

# Monoclonal Antibodies (and friends) As Drugs ....

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COLUMBIA UNIVERSITY  
MEDICAL CENTER

*Herbert Irving Comprehensive Cancer Center*

# Presenter Disclosure Information

*Charles G. Drake, MD, PhD*

The following relationships exist related to this presentation:

*Consulting Fees (e.g., advisory boards): Agenus, Astra Zeneca - Medimmune, BMS, Compugen, F-star, ImmunExcite, Janssen, Merck, NexImmune, Potenza Therapeutics, Roche/Genentech, Sanofi Aventis, Tizona*

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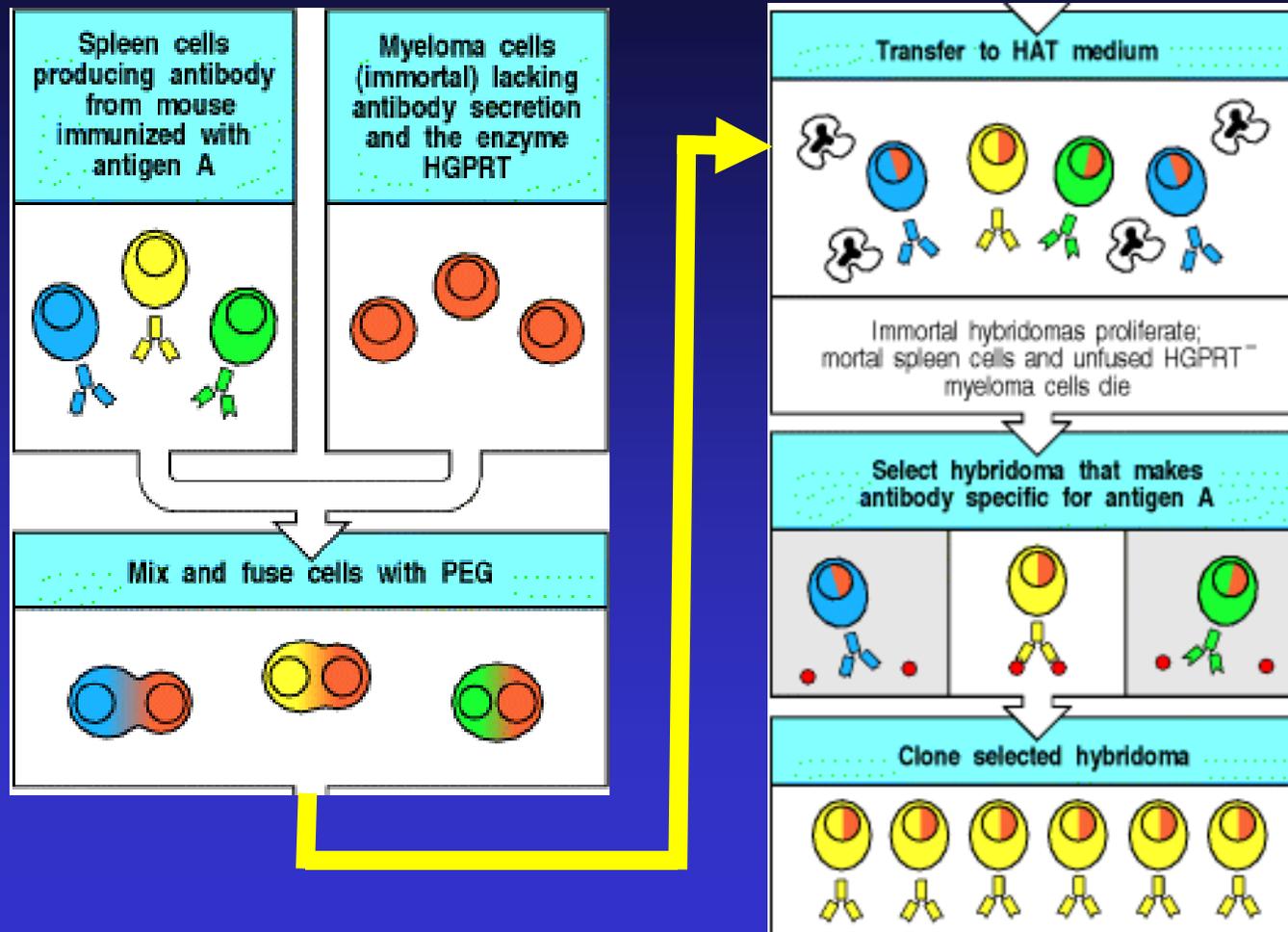
*Sponsored Research; Aduro Biotech, BMS, Janssen*

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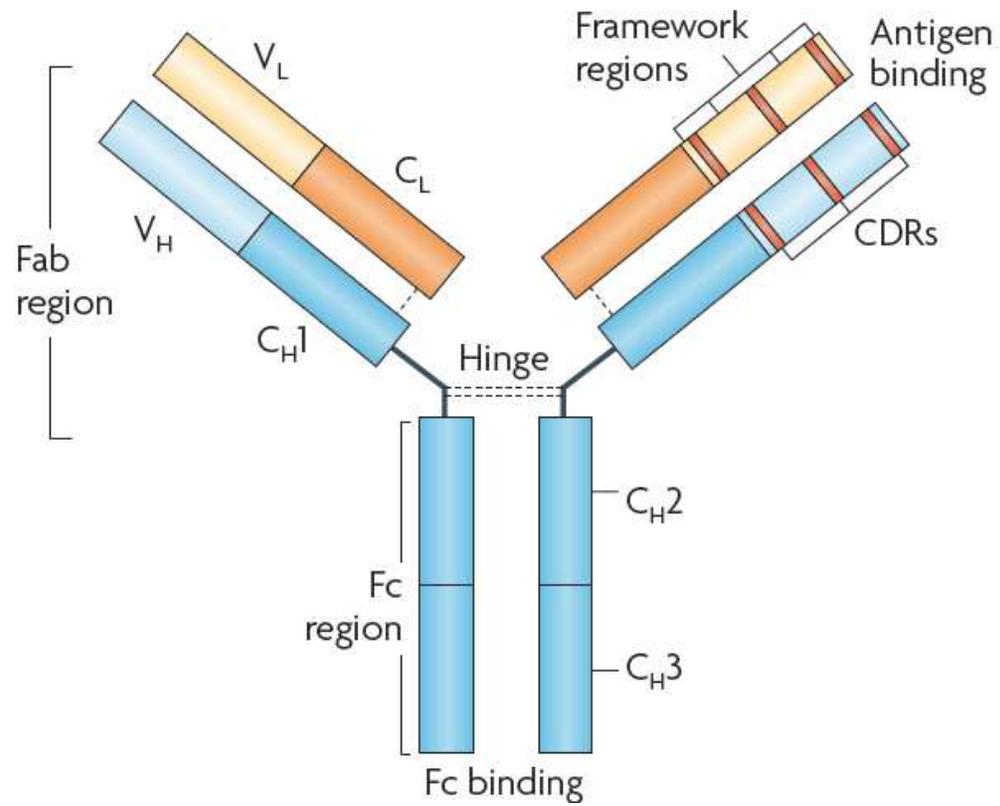
# Learning Objectives

- Briefly review how monoclonal antibodies are generated
- Understand the FOUR basic Monoclonal Antibody (Mab) Types in the Clinic
- List the FOUR Major Mechanisms of Action of Mab clinically
- Know the Differences Between the FOUR IgG Types in humans
- List the FOUR Fc Gamma Receptors (FcγR)
- Introduce FOUR Modified Antibody Technologies

# Where DID monoclonal antibodies come from?

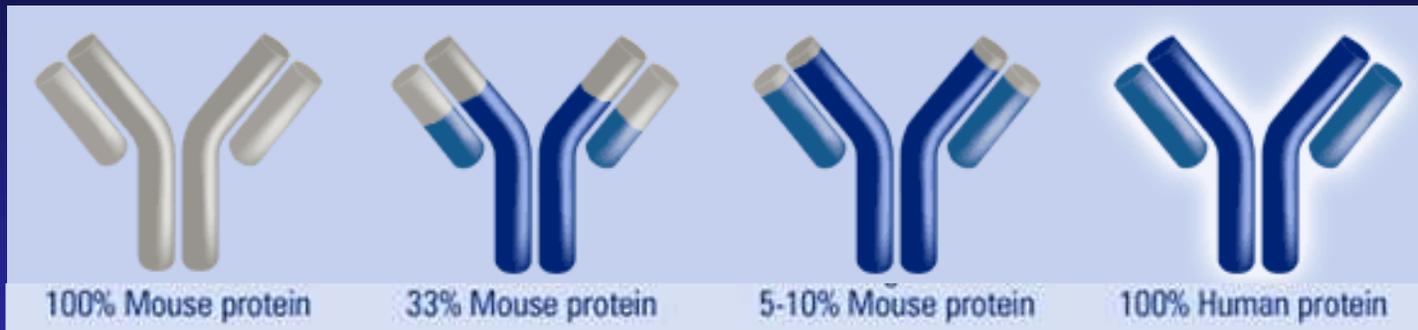


# Antibody Structure



Hansel et. al, *Nature Rev Drug Discovery*, 2010: 9:325.

# 4 Kinds of Monoclonal Antibodies



Mouse

Chimeric

Humanized

Human

“o”

“xi”

“zu”

“u”

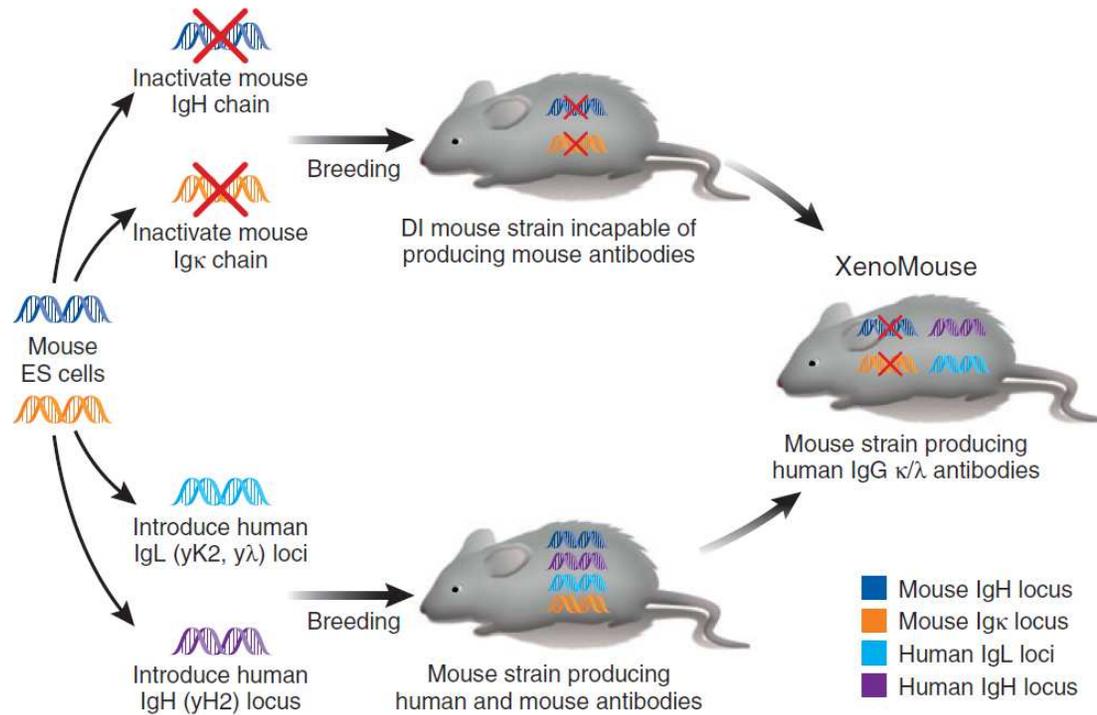
Muromonab

Rituximab

Trastuzumab

Ipilimumab

# How the Mice Were Made

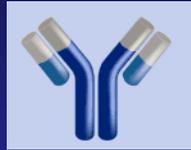


Jakobovits A. et al, *Nature Biotechnology*, 2007: 25:1134-1143.

## Rituximab - History

**FIRST monoclonal antibody approved for cancer treatment (1997)**

**A chimeric antibody**



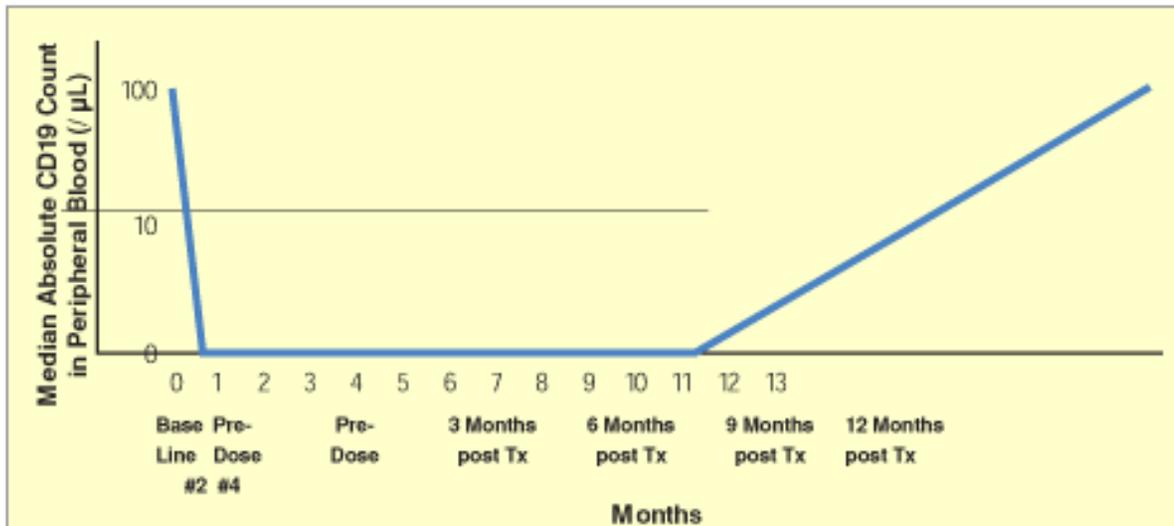
**Approved For CD20+ Non-Hodgkin's Lymphoma (NHL)**

- **Initial Treatment (follicular or diffuse)**
- **Maintenance AFTER chemotherapy**
- **Relapse of low-grade NHL**

**Approved for Rheumatoid Arthritis (2006)**

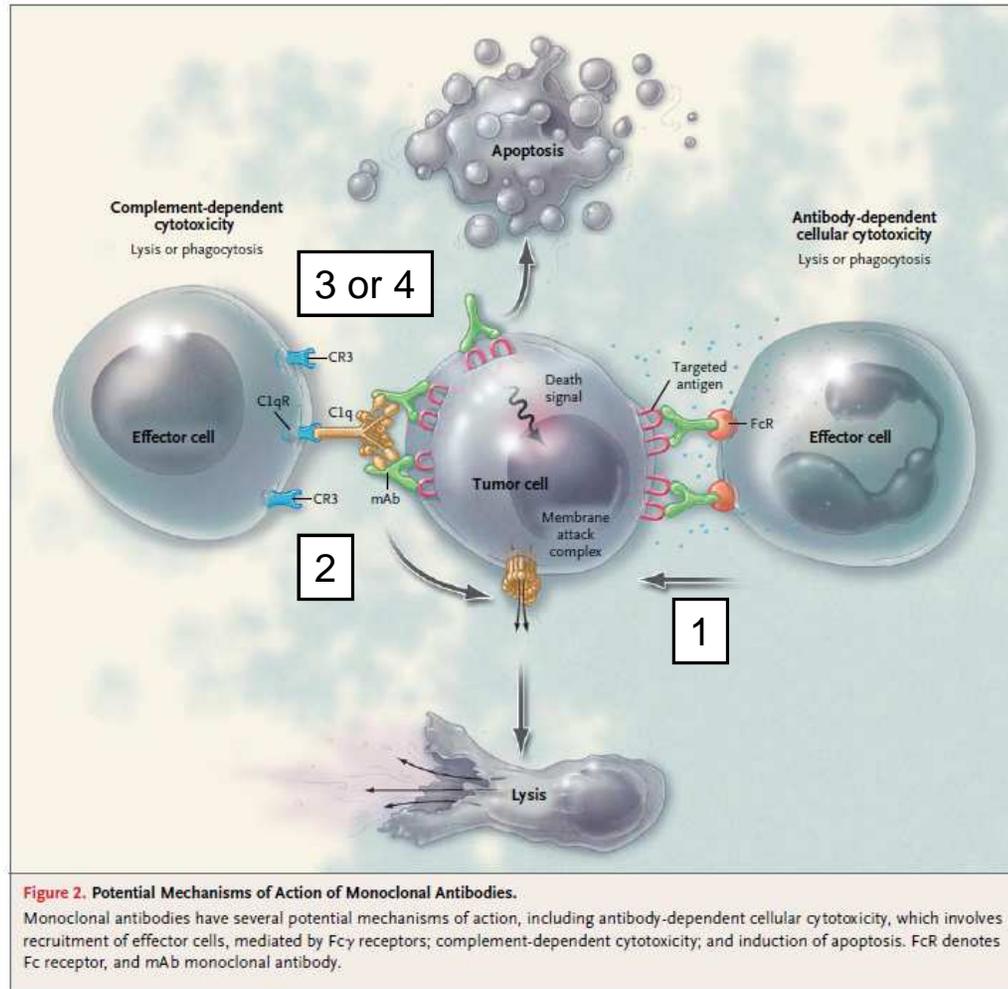
- **With methotrexate if anti-TNF therapy fails**

# Activity



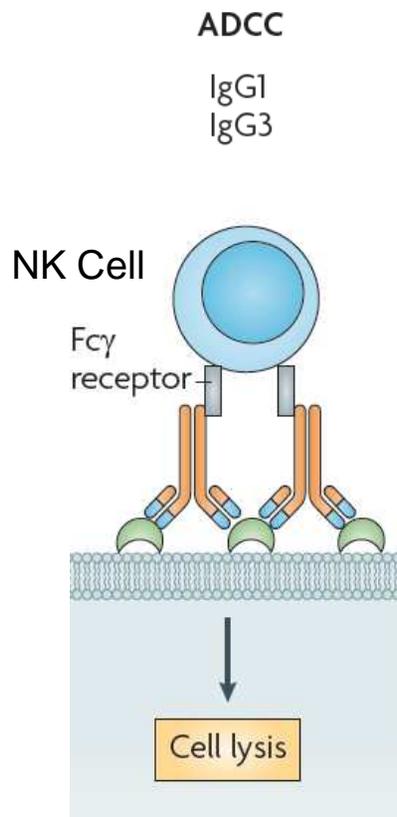
† CD19+ is usually coexpressed on B cells expressing CD20+.

B-cell marker levels<sup>†</sup> from baseline to one year following Rituxan therapy (N=166)<sup>3</sup>



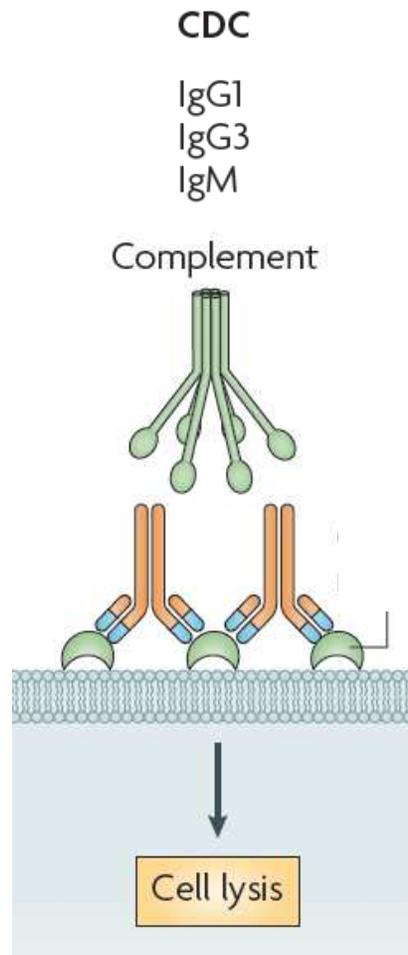
- 1) ADCC
- 2) CDCC
- 3) Antagonist  
= blocking
- 4) Agonist =  
signaling

# Antibody Dependent Cellular Cytotoxicity (ADCC)

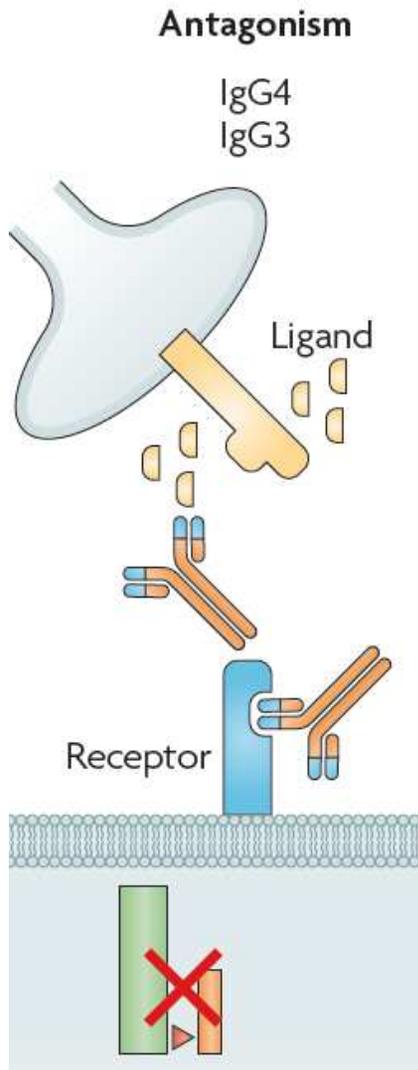


- a) Mediated (mostly) by Natural Killer (NK) Cells, Macrophages or Neutrophils
- b) Killing requires binding to Fc Gamma Receptor(s) (Fc $\gamma$ RIII)
  - a) Binding to Fc Gamma Receptors requires glycosylation of the Fc region
  - b) Increase ADCC by modifying glycosylation of Fc
  - c) Decrease ADCC using antibodies that lack glycosylation

# Complement Dependent Cytotoxicity (CDC)



- a) Requires antibody cross-linking / proximity
- b) Differential effects in humans with polymorphisms in C1Q
- c) Monoclonal antibodies rarely engineered to function via CDC

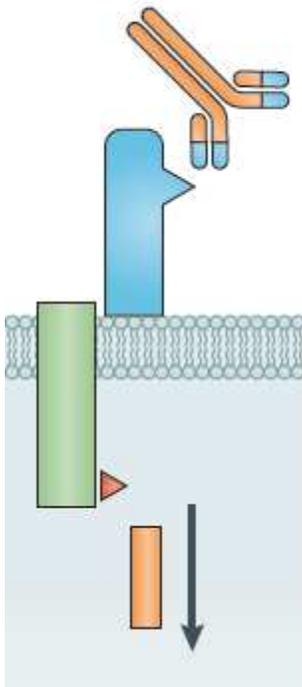


## Antagonist (blocking)

- a) Can block EITHER a receptor OR a ligand
- b) Ligand may be soluble (like  $\text{TNF}\alpha$ )
  - a) Fc function not desirable, usually use IgG4
  - b) Can eliminate ADC from IgG4 by decreasing Fc glycosylation

## Signalling

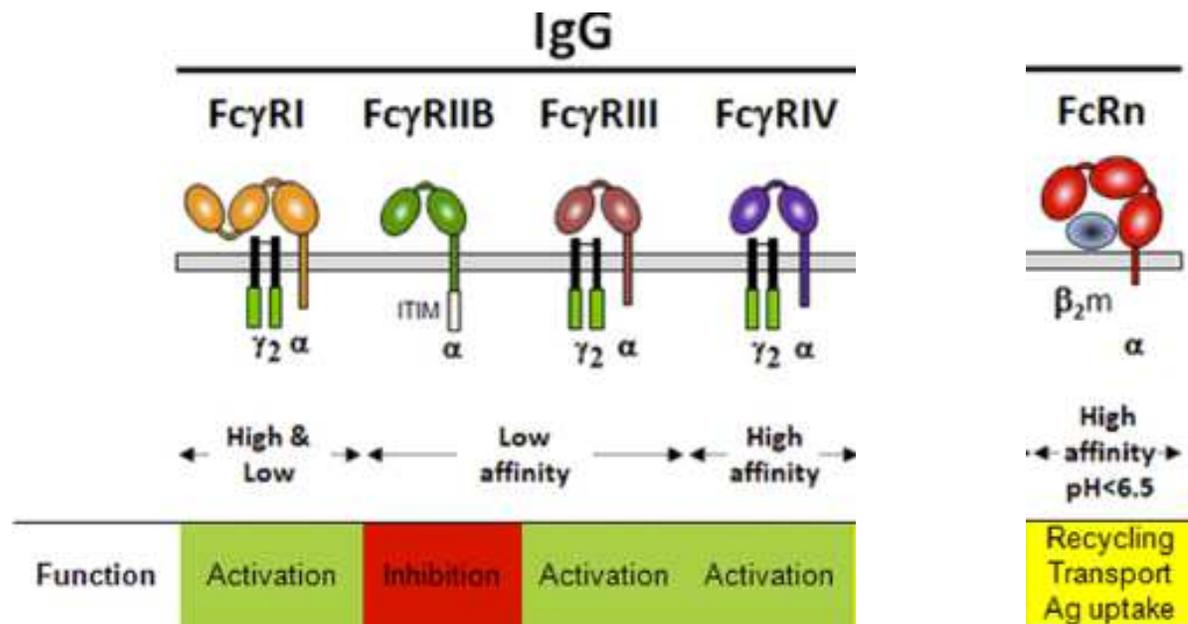
IgG4



## Agonist (Signalling)

- a) Activating antibodies in development for cancer immunotherapy
- b) Examples include anti-CD40 and anti-41BB
- c) Usually require cross linking for function  
Exception = “superagonists”

## There are FOUR Major Fcγ Receptors (And it Matters)



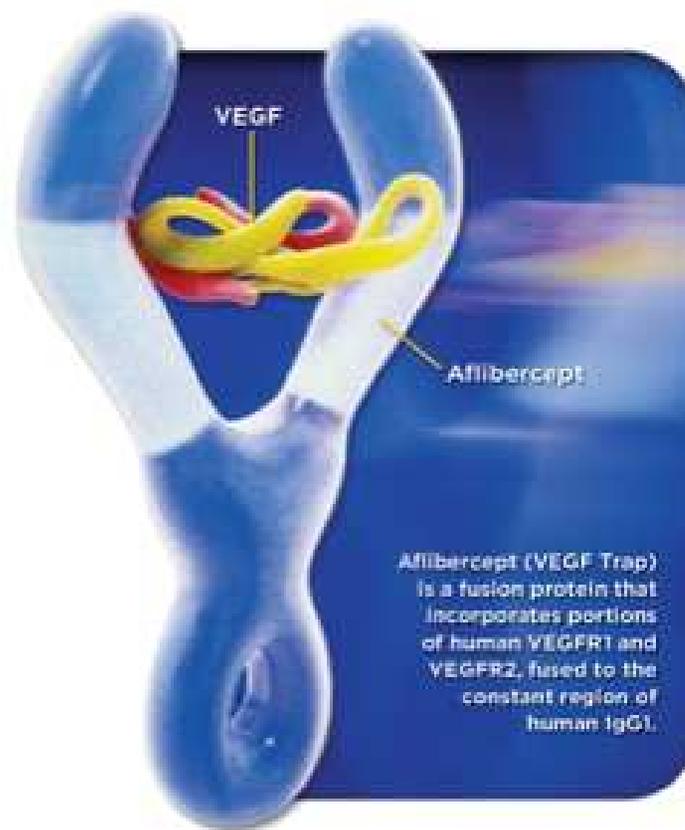
## There are FOUR Sub-Types of Human IgG

| Isotype | Species | ADCC | CDC  | Half Life |
|---------|---------|------|------|-----------|
| IgG1    | Human   | +++  | +++  | 21        |
| IgG2    | Human   | +/-  | +    | 21        |
| IgG3    | Human   | +++  | ++++ | 7         |
| IgG4    | Human   | +/-  | -    | 21        |

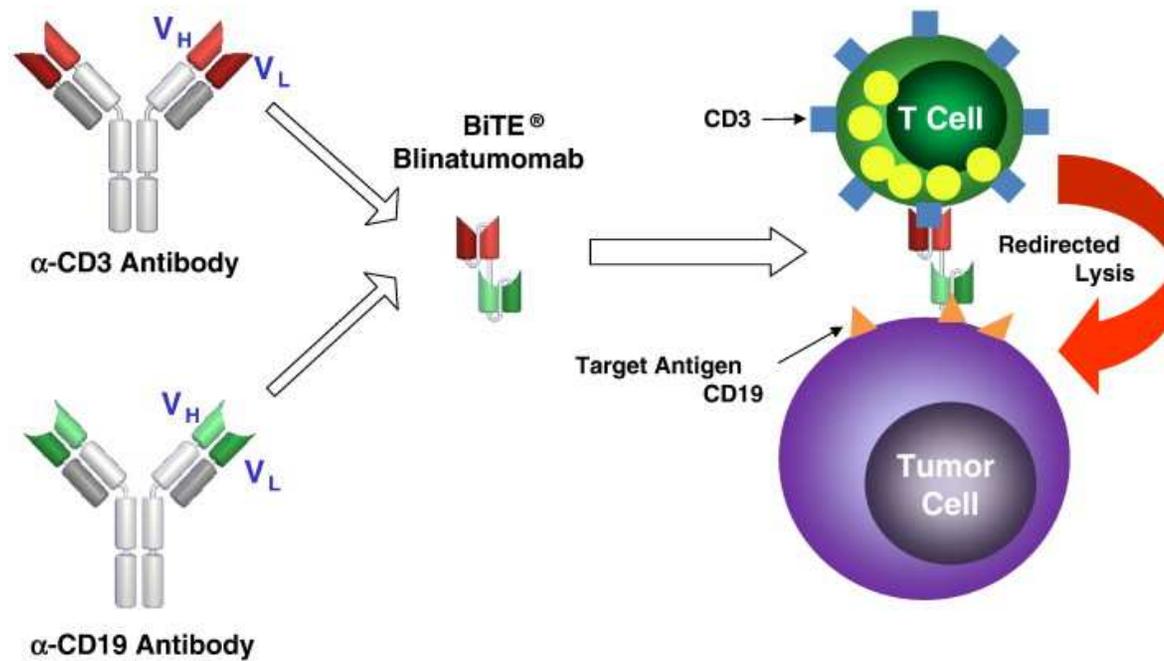
- For any IgG, Can modify hinge region to increase half-life
  - Bind more strongly to recycling receptor FcRN = more recycling = LONGER half life
  - Bind less strongly to FcRN = SHORTER half life

# Modified Antibodies

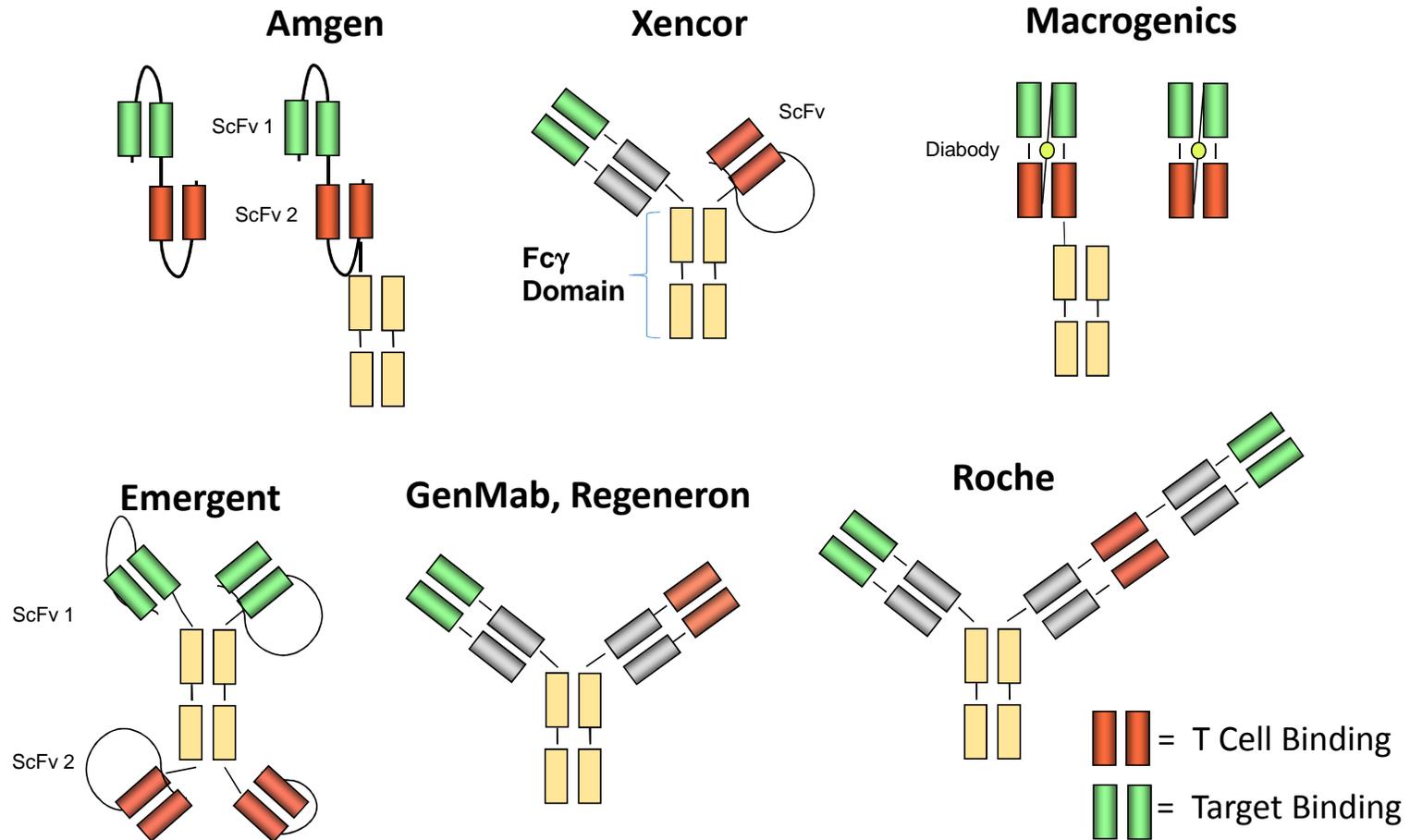
# TRAP Molecules (Aflibercept)



# Single-Chain Dual Specificity (BiTE)

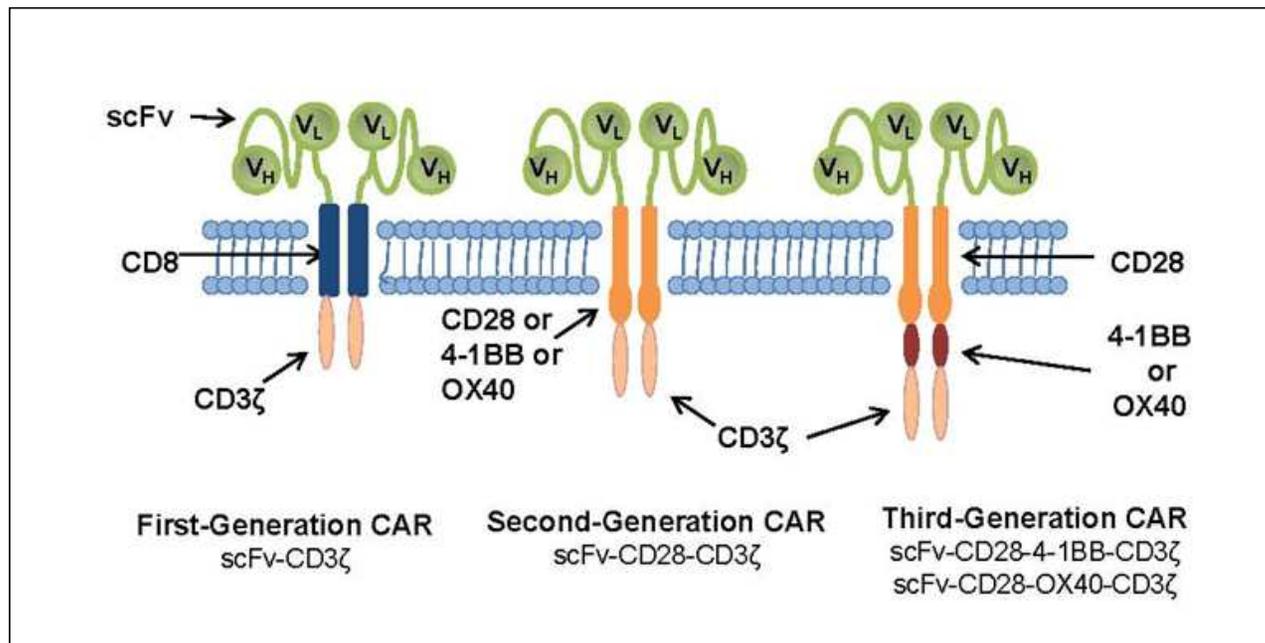


# Other T Cell-engaging Antibodies in Development

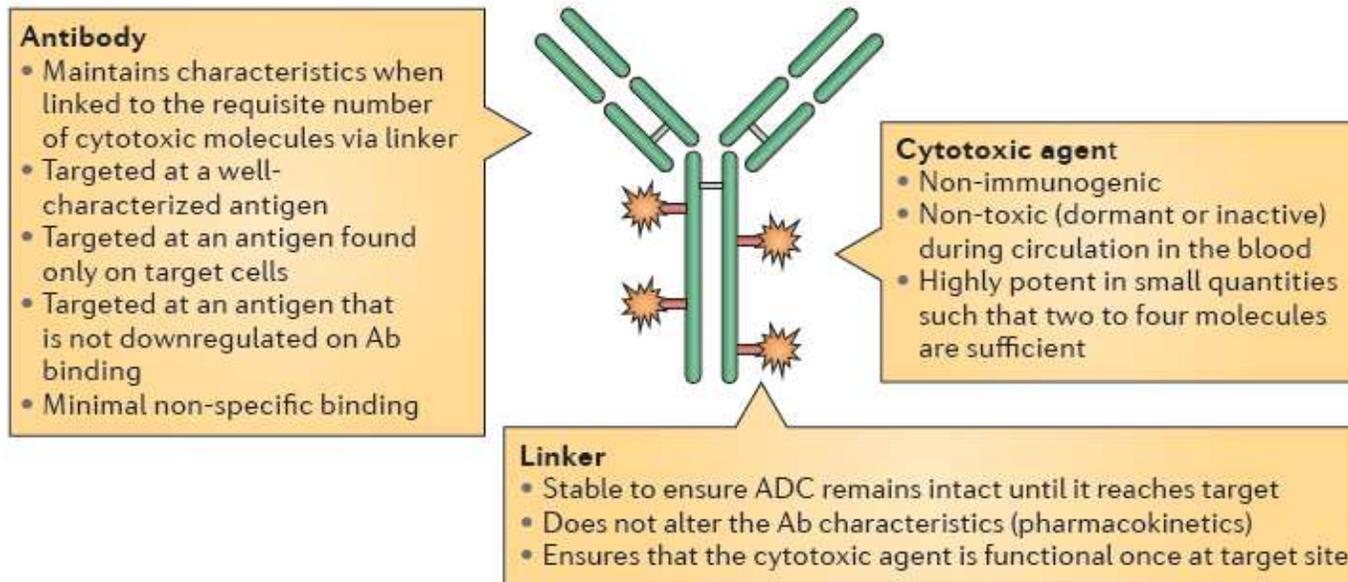


Slide Courtesy of Dr. Patrick Baeuerle

# Chimeric Antigen Receptors



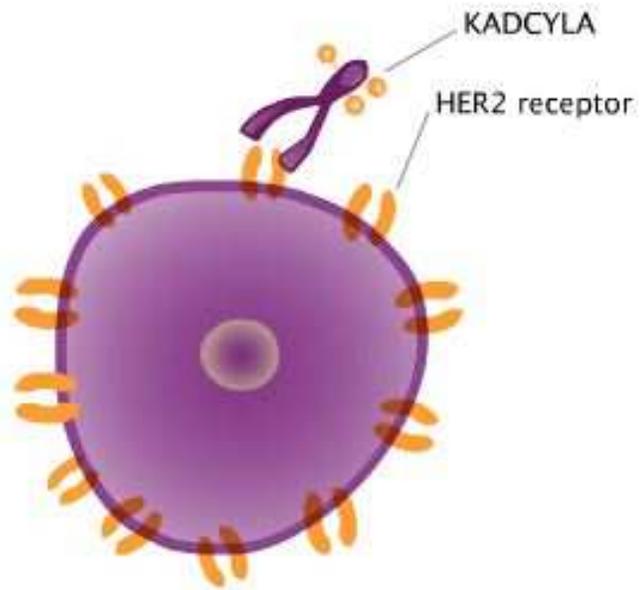
# Antibody Drug Congugates (ADC)



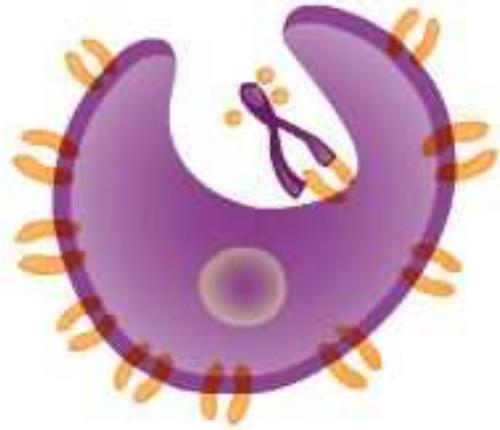
# T-DM1 Mechanism of Action (with drama)

[Click to see video](#)

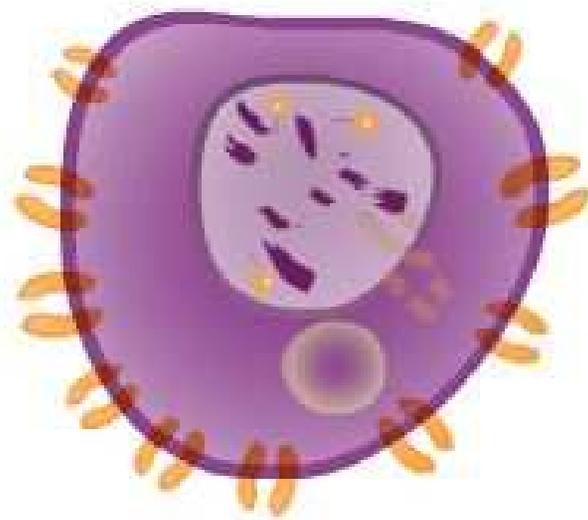
# 1: Binding



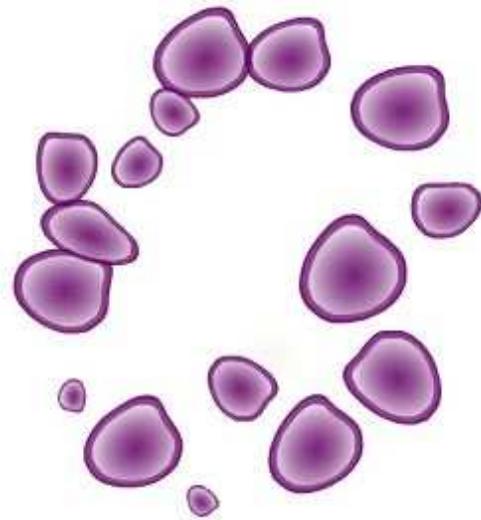
## 2: Internalization



### 3: Dissociation



## 4: Target Cell Lysis !



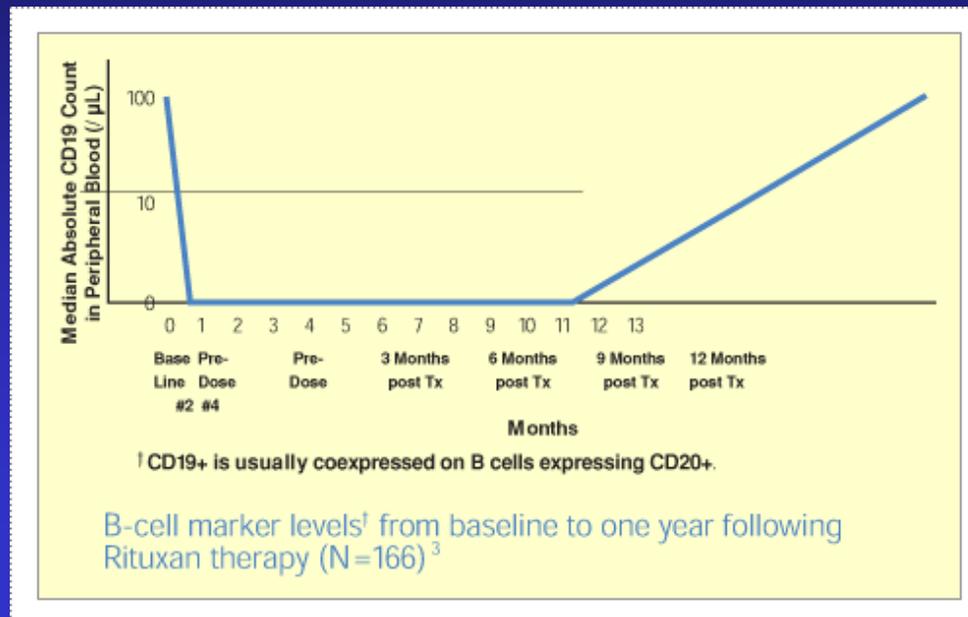
# Examples

# Rituximab (Rituxan)

“xi” = Chimeric

First Monoclonal Antibody Approve to Treat Cancer (1997)

IgG1 (ADCC)

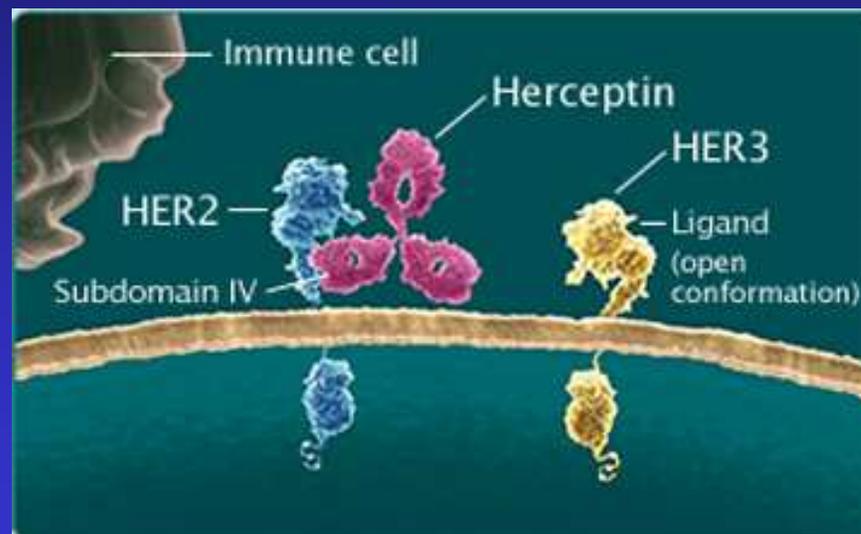


# Trastuzumab (Herceptin)

“zu” = Humanized

IgG1

MOA = prevent dimerization / ADCC



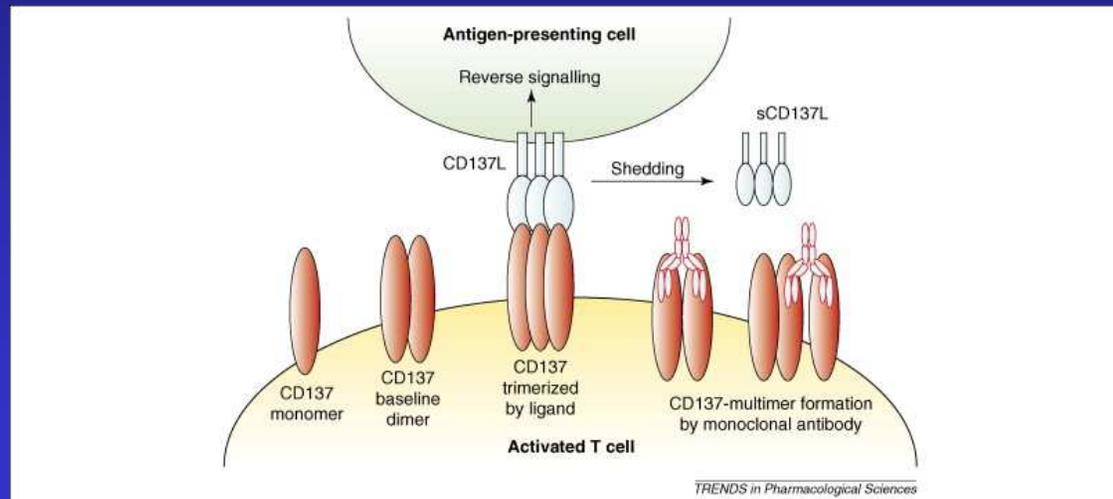
# Urelumab (Anti-4-1BB)

“u” = Fully Human

IgG4

Agonist

In Phase I



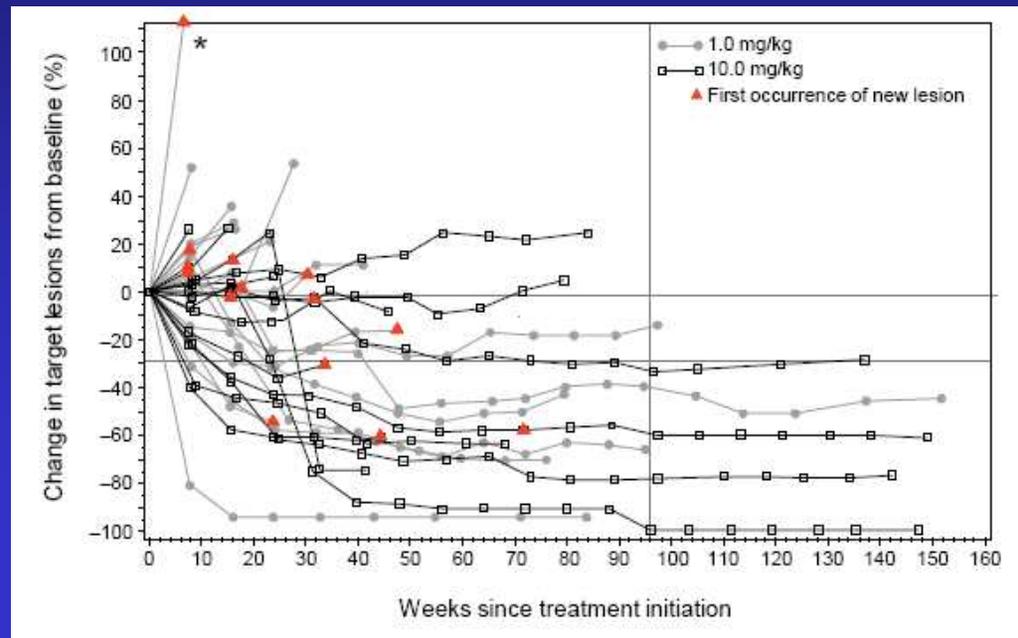
## Nivolumab (Anti-PD-1)

“u” = Fully Human

IgG4 with modified hinge region

Antagonist

FDA approved in Melanoma, NSCLC, RCC, H&N etc.



# Summary

- Monoclonal Antibodies = Drugs
- Prominent in Cancer Immunotherapy and Rheumatology
- Novel Technologies In Development
- Engineered Modifications to Fc Region affect multiple properties, especially half life

Q1. While employed at a small Bethesda biotech, you use RNAseq to identify a novel cell surface molecule of unknown function (BT1) that appears to you be exclusively expressed on big toe cancer cells. Seeking to treat cancer, you call your antibody engineering division and have them start developing a human:

- A. IgG4 antibody because you want to block signaling through BT1
- B. IgG1 antibody because you want to kill cells expressing BT1
- C. IgG3 antibody optimized for CDCC
- D. High affinity antibody of any type, which you will later use to generate an antibody-drug conjugate (ADC)
- E. B or D

Q2. Your splendid engineering group generates a lovely IgG4 antibody with nice affinity to BT1, which you rapidly take to the clinic. Unfortunately, Phase I pharmacokinetic data show that the antibody of that particular IgG4 is unfavorable, with a half-life of only 8 days *in vivo*. In order to increase half life they might:

- A. Substitute the natural hinge region with a modified version
- B. Make Fc modifications to increase binding to the recycling receptor FcRN
- C. Decrease binding to the recycling receptor
- D. Change approaches and generate a bi-specific antibody instead
- E. A or B

## Recommended Reading

1. Sliwkowski, M.X. and I. Mellman. 2013. Antibody therapeutics in cancer. *Science* 341:1192-1198.
2. Nimmerjahn, F. and J.V. Ravetch. 2012. Translating basic mechanisms of IgG effector activity into next generation cancer therapies. *Cancer Immun.* 12:13.
3. Hansel, T.T., H. Kropshofer, T. Singer, J.A. Mitchell, and A.J. George. 2010. The safety and side effects of monoclonal antibodies. *Nat. Rev. Drug Discov.* 9:325-338.
4. [DiLillo DJ](#), [Ravetch JV](#), 2014. Fc-Receptor Interactions Regulate Both Cytotoxic and Immunomodulatory Therapeutic Antibody Effector Functions. [Cancer Immunol Res.](#) 7:704-13.