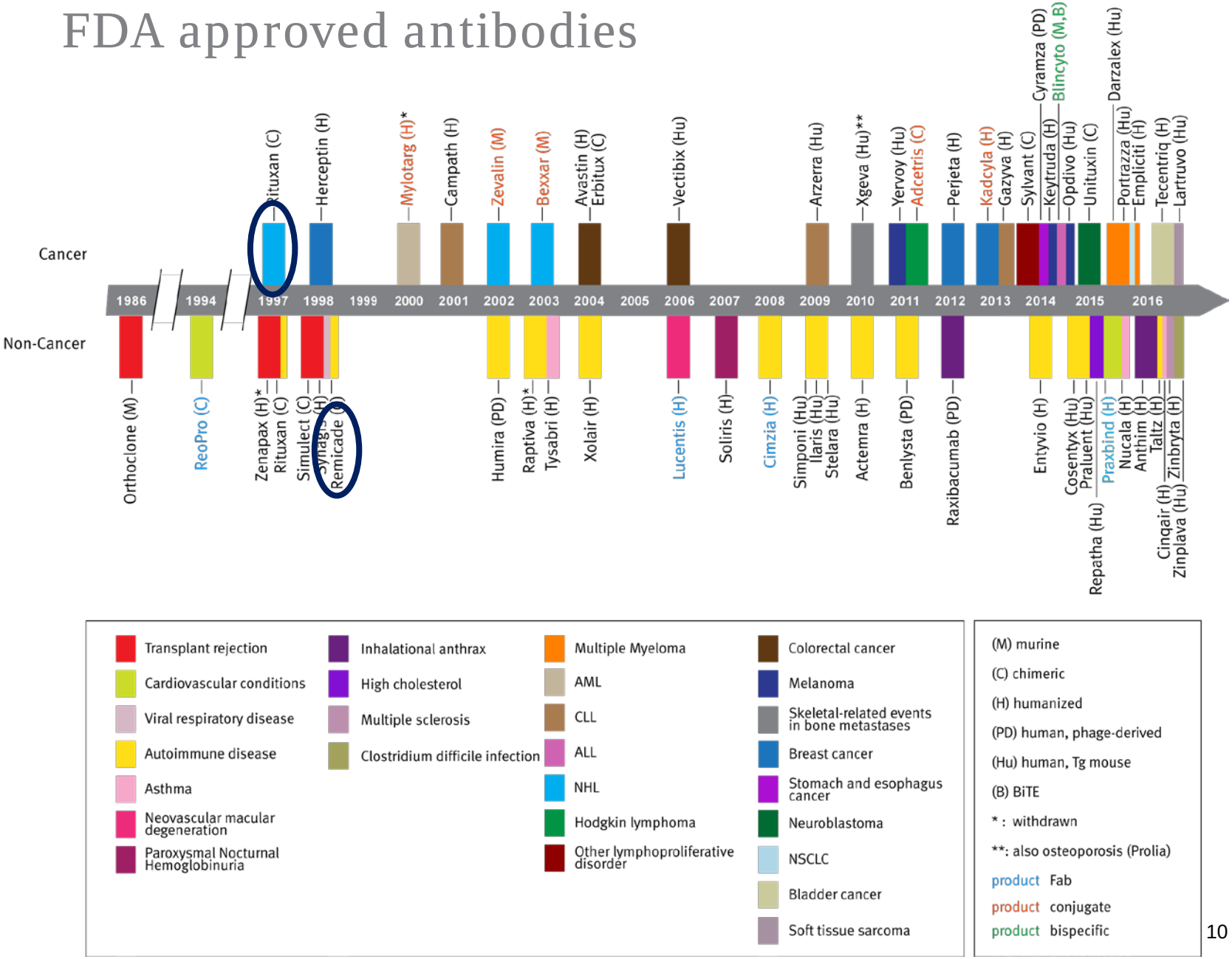
Top ten biopharmaceutical drugs by revenue - 2015

Name	Lead company	Molecule type	Approved indication(s)	2015 worldwide sales ($ millions)	
				US	Worldwide
Humira	AbbVie	mAb	RA, juvenile RA, Crohn's disease, PA, psoriasis, ankylosing spondylitis, UC, Behçet syndrome	8,405.00	13932.00
Harvoni	Gilead Sciences	Small molecule	Hepatitis C (Antiviral)	10,090.00	13,864.00
Enbrel	Amgen	Protein	RA, psoriasis, ankylosing spondylitis, PA, juvenile RA	5,099.00	9,008.70
Rituxan	Roche	mAb	RA, chronic, lymphocytic leukemia/small-cell lymphocytic lymphoma; non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies-associated vasculitis, indolent non-Hodgkin's lymphoma, diffuse large B-cell lymphoma	3,947.20	7,395.00
Lantus	Sanofi	Peptide	Diabetes mellitus, type I, diabetes mellitus, type II	4,467.90	7,095.40
Avastin	Roche	mAb	Colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, ovarian cancer, brain cancer (malignant glioma; AA and GBM), cervical cancer	3,209.40	7,014.20
Herceptin	Roche	mAb	Breast cancer, gastric cancer	2,502.30	6862.60
Remicade	Johnson & Johnson	mAb	RA, Crohn's disease, psoriasis, UC, ankylosing spondylitis, Behçet Syndrome, PA	4,453.00	6,826.10
Prevnar 13	Pfizer	Vaccine	Pneumococcal (*Streptococcus pneumoniae*) Vaccines (Antibacterial)	4,026.00	6,246.00
Revlimid	Celgene	Small molecule	Multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma - NHL	3,534.40	5,800.90

mAb, monoclonal antibody; AA, Anaplastic astrocytoma; GBM, glioblastoma; non-Hodgkin's lymphoma; PA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis. Source: BioMedTracker and Medtrack, a product of Informa Pharma Intelligence.

Nature Biotechnol. 2016; 34: 709-715

FDA approved antibodies

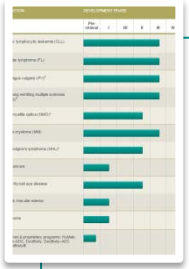


Genmab: Innovating Antibodies, Improving Lives

Creating & developing human antibodies to treat cancer

Arzerra® (ofatumumab) our first approved antibody, reached market in < 8 years

DARZALEX (daratumumab), one of 10 drugs with transformative potential



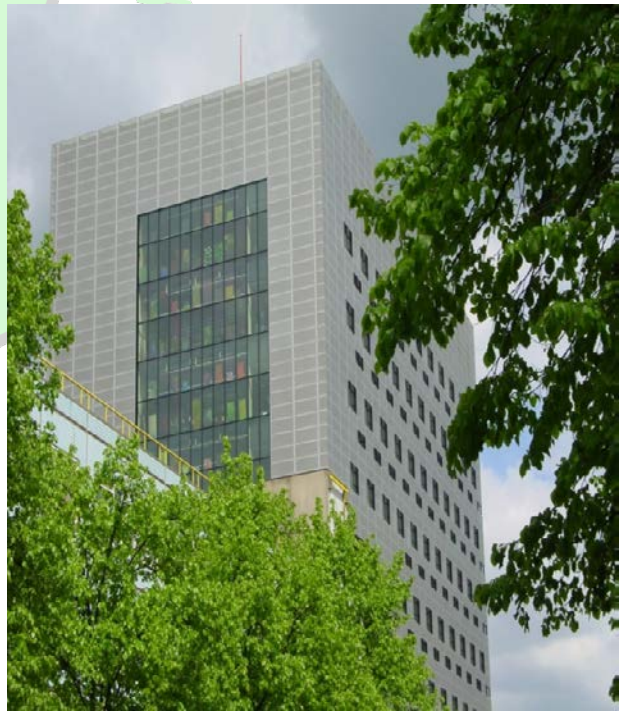
Broad pipeline of innovative drugs

Passion for innovation

- 2 proprietary antibody technologies
- Numerous collaborations for product development

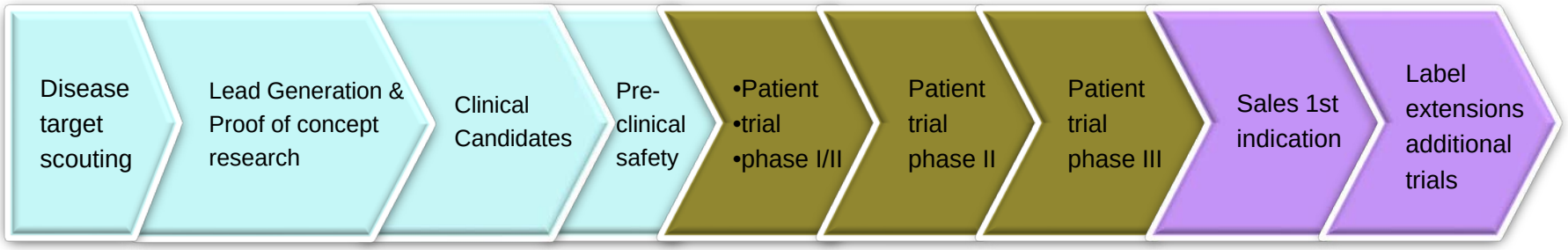
Genmab
Organization

- **Copenhagen, DK**
  - **Headquarters**
  - **Clinical Development**
- **Utrecht, NL**
  - **Discovery**
  - **Research & Pre-Clinical Development**
- **Princeton, NJ**
  - **Finance**
  - **Business Development**



Genmab

Integrating Science with Antibody Product Development



Target identification
Target validation

Antibody generation
Assay development

PoC studies
MoA studies
Indication selection

Cell line development

Toxicology studies

Bio-analytical assay development
Manufacturing research
Process optimization

Product positioning research

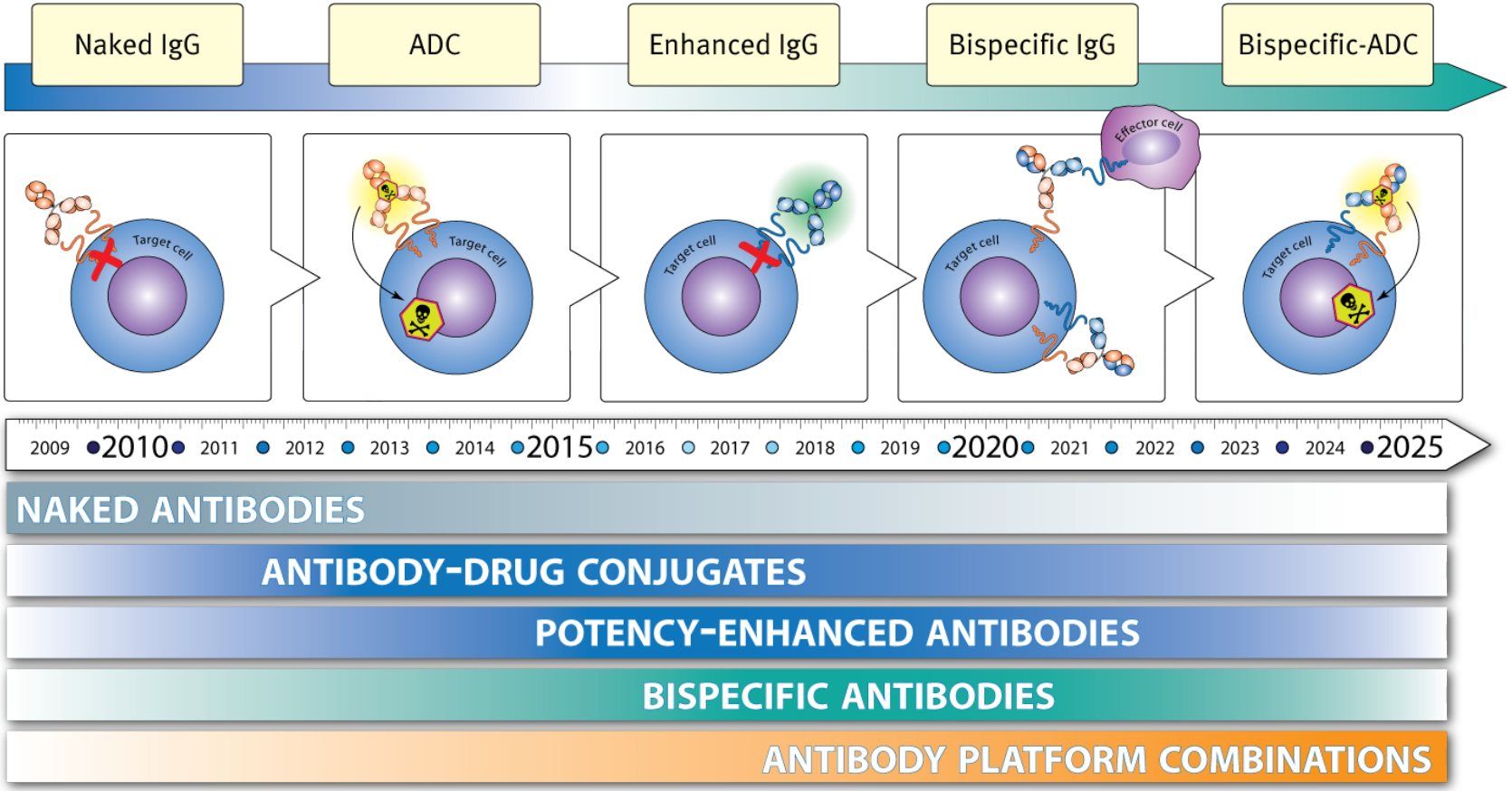
PoC studies additional indications

Technology innovation
Antibody Product and Format innovation

Genmab Research & Development Center

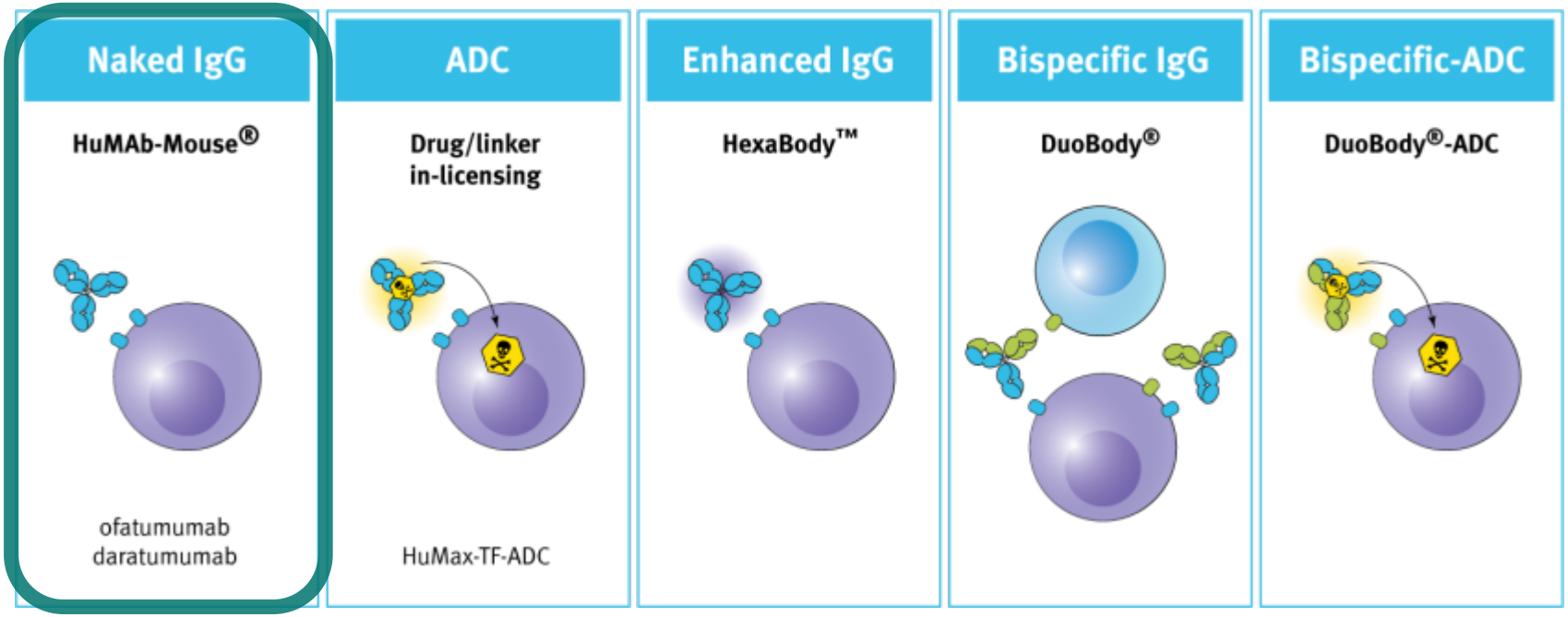
Antibody product development

Therapeutic antibody landscape



Antibody product development

Naked antibodies



- Daratumumab
  - First-in-class therapeutic CD38 antibody
  - In development for treatment of multiple myeloma, Non-Hodgkin's Lymphoma, NKT-cell lymphoma, MyeloDysplastic Syndromes, solid cancers and amyloidosis

Multiple Myeloma

Cancer of plasma cells

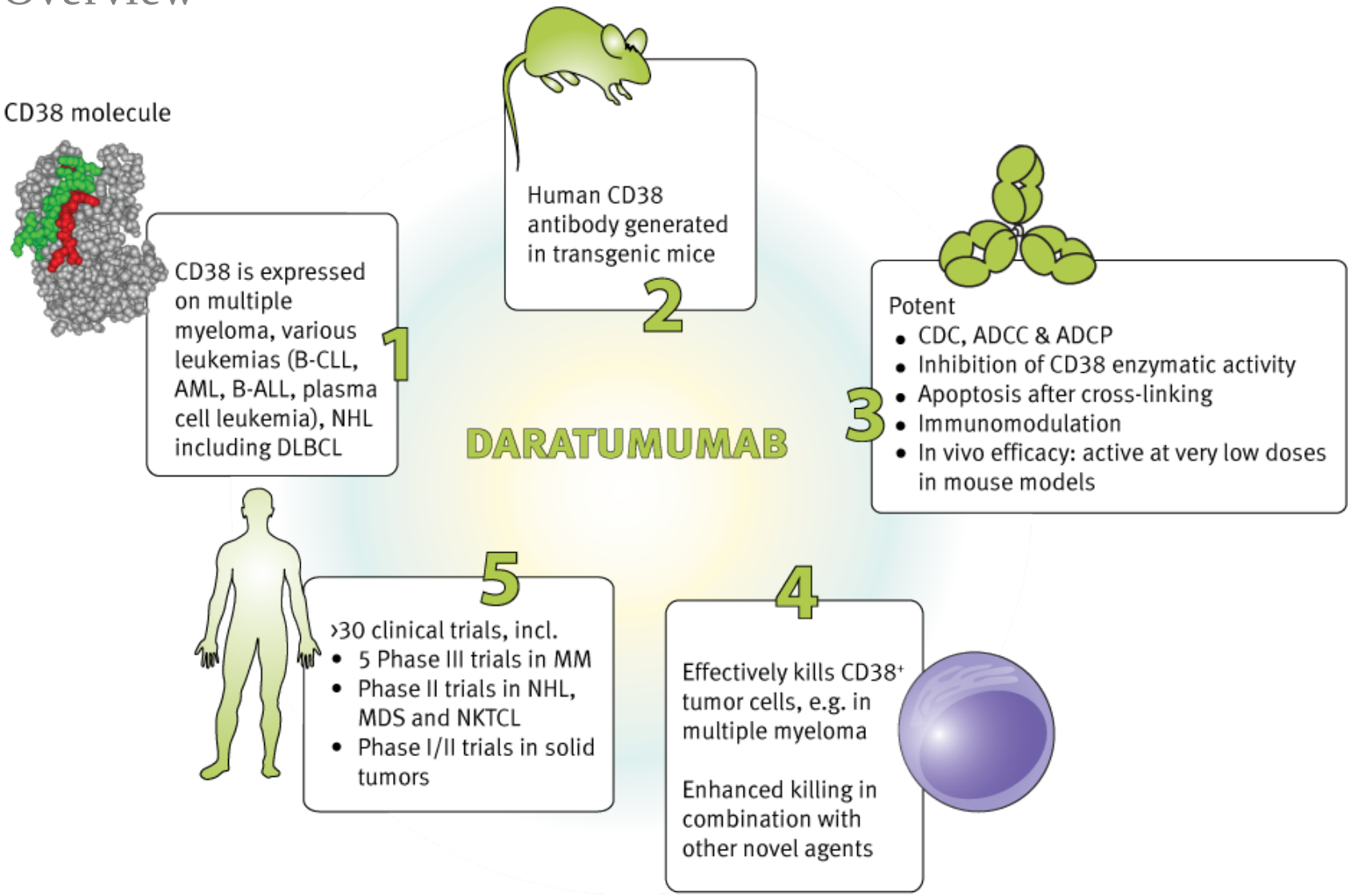
- In bones
  - Fractures
- In bone marrow
  - Infections
  - Fatigue
  - Bleeding
  - Kidney problems

10-15% of all hematological cancers

- Most prevalent hematological cancer in people over 65
- Hard to treat - life expectancy ~6-7 years

Urgent Need for New Treatments

Daratumumab
Overview

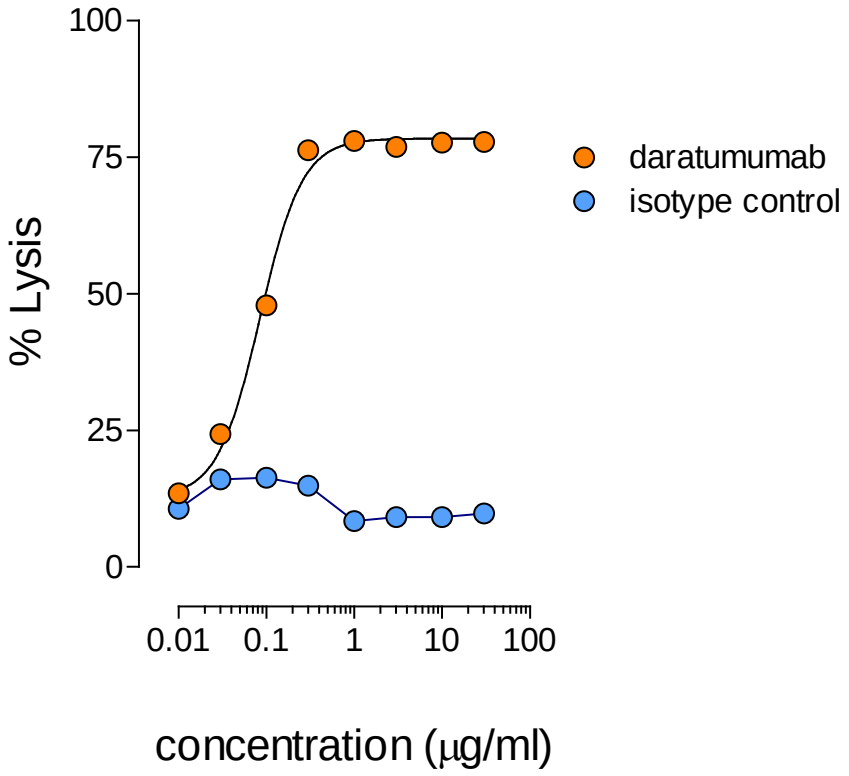


Daratumumab induces potent CDC

Fresh MM tumor cells

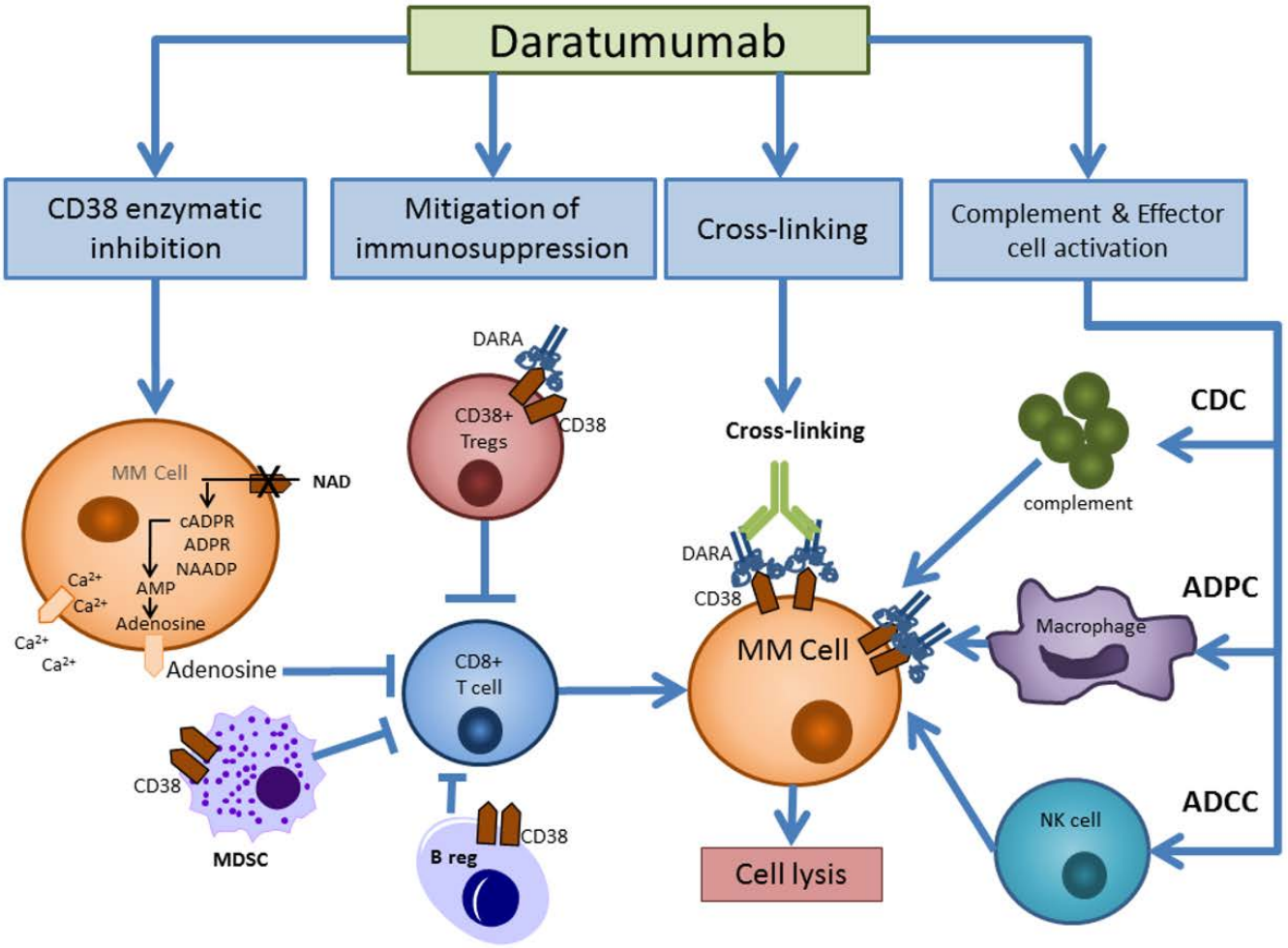
Patient	Clinical status	Lysis (%)
1	relapse	+++
2	relapse	-
3	relapse	+++
4	Untreated	+++
5	Relapse	+++
6	Relapse	++
7	Relapse	+
8	untreated	+++
9	relapse	+
10	relapse	++
11	relapse	-
12	relapse	++
13	relapse	+++

Representative example of DARA-induced lysis



De Weers et al. J Immunol 2011; 186:1840-1848

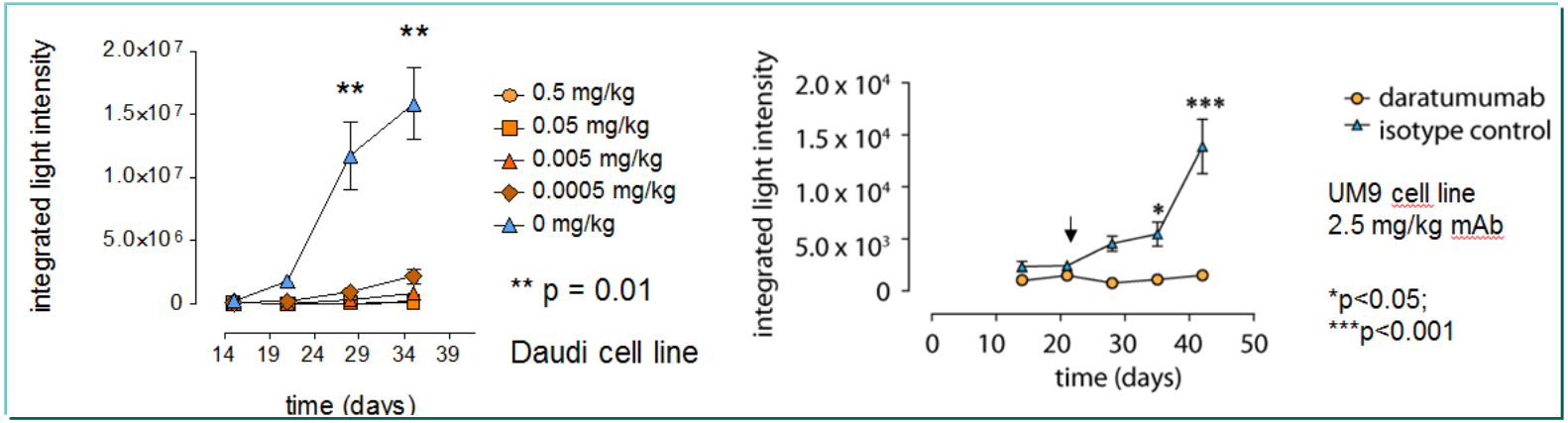
Daratumumab: Multiple Mechanisms of Action



Daratumumab blocks tumor growth *in vivo*

Prophylactic model

Therapeutic model



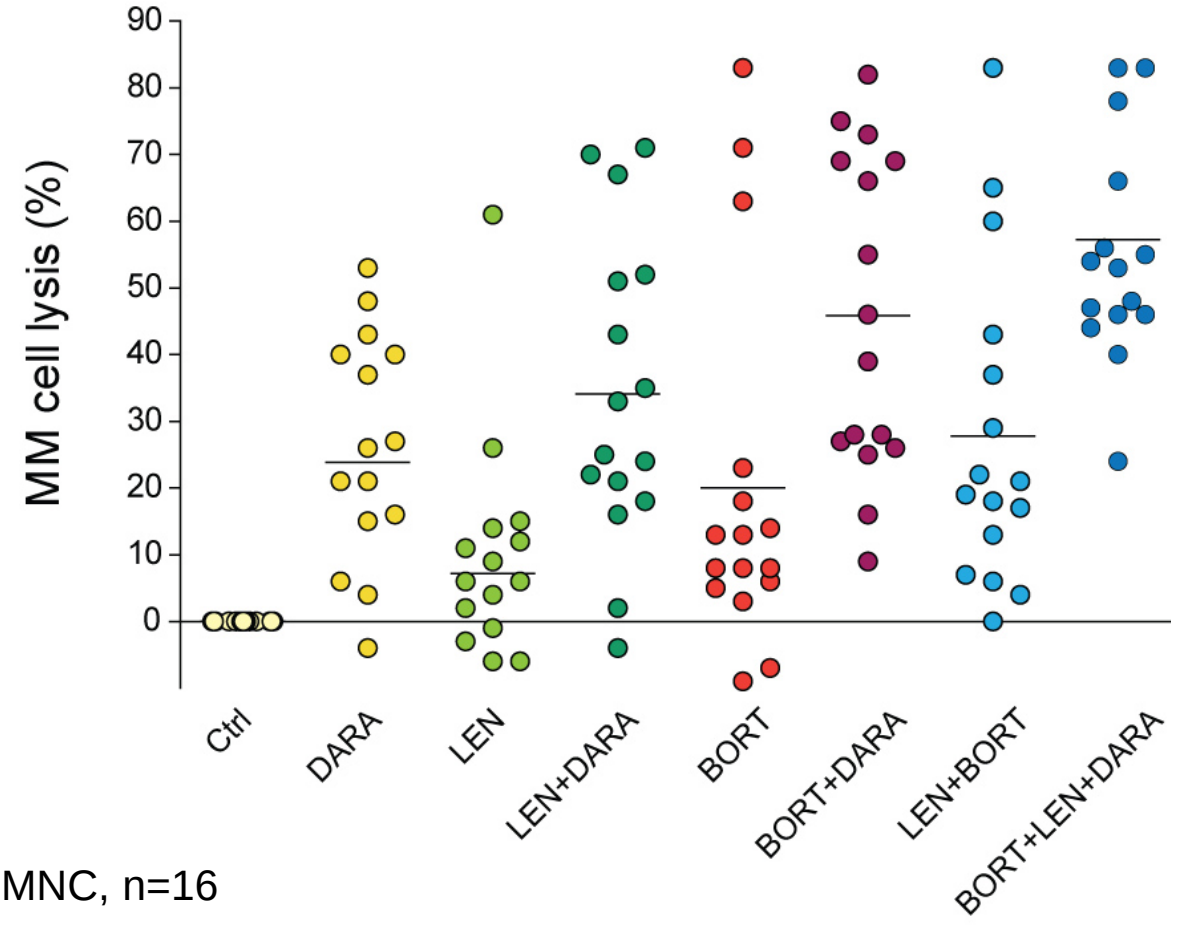
DARA is effective at sub-saturating doses

DARA common half-maximal effect dose:

- 0.0013 µg [95% C.I. 0.00036 µg; 0.0043 µg],
- 0.065 µg/kg [95% C.I. 0.018 µg/kg; 2.15 µg/kg]

De Weers et al. J. Immunol. 2011; 186:1840-1848

Daratumumab enhances MM cell killing by key chemotherapeutic agents for MM



LEN: 3 µM lenalidomide
BORT: 3 nM bortezomib
DARA: 10 µg/mL daratumumab

- BM-MNC, n=16
- *** p<0.001

Van der Veer et al. Blood Cancer J. 2011; 1:e41
Van der Veer et al. Haematologica 2011; 96: 284-290

Efficacy in Monotherapy

Combined Analysis of Monotherapy Studies

Daratumumab as a single agent

- Approved by FDA and conditionally approved by EMA in relapsed/refractory multiple myeloma[1,2]

Patients received a median of 5 prior lines of therapy

- 86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]

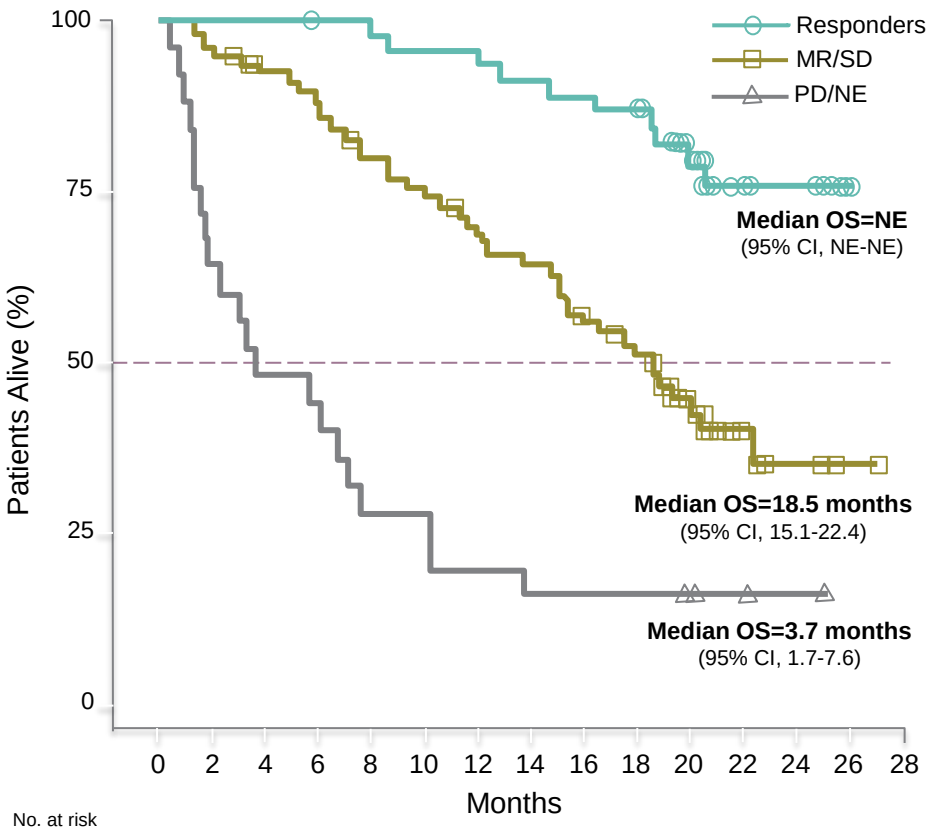
Median overall survival (OS): 20.1 months[3]

- 2-year OS was ~75% in responders
- Median OS was 18.5 months MR/SD patients

ORR = 31%[3]

ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Overall Survival[4]



No. at risk

Responders	46	46	46	45	44	43	43	41	40	39	28	12	12	2	0
MR/SD	77	74	67	63	57	53	48	45	38	34	20	8	4	1	0
PD/NE	25	16	12	11	7	7	5	4	4	4	3	2	1	0	0

MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

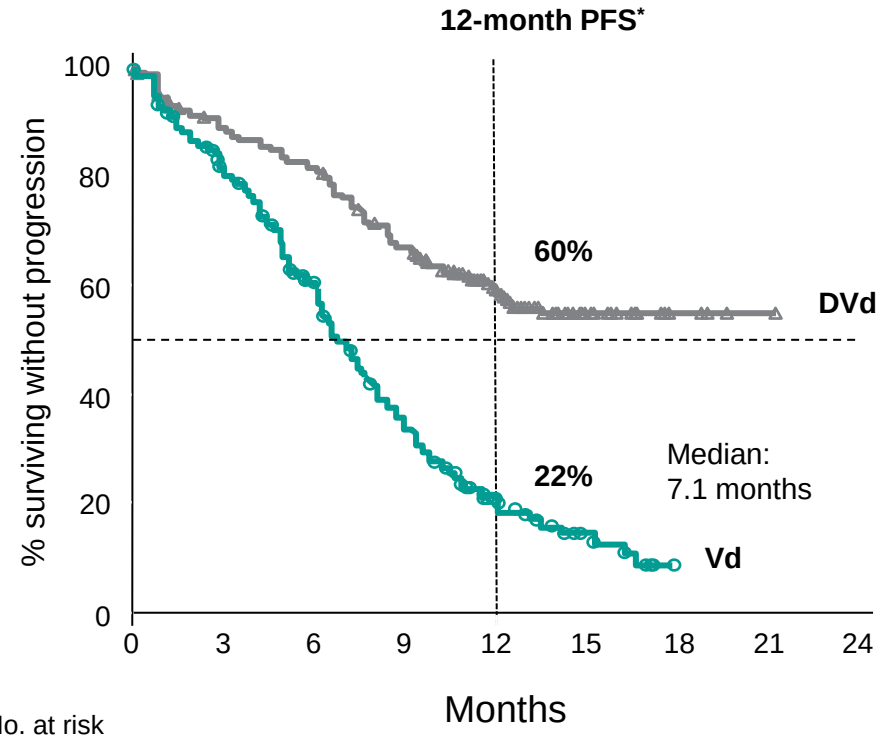
1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016;128(1):37-44
4. Data presented at ASCO 2016

Updated Efficacy: CASTOR & POLLUX

Phase III Relapsed or Refractory Multiple Myeloma

CASTOR

Dara + Bort + Dex (DVd)



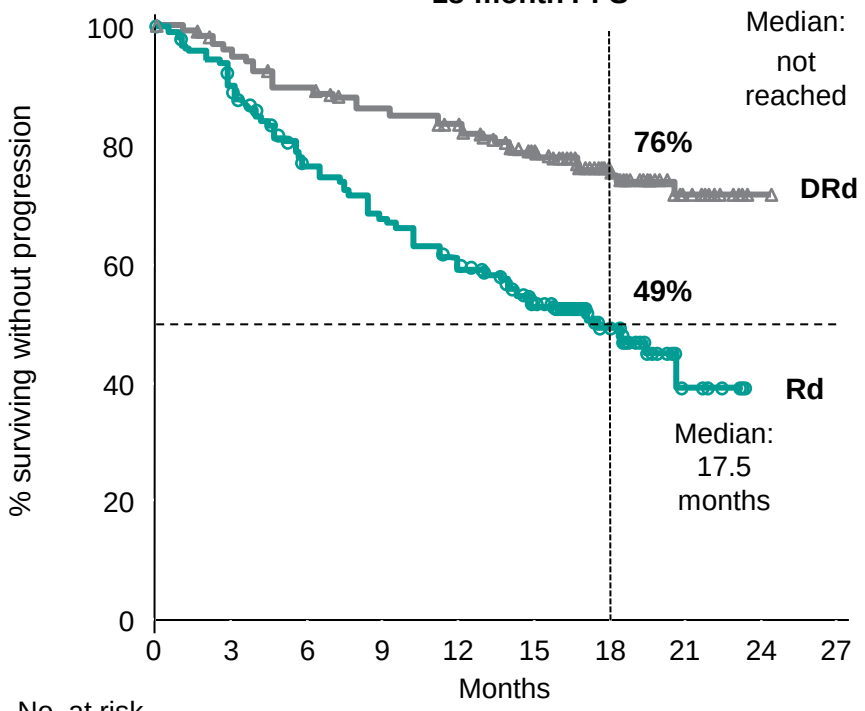
No. at risk

Vd	247	182	129	73	23	9	0	0	0
DVd	251	215	198	160	91	33	5	1	0

Hazard Ratio=0.33	DVd	Vd
ORR	84%	63%
≥ CR	26%	10%

POLLUX

Dara + Len + Dex (DRd)



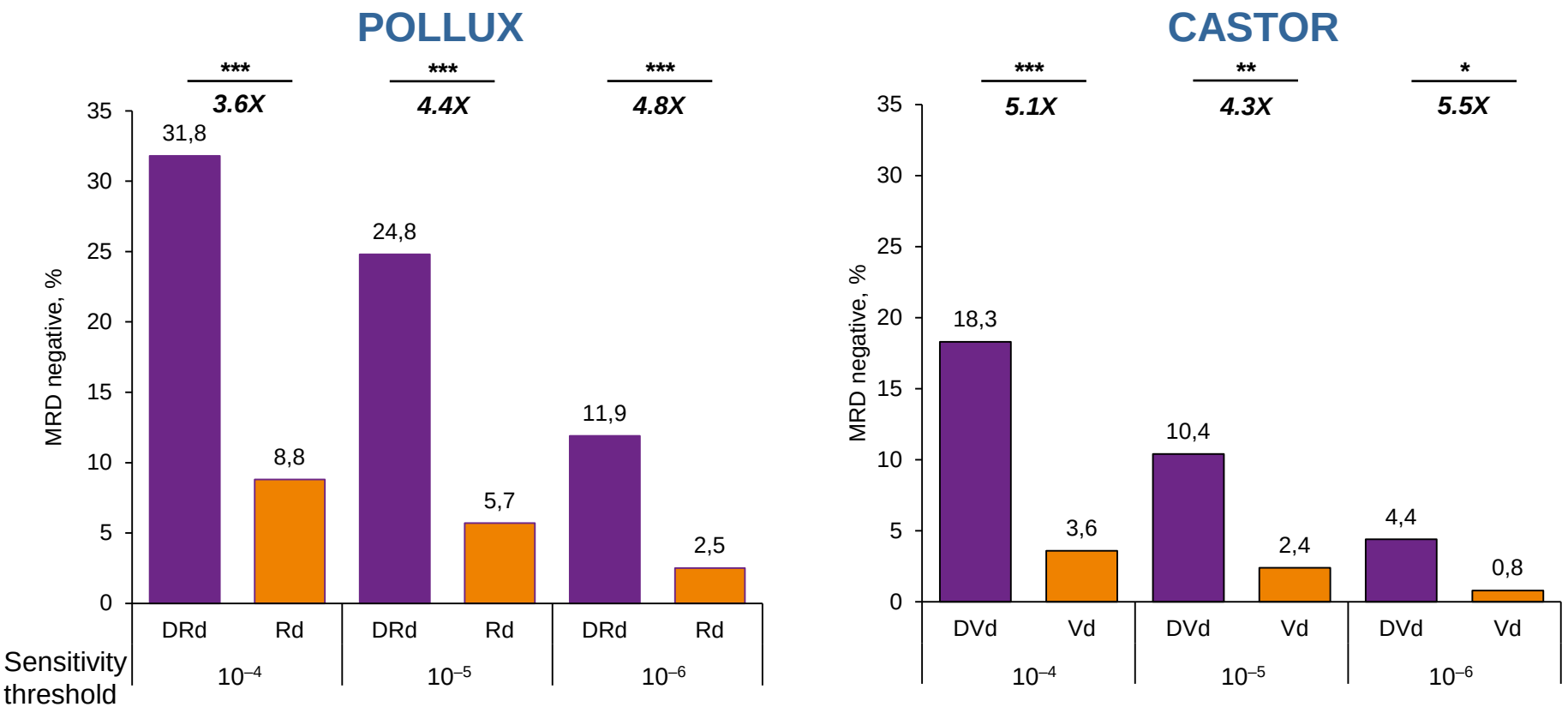
No. at risk

Rd	283	249	206	181	159	132	48	5	0	0
DRd	286	266	249	237	227	194	82	15	1	0

Hazard Ratio=0.37	DRd	Rd
ORR	93%	76%
≥ CR	46%	20%

Presented at ASH – San Diego, Dec. 2016

Proportion of MRD-negative Patients at 10^{-4}, 10^{-5}, and 10^{-6} Thresholds



- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

*** ***P*** **<0.0001**
** ***P*** **<0.005**
* ***P*** **<0.05**

P values calculated using likelihood-ratio chi-square test.

Expansive Daratumumab Clinical Development

Multiple Myeloma

Indication	Disease Stage	Therapy	No. Pts*	Development Phase
				I / I/II / II / III
Multiple Myeloma**	High Risk Smoldering	Mono	108	✓ SMM2001 (CENTAURUS)
	Front line (transplant & non-transplant)	Dara + VMP	700	✓ MMY3007 (ALCYONE)
		Dara + Rd	730	MMY3008 (MAIA)
		Dara + VTd	1,080	MMY3006 (CASSIOPEIA)
		Dara + RVd	216	MMY2004
		Multi combo Study (6 arms)	250	MMY1001 (EQUULEUS)
	Relapsed or Refractory	Dara + Rd	571	✓ MMY3003 (POLLUX)
		Dara + Vd	498	✓ MMY3004 (CASTOR)
		Dara + K + Dex	450	Announced
		Dara +Pom + Dex	155	H-35360
		Subcutaneous	128	MMY1004 (PAVO)
		Dara + Tecentriq	214	GO29695
		Dara + durvalumab	258	FUSION
		Dara + Opdivo	375	CA209-039
		Dara + Opdivo	TBC	Announced

*Approx. no. based on clinicaltrials.gov **Maintenance integrated into some study protocols

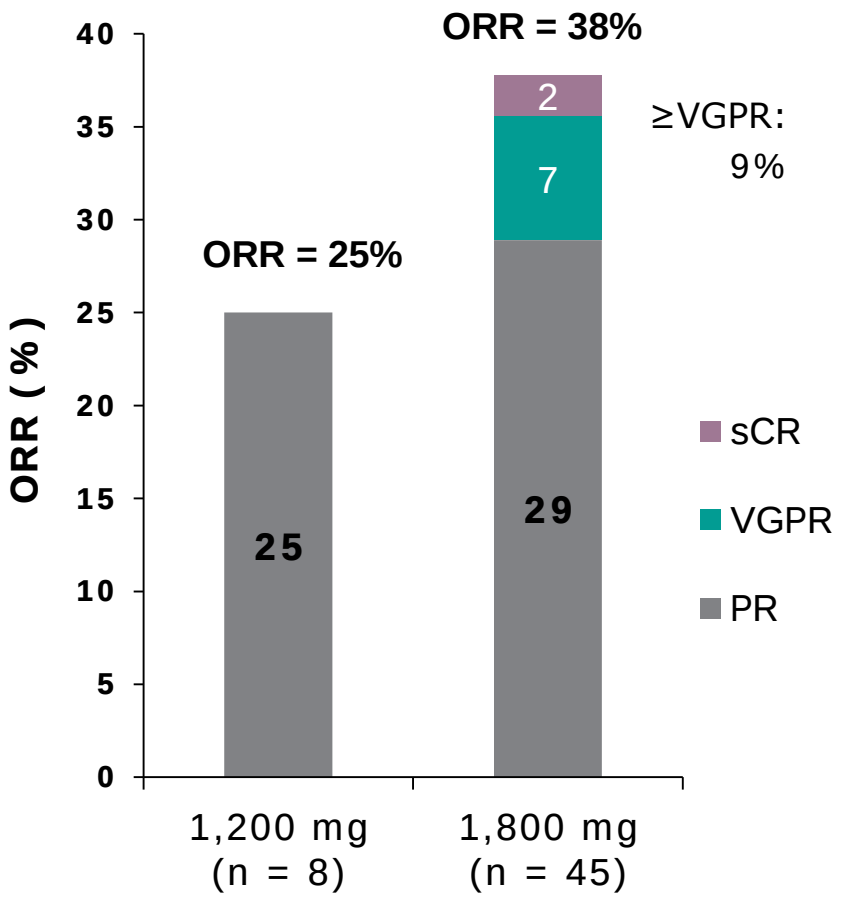
V = bortezomib , MP = melphalan-prednisone , T = thalidomide , d= dexamethasone, R = lenalidomide

✓ Fully Recruited

Select Studies

Subcutaneous Daratumumab

Data PhIb PAVO Study in Relapsed or Refractory MM



Faster Infusion time

- 1,800 mg dose: ~30min
- First IV infusion: 7 hrs

Lower IRR incidence

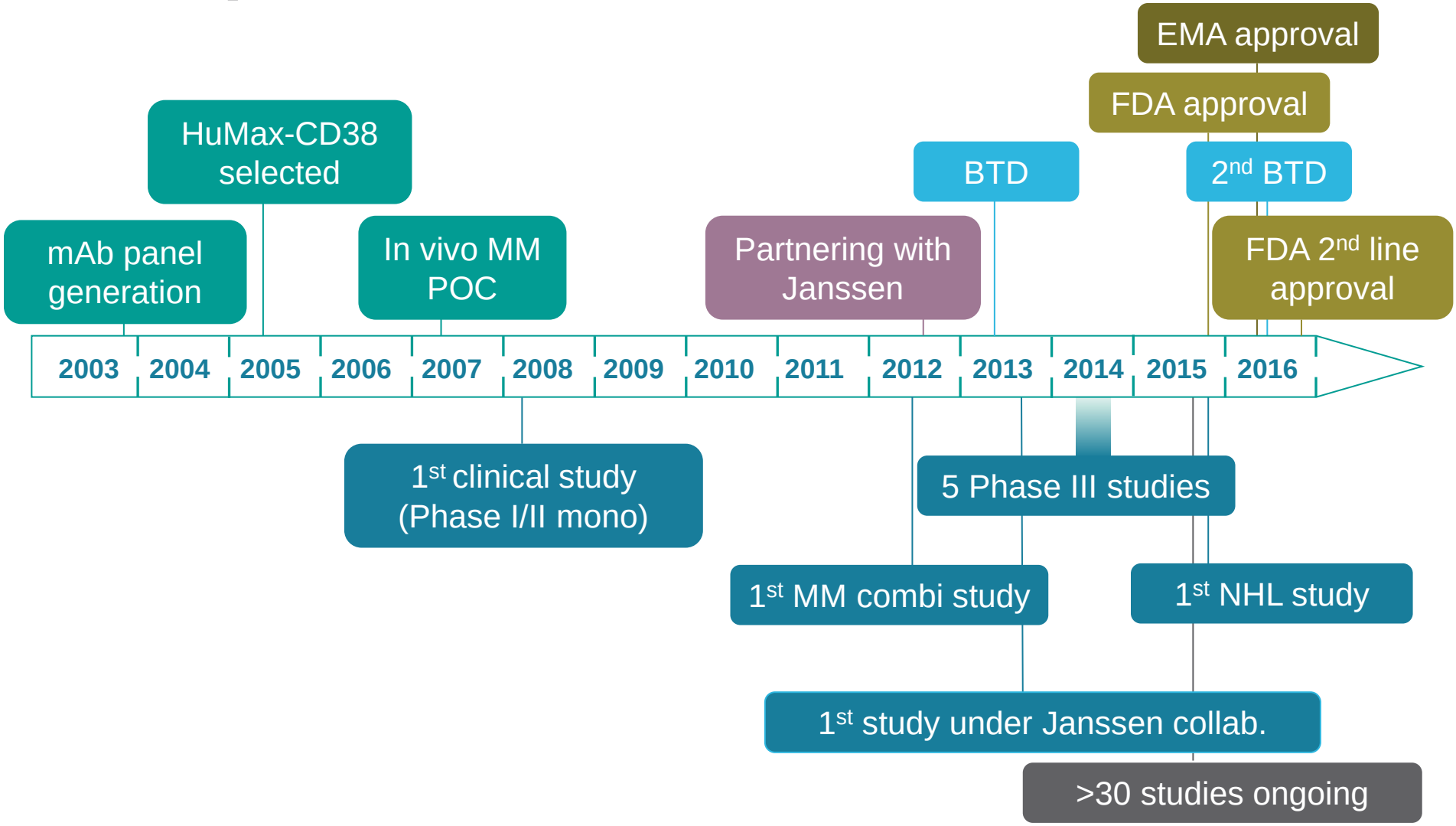
- 1,800 mg dose: 24%
- 16 mg/kg IV dose: 48%

PK profile of 1,800 mg dose consistent with 16 mg/kg IV dose

Presented at ASH – San Diego, Dec. 2016

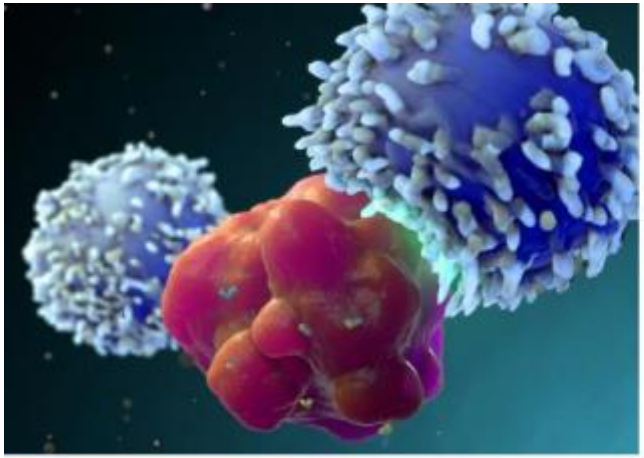
DARZALEX™ (daratumumab): Exciting Progress

Development Time Line



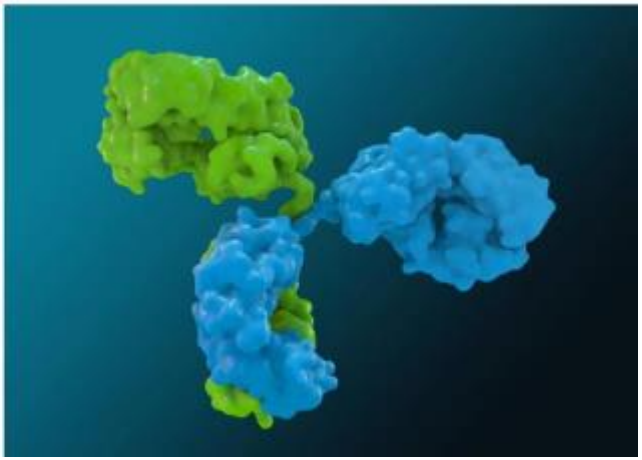
We Aim to Harness the Potency of the Immune System:
Basic Immunological Principles to Products & Technologies

The power of our immune system inspires us.



We are curious to understand basic immunological principles…

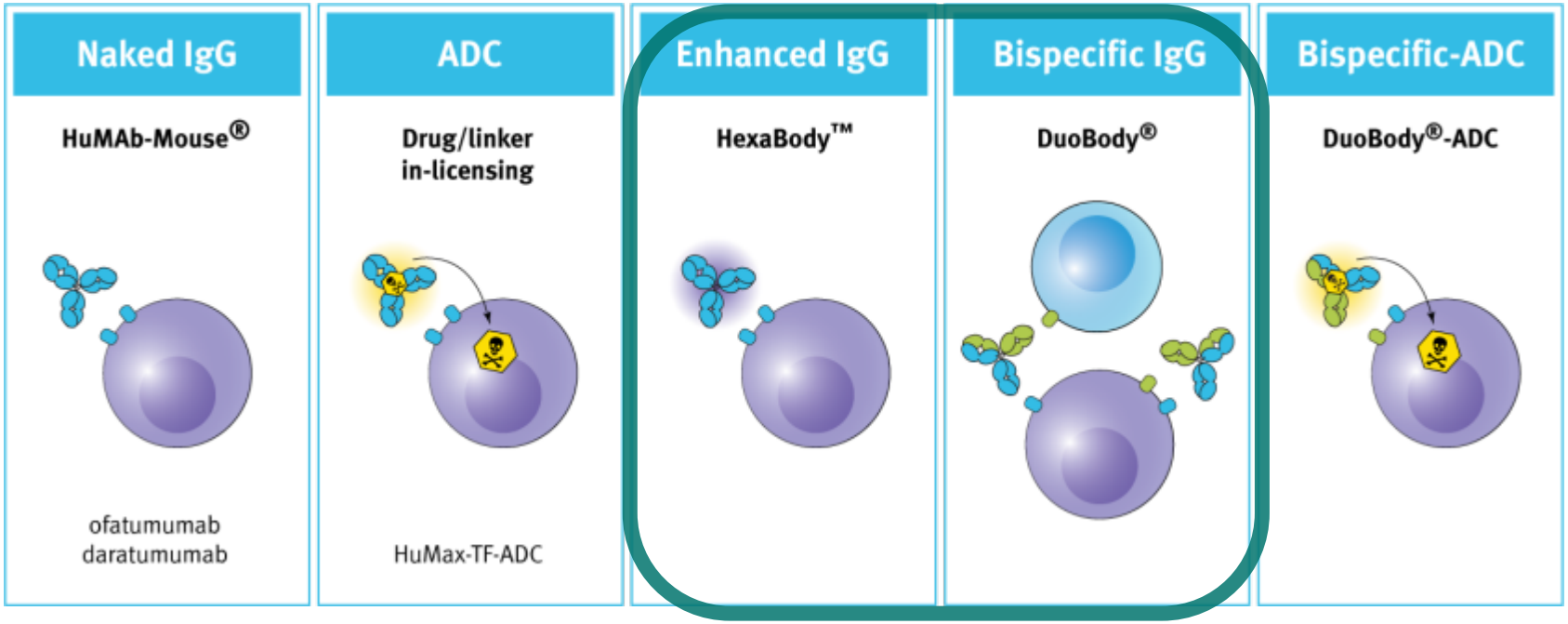
…and translate those to practical applications,



…innovative antibody products and technologies.

Antibody product development

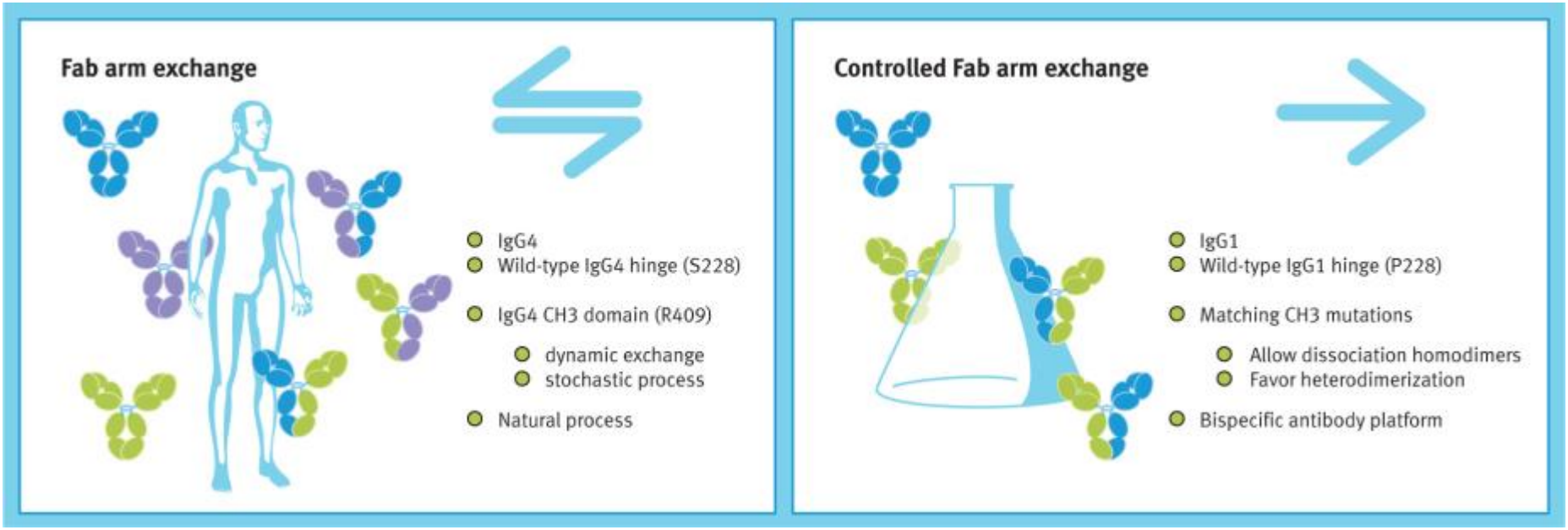
DuoBody & HexaBody technologies



- DuoBody technology
  - Platform for creation of bispecific antibodies
  - BsAb can engage two therapeutic targets
- HexaBody technology
  - Enables antibodies to readily form clusters of 6 (hexamers)
  - Induces & enhances target cell killing

From science to bispecific antibody platform
Controlled Fab-arm exchange

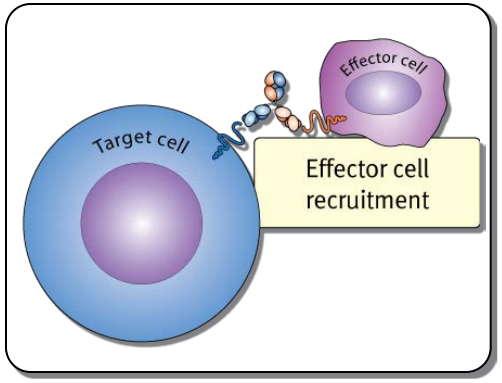
**DuoBody platform is based on Fab-arm exchange,
a naturally occurring process for generating bispecificity**

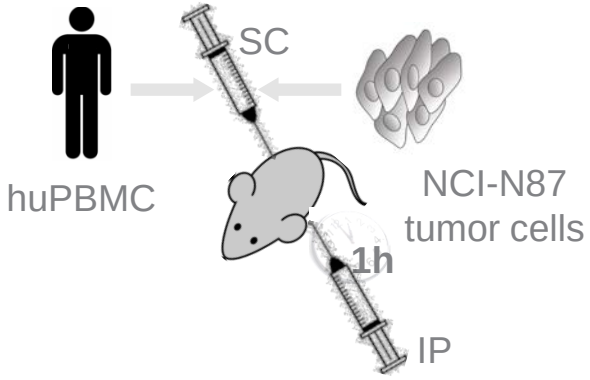


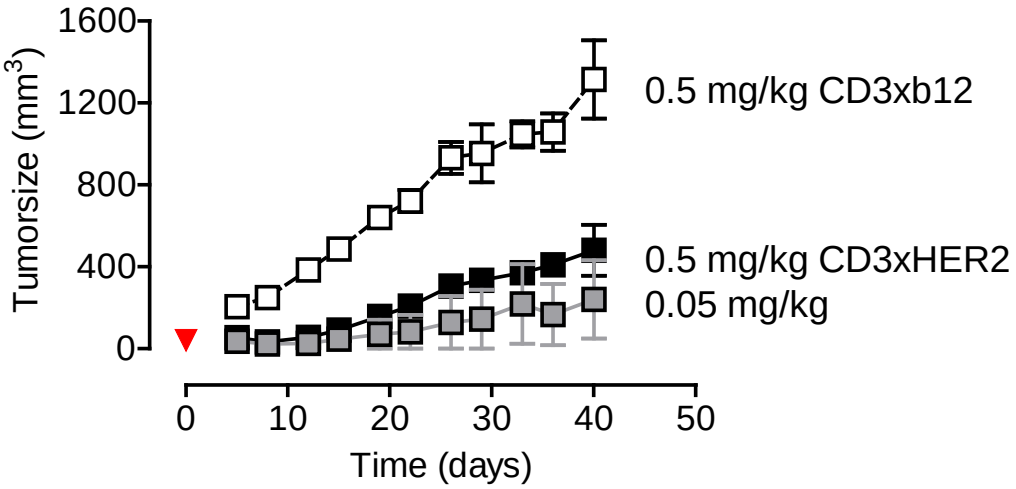
Van der Neut Kolfschoten et al; Science 317, 1554-1557 (2007)
Labrijn et al; Nat Biotechnol 27, 767-771 (2009)
Labrijn et al; J Immunol. 187, 3238-3246 (2011)
Rose et al; Structure 19,1274-1282 (2011)

Duobody
Proof-of-concept - Potent therapy at low dose

- Example: CD3 x tumor target bispecific antibodies recruit T-cells to specifically kill tumor cells





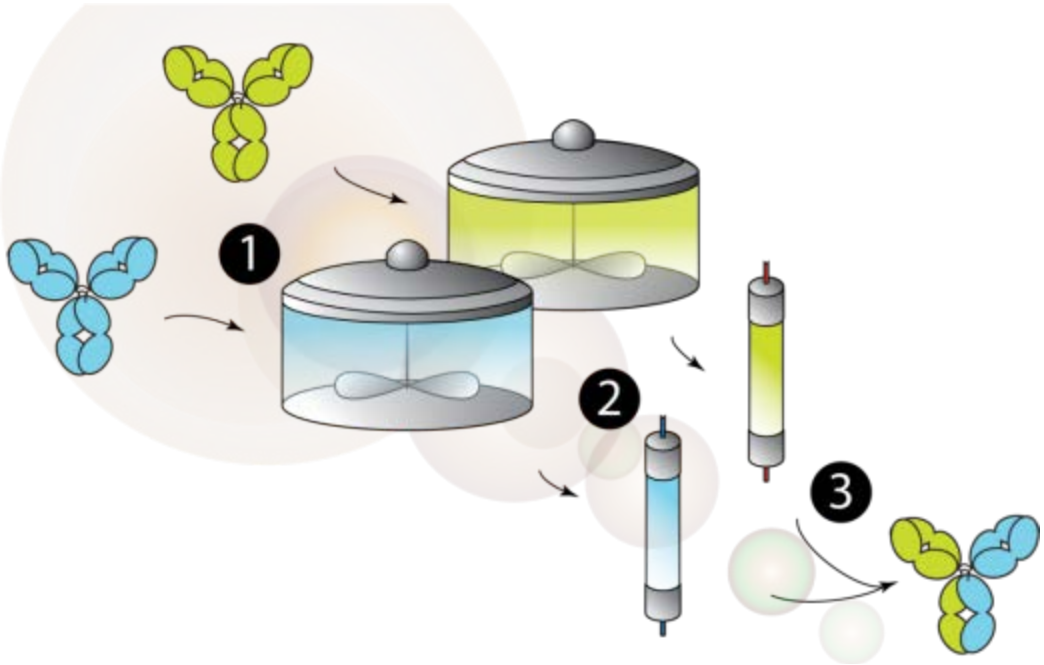


Labrijn et al. PNAS 2013; 110; 5145-5150

DuoBody platform - simple post-production process

Manufacturing based on standard unit operations for IgG1

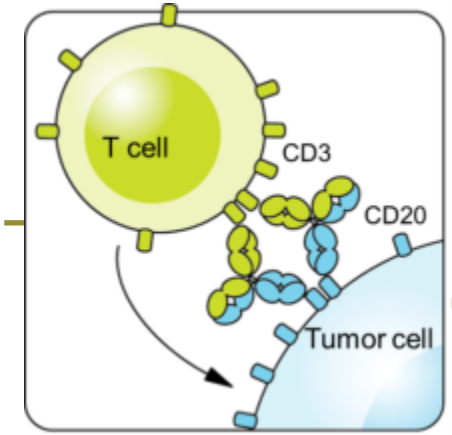
- Separate expression of the two parental antibodies
- Purification using standard downstream processes
- Highly efficient generation of bispecific antibodies using disposable technologies at required scale



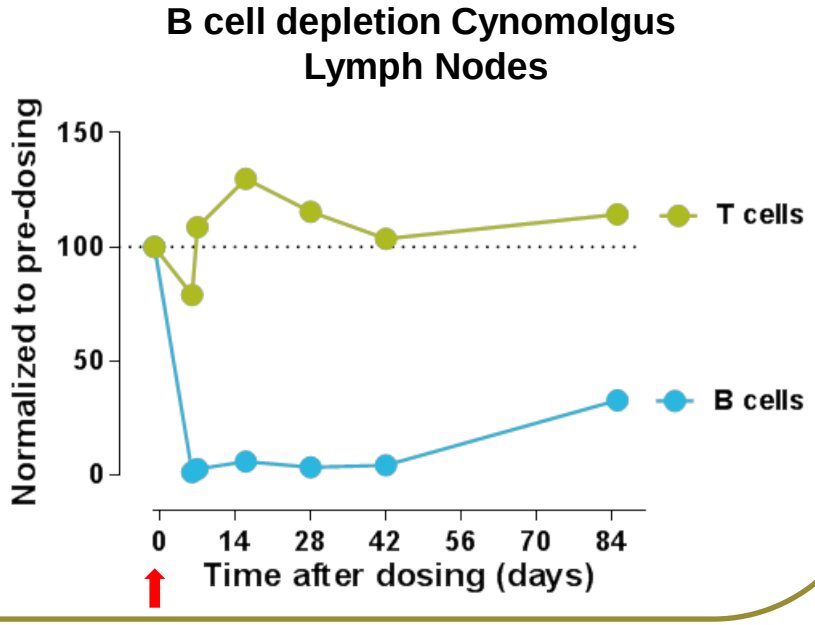
DuoBody

DuoBody CD3xCD20
Key Characteristics

Humanized IgG1 bispecific antibody



- DuoBody platform
- Regular half life
- Non-activating Fc-domain
- Potently activates T cells to kill CD20^{+} tumor cells
- Cynomolgus CD3 & CD20 x-reactive
  - Potent Cynomolgus B cell depletion (peripheral blood, lymph nodes)
- 2017 IND candidate



Cutting Edge Capabilities: Immuno-Oncology

Turning Cancer into a Chronic Condition

Innovating cancer treatment

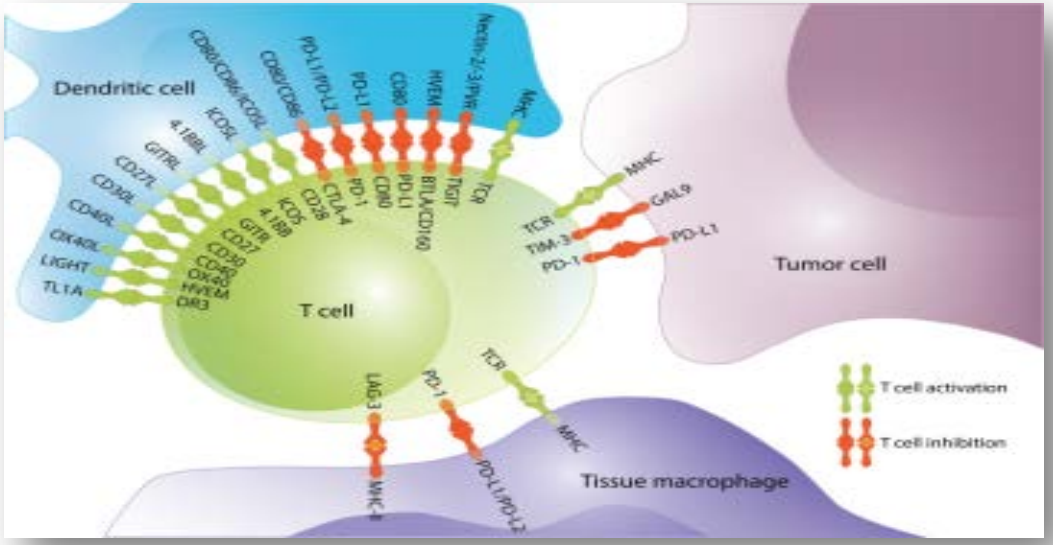
- Activate patient's own immune system
- Long duration of response
- Potential game changer
- >$50B market

DuoBody technology

- Robust & versatile bispecific antibody platform
- Screening multiple combinations in final therapeutic format
- Combined targeting immune check points
- Current Partnerships
  - Aduro Biotech
  - BioNTech

daratumumab + anti-PD-L1 / PD-1

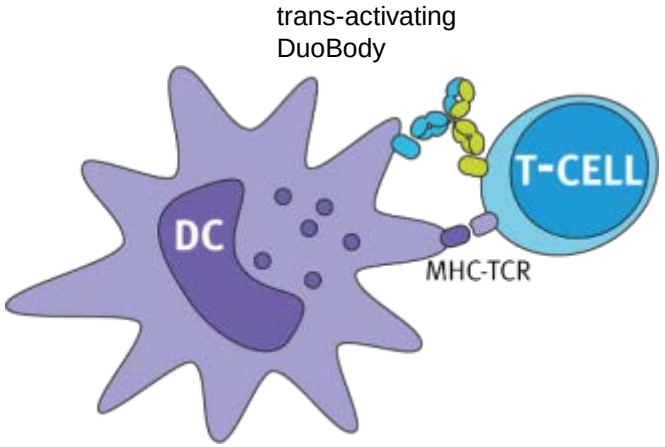
- Multiple studies started in 2016 & 2017
- PhIb/II studies in combi. w/Tecentriq (Genentech) in relapsed / refractory MM & solid tumor
- PhII study in combi. w/ durvalumab (Celgene) in relapsed / refractory MM
- Ph Ib/II in combi. w/Opdivo (BMS) in solid tumors & MM



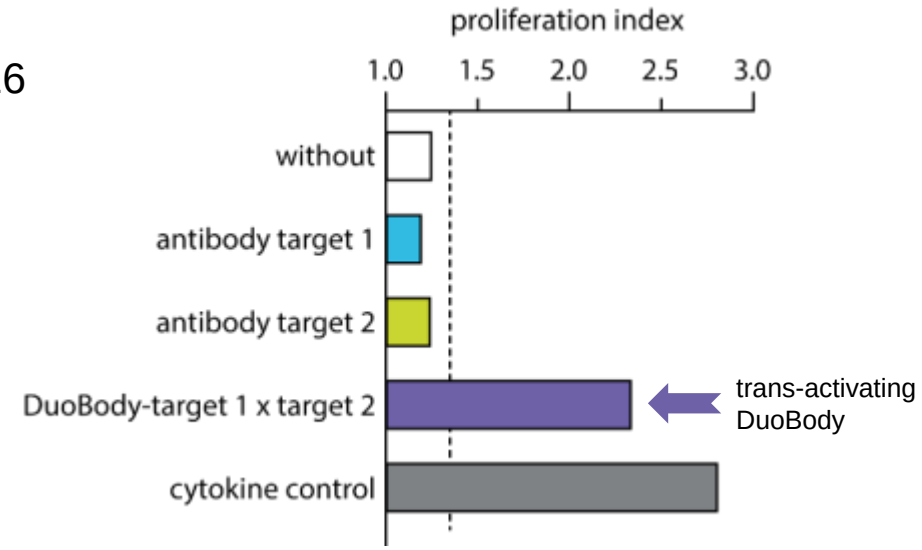
DuoBody - Target 1 x Target 2

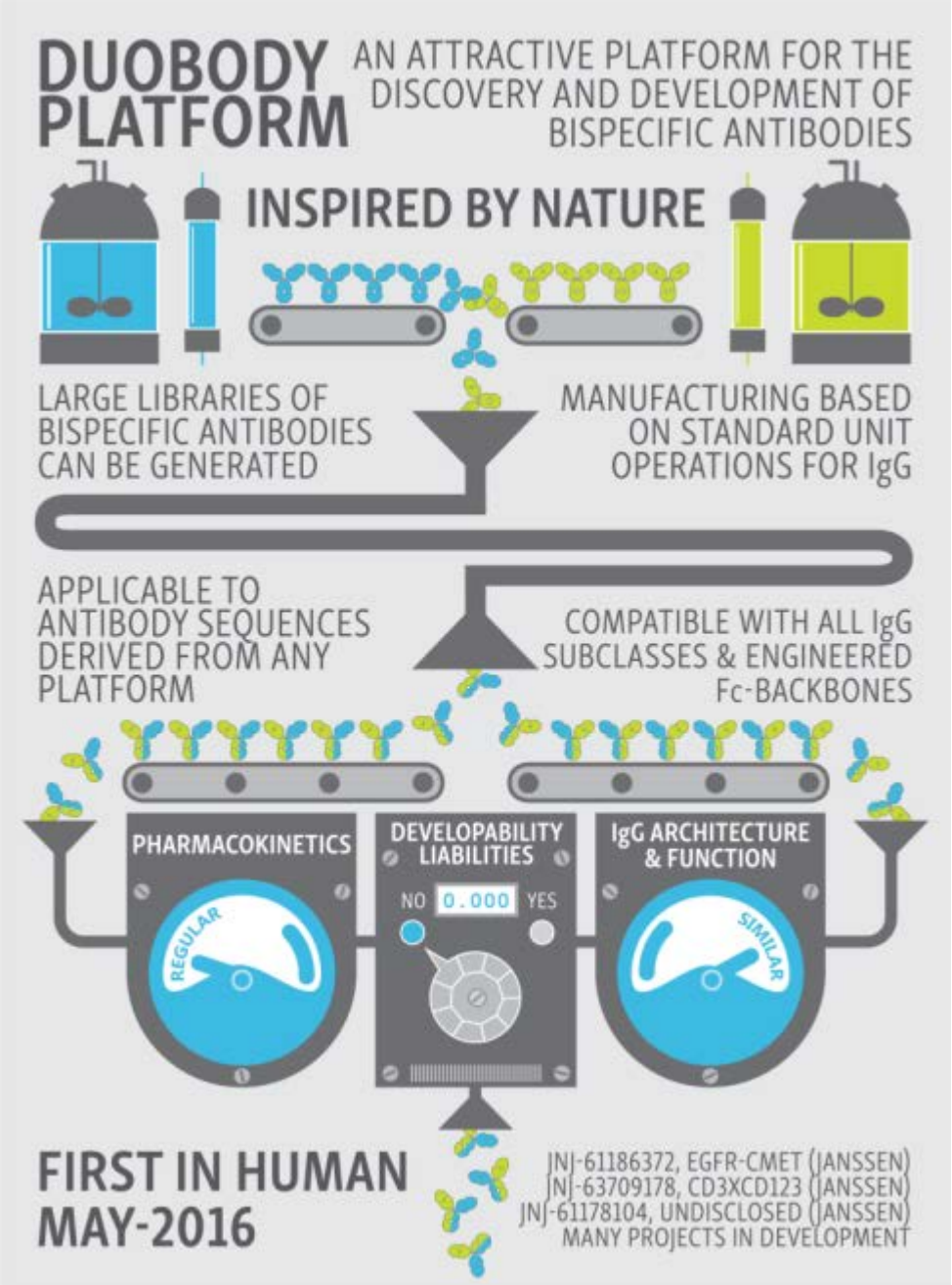
Trans-activation Principle

- Trans-activating bispecific antibody targeting two checkpoint activators, resulting in conditional activation of cytotoxic T cells
- Bispecific combination of T cell target with Antigen Presenting Cell (DC) target
- Enhances DC-mediated licensing of T-cells
- Accelerates antigen-specific killing of tumor cells via MHC-TCR interaction
- Solid tumor indications
- Clinical Candidate selection: Q4 2016
- 2018 IND candidate
- Collaboration with BioNTech



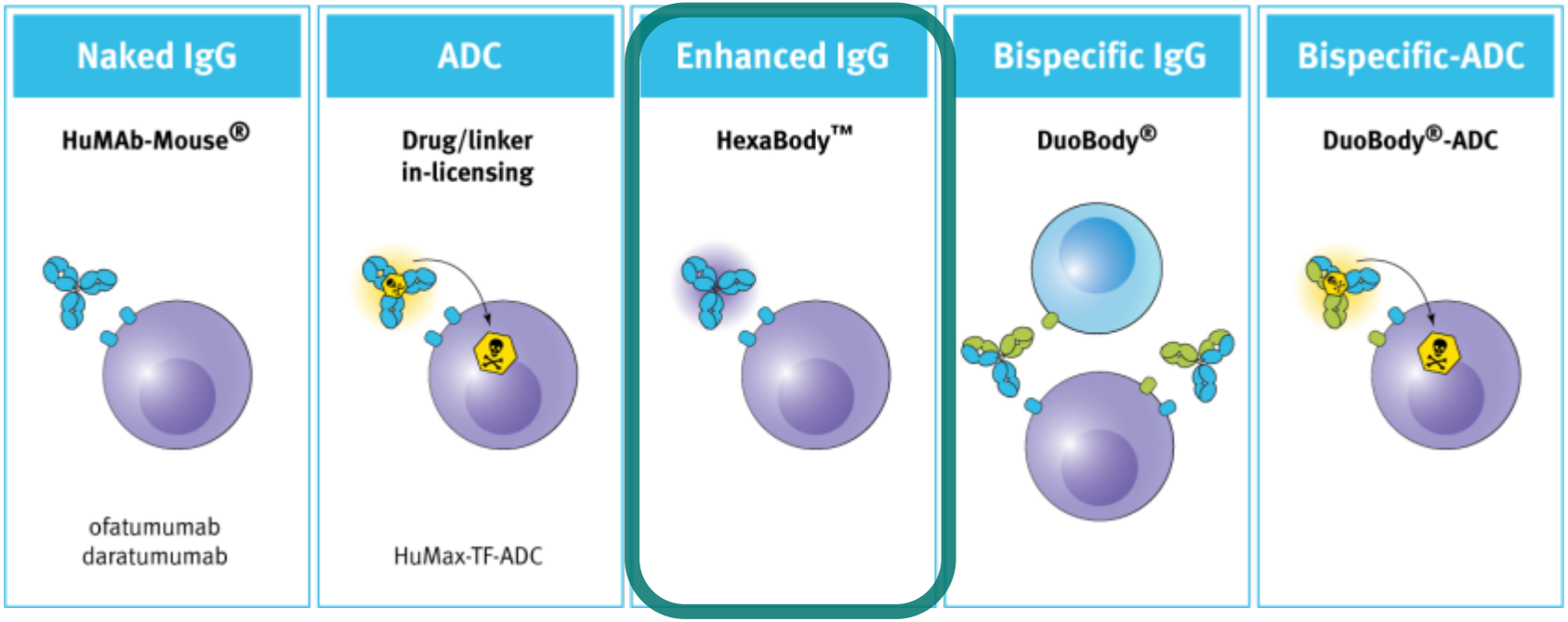
Cytotoxic CD8+ T cells




DUOBODY PLATFORM
AN ATTRACTIVE PLATFORM FOR THE DISCOVERY AND DEVELOPMENT OF BISPECIFIC ANTIBODIES
INSPIRED BY NATURE
LARGE LIBRARIES OF BISPECIFIC ANTIBODIES CAN BE GENERATED
MANUFACTURING BASED ON STANDARD UNIT OPERATIONS FOR IgG
APPLICABLE TO ANTIBODY SEQUENCES DERIVED FROM ANY PLATFORM
COMPATIBLE WITH ALL IgG SUBCLASSES & ENGINEERED Fc-BACKBONES
PHARMACOKINETICS
REGULAR
DEVELOPABILITY LIABILITIES
NO
0.000
YES
IgG ARCHITECTURE & FUNCTION
SIMILAR
FIRST IN HUMAN MAY-2016
JNJ-61186372, EGFR-CMET (JANSSEN)
JNJ-63709178, CD3XCD123 (JANSSEN)
JNJ-61178104, UNDISCLOSED (JANSSEN)
MANY PROJECTS IN DEVELOPMENT

Antibody product development

HexaBody technology



- HexaBody platform
  - Builds on natural antibody biology - minimal engineering
  - Enables antibodies to readily form clusters of 6 (hexamers)
  - Induces & enhances target cell killing after binding via CDC
  - CDC capability to essentially any antibody

Complement Is Activated by IgG Hexamers Assembled at the Cell Surface

Christoph A. Diebolder,[1,2]* Frank J. Beurskens,[3]* Rob N. de Jong,[3] Roman I. Koning,[2] Kristin Strumane,[3] Margaret A. Lindorfer,[4] Marleen Voorhorst,[3] Deniz Ugurlar,[1] Sara Rosati,[5] Albert J. R. Heck,[5] Jan G. J. van de Winkel,[3,6] Ian A. Wilson,[7,8] Abraham J. Koster,[2] Ronald P. Taylor,[4] Erica Ollmann Saphire,[9] Dennis R. Burton,[8,9,10] Janine Schuurman,[3] Piet Gros,[1]† Paul W. H. I. Parren[3]†

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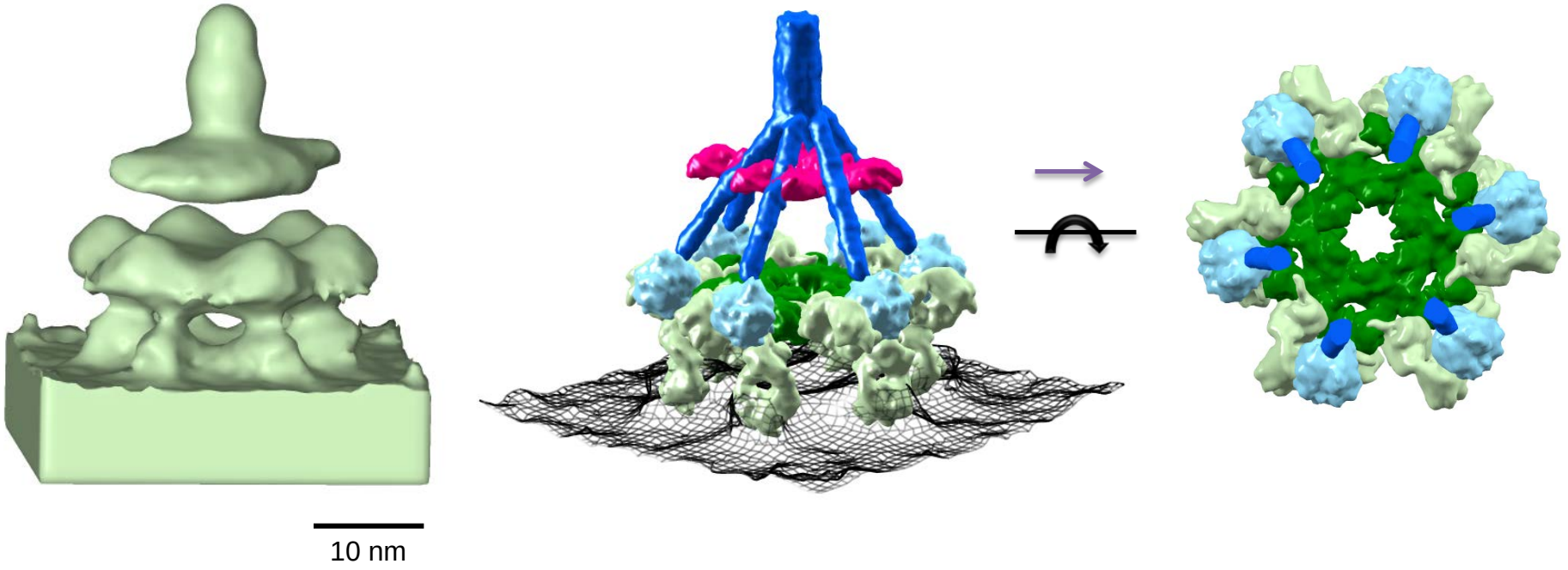
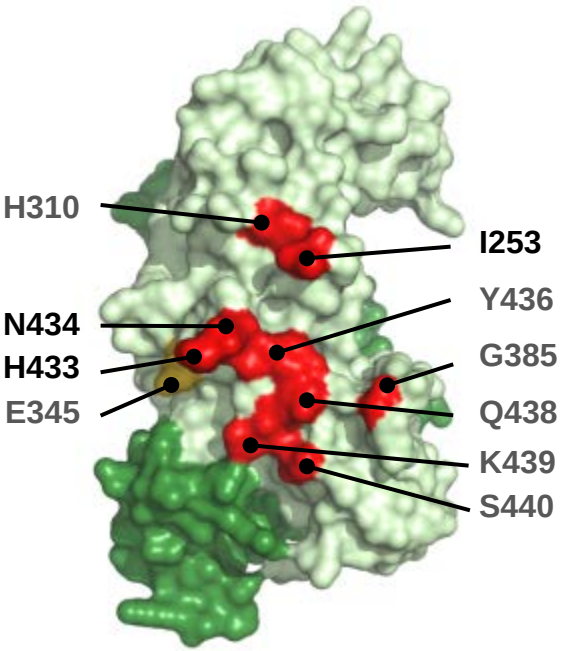
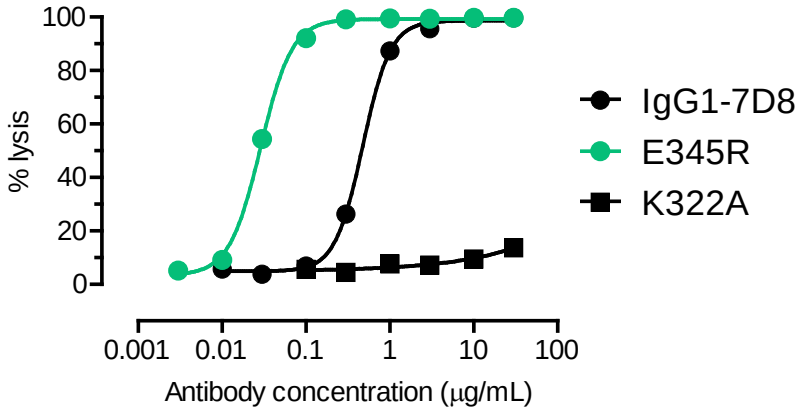


IgG1 hexamerization by intermolecular Fc:Fc interactions is critical for C1q binding and complement activation

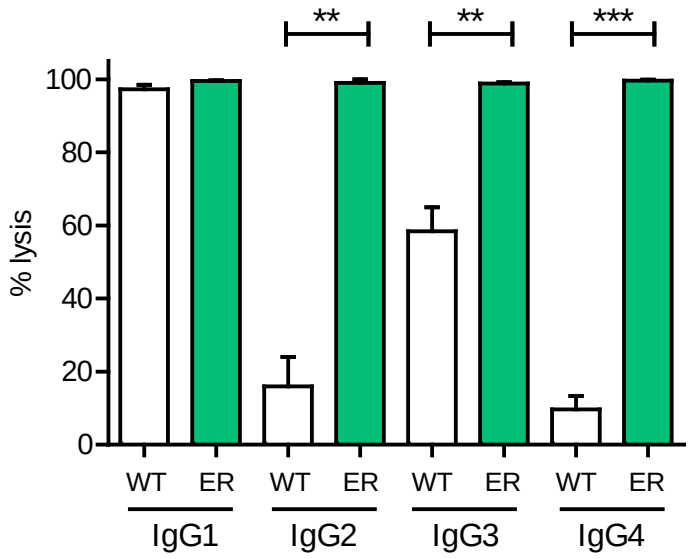
IgG1 hexamers: Fc:Fc interactions can be increased and is generally applicable



CDC anti-CD20



CDC anti-CD38

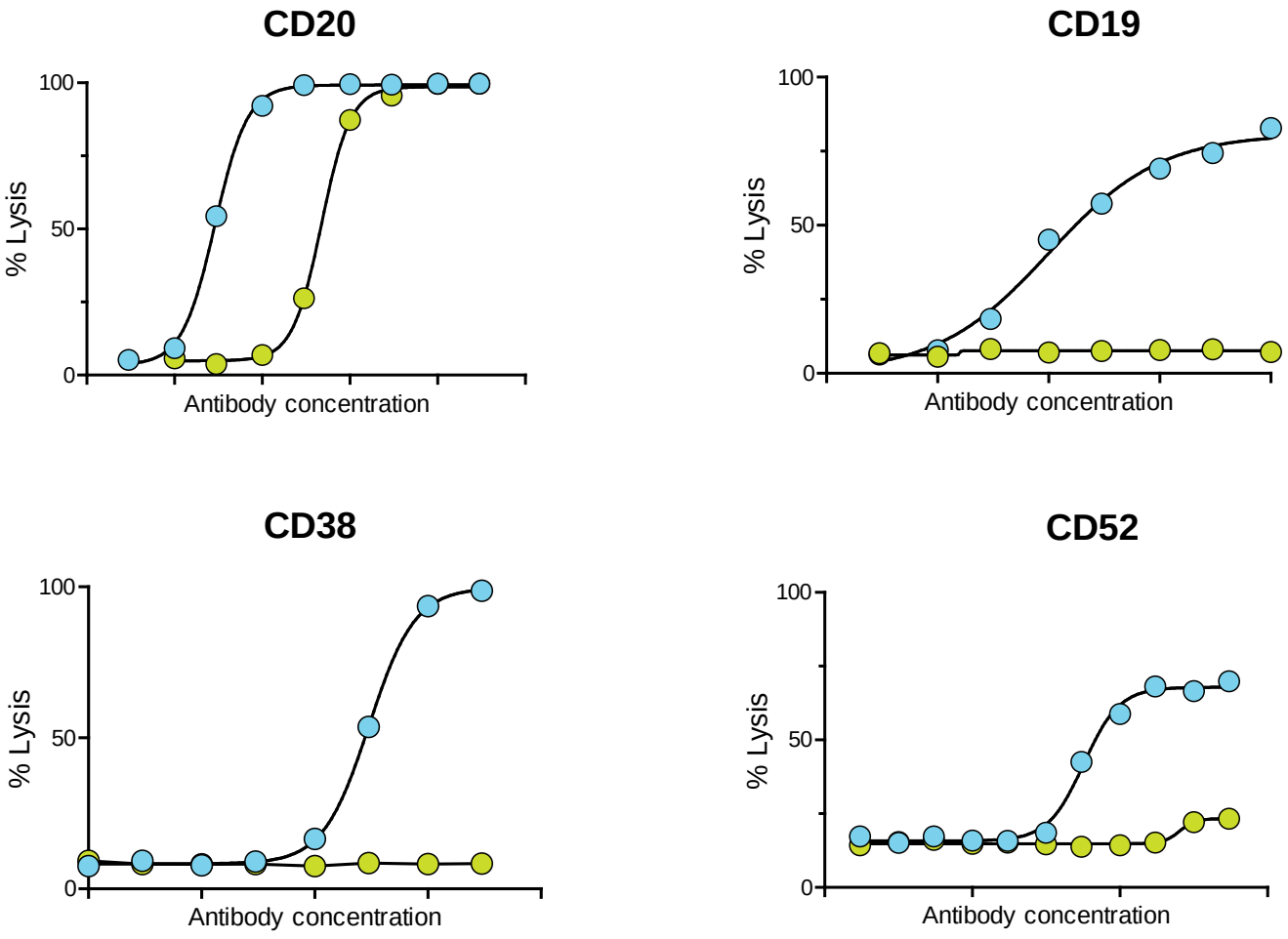


**P ≤ 0.01; *** P ≤ 0.001
Two-sided unpaired t-test with Welch's correction

Diebolder et al. Science 343:1260-3 (2014)

HexaBody – Proof of Concept

Enhanced CDC Applicable to Wide Range of Targets



HexaBody-DR5/DR5

Targeting DR5 for Cancer Therapy

DR5 (death receptor 5)

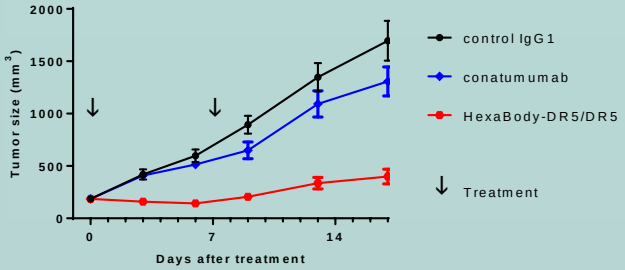
Cell surface receptor that mediates programmed cell death

In normal physiology, binding of TRAIL ligand results in DR5 clustering & cell death

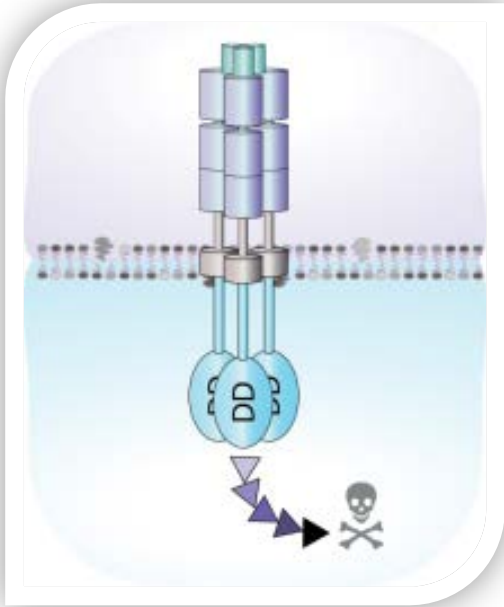
Targeting DR5 for treatment of cancer

- Agonistic DR5 mAb induce apoptosis after crosslinking
- Agonistic DR5 antibodies have shown limited anti-tumor activity in the clinic

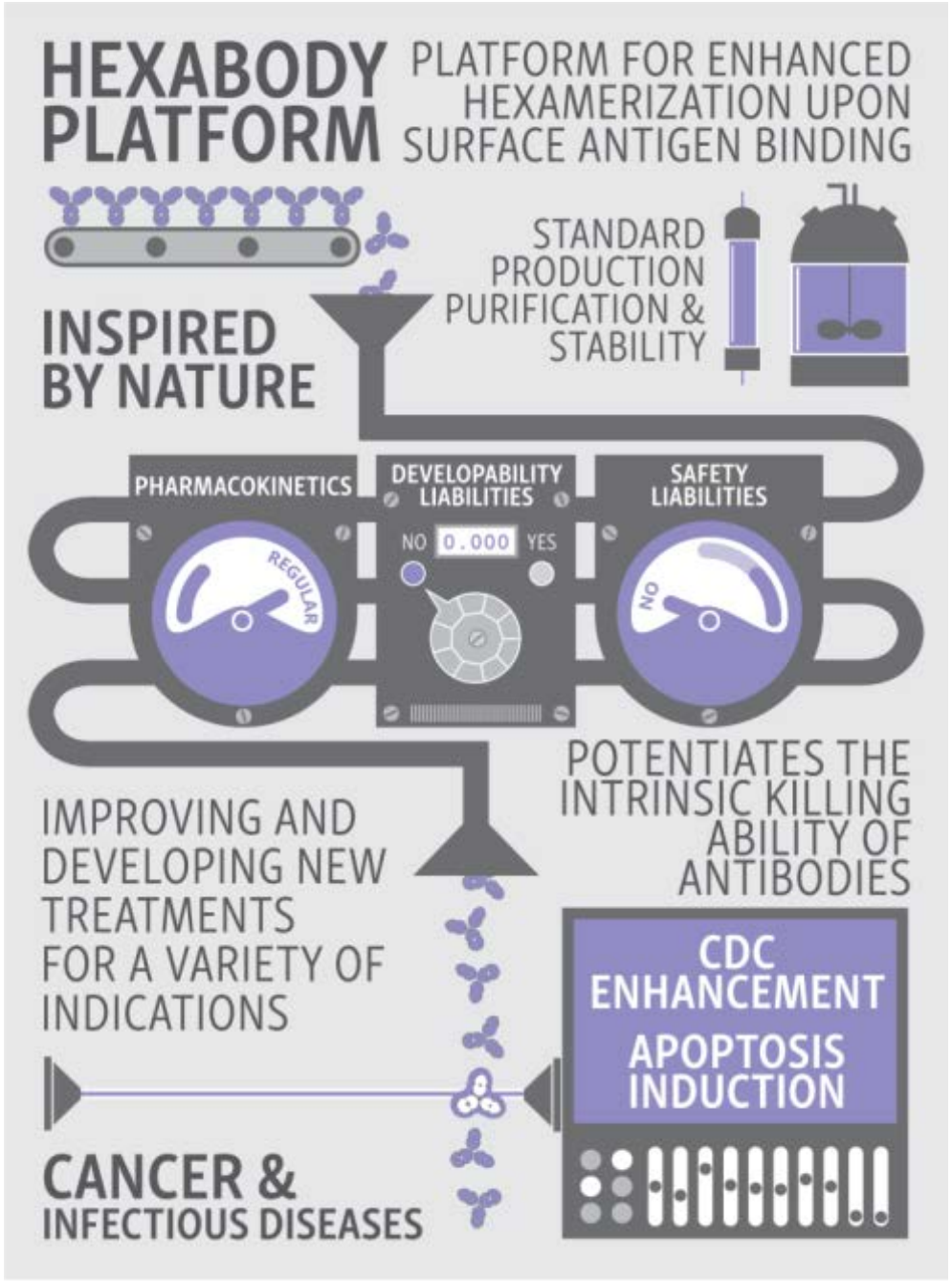
Mouse xenograft model



- Need for increased therapeutic potency
- Use HexaBody technology to induce clustering & activation of DR5 molecules, without a need for additional crosslinking
- Combination of two HexaBody molecules against two non-overlapping DR5 epitopes induces maximal cell death



DR5 activation induces cell death


HEXABODY PLATFORM
PLATFORM FOR ENHANCED HEXAMERIZATION UPON SURFACE ANTIGEN BINDING
INSPIRED BY NATURE
STANDARD PRODUCTION PURIFICATION & STABILITY
PHARMACOKINETICS
DEVELOPABILITY LIABILITIES
SAFETY LIABILITIES
NO
0.000
YES
REGULAR
NO
POTENTIATES THE INTRINSIC KILLING ABILITY OF ANTIBODIES
IMPROVING AND DEVELOPING NEW TREATMENTS FOR A VARIETY OF INDICATIONS
CDC ENHANCEMENT
APOPTOSIS INDUCTION
CANCER &
INFECTIOUS DISEASES

Take Home Messages

- Antibodies rapidly become key therapeutic class
- Therapeutic antibodies at the heart of cancer treatment
- Trends:
  - Move ⟶ fully human mAb
  - Move ⟶ adjuvant setting
  - Novel antibody formats
    - Bispecifics
    - Potency enhanced mAb
  - Antibody-drug conjugates
    - Chemo therapeutics
    - Alpha-emitt., Nanoparticles,etc
  - Ab format combinations

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Paul Parren, Frank Beurskens

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Thank you

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