Monoclonal Antibodies as Drugs

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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

Intellectual Property/Patents: Aduro Biotech, BMS, Potenza Therapeutics

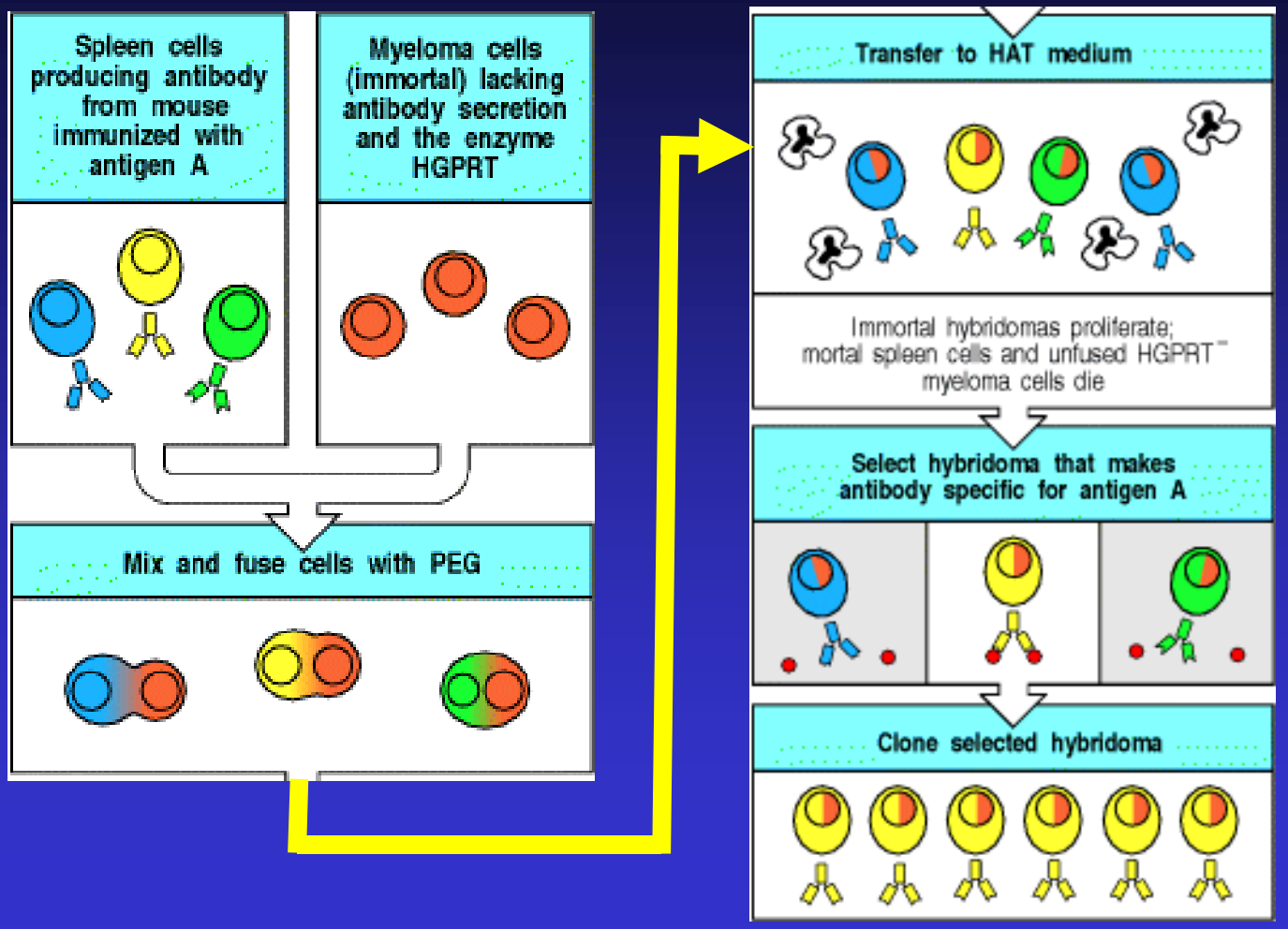
Sponsored Research; Aduro Biotech, BMS, Janssen

Ownership Interest (stocks, stock options, or other ownership interest excluding diversified mutual funds):, Compugen, ImmunExcite, NexImmune, Potenza, Tizona

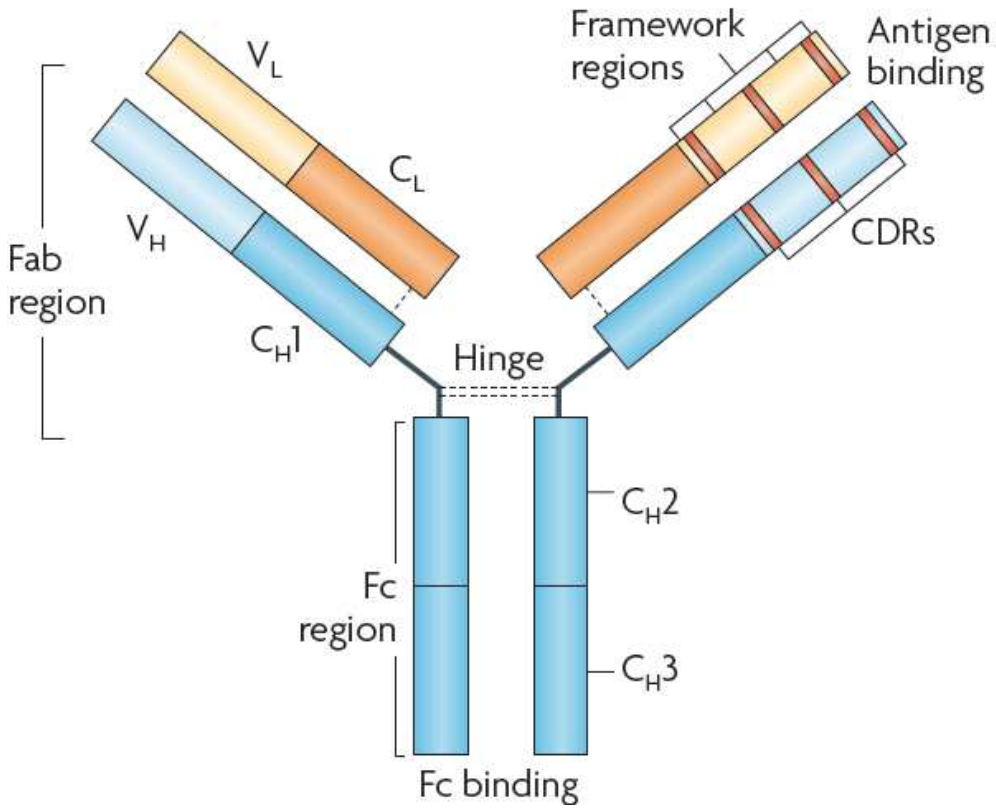
Key Take-Aways

- 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 (FcgR)
- Introduce FOUR Modified Antibody Technologies

Where do monoclonal antibodies come from?

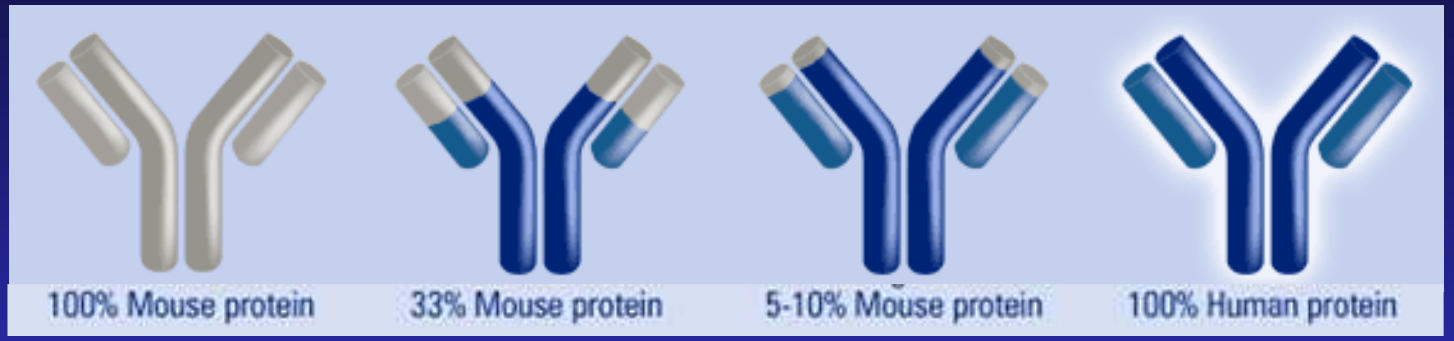


Antibody Structure



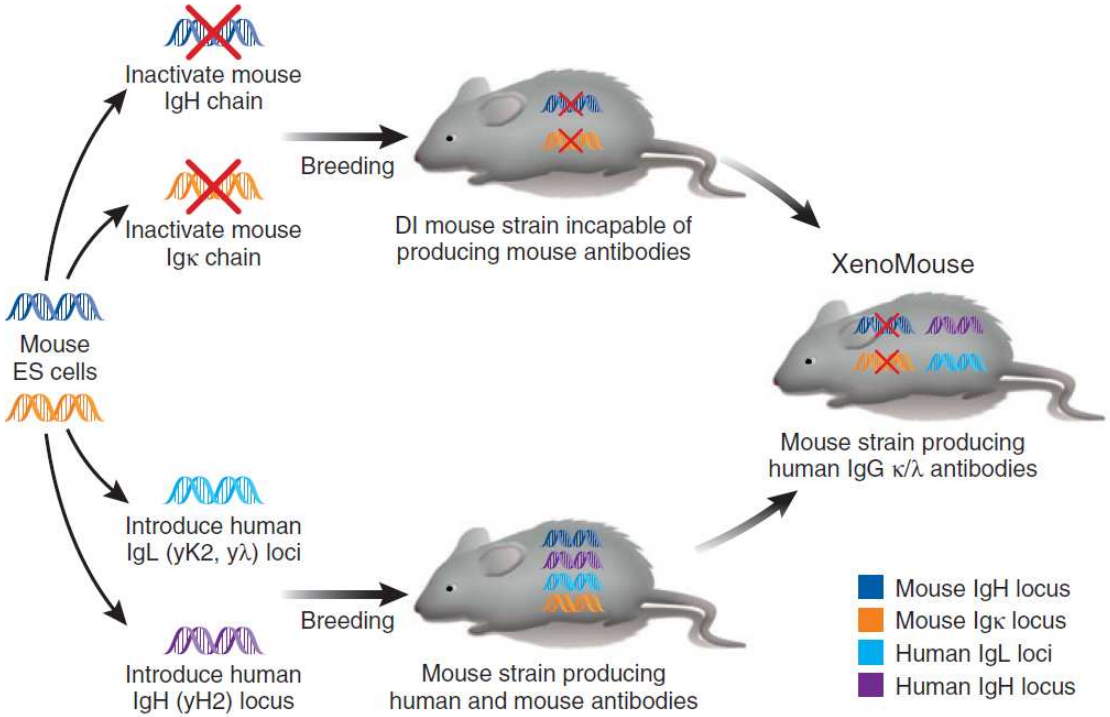
Hansel et. al, *Nature Rev Drug Discovery*, 2010: 9:325.

4 Kinds of Monoclonal Antibodies



Mouse	Chimeric	HumaniZed	Human
“o”	“xi”	“zu”	“u”
Mur**O**monab	Ritu**XI**mab	Trastu**ZU**mab	Ipilim**U**mab

How the Mice Were Made

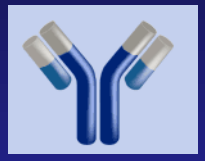


Jakobovits A. et al, *Nature Biotechnology*, 2007: 25:1134-1143.

Rituximab - History

FIRST monoclonal antibody approved for cancer treatment (1997)

A chimeric antibody



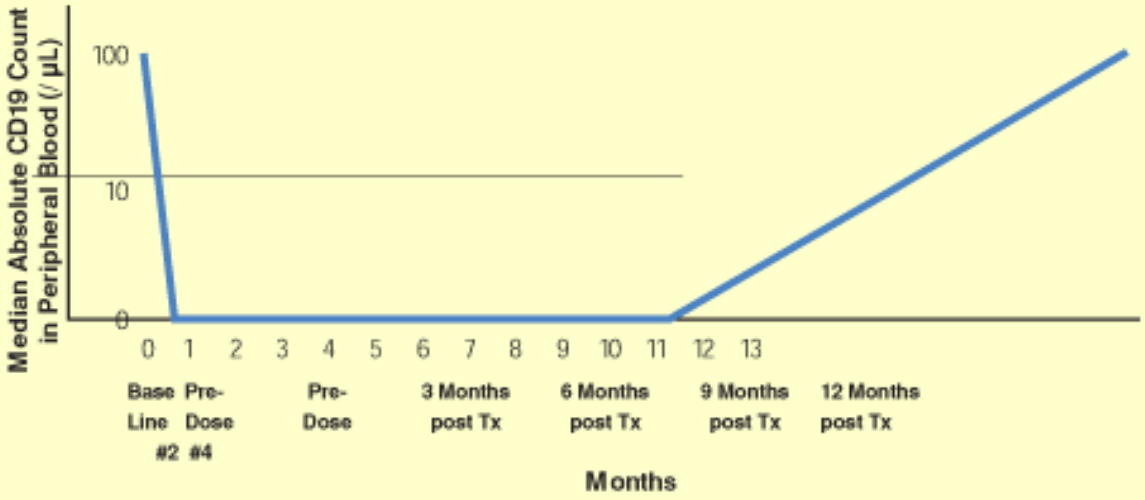
Approved For CD20+ Non-Hodgkin's Lymphoma (NHL)

- **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† from baseline to one year following Rituxan therapy (N=166)[3]

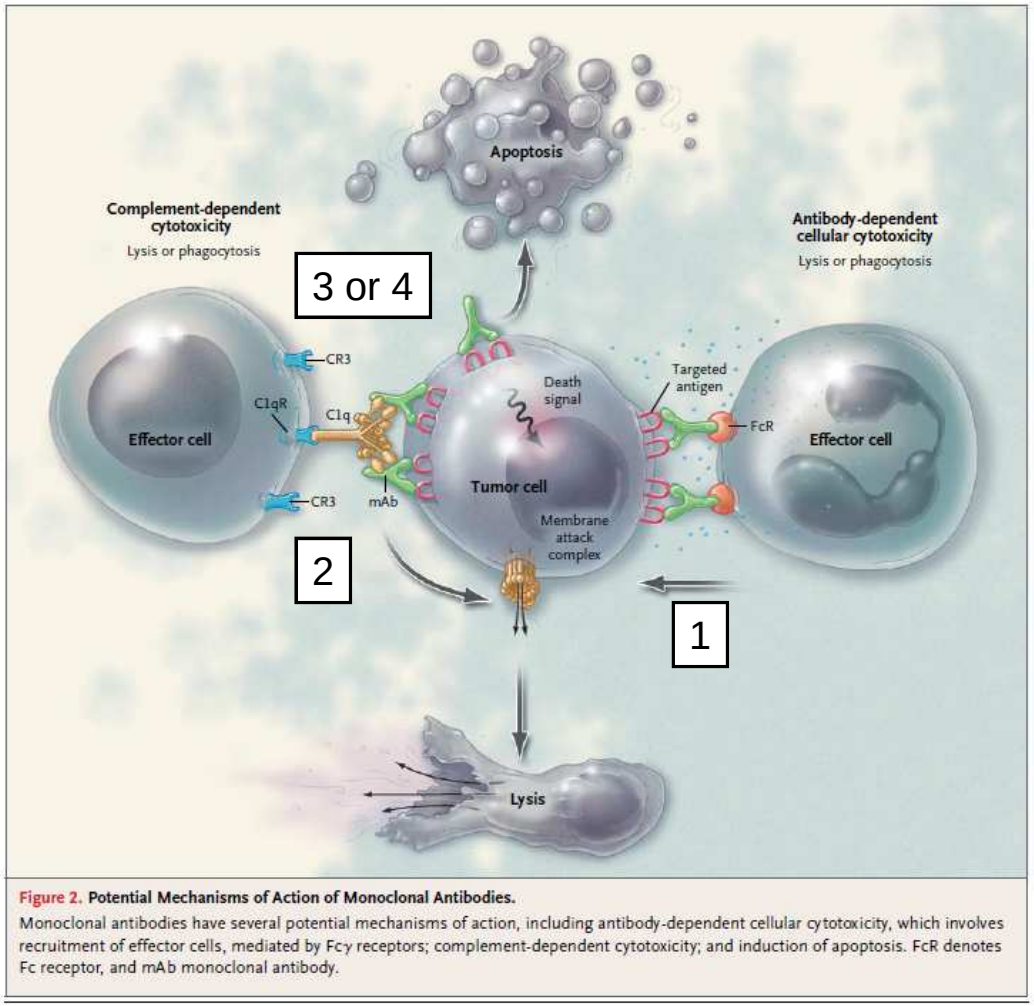


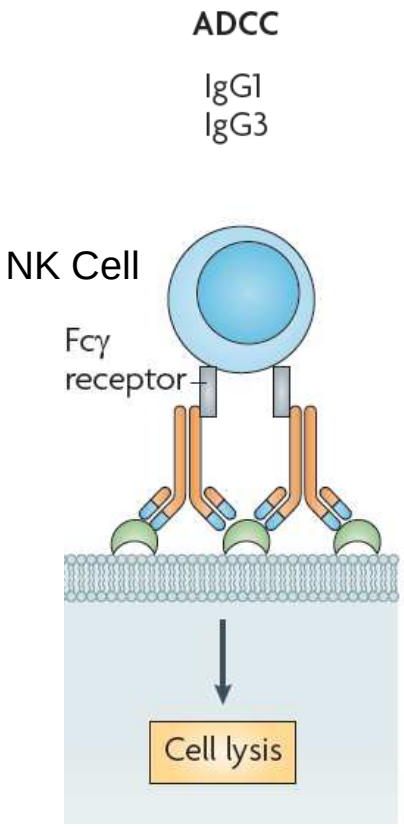
Figure 2. Potential Mechanisms of Action of Monoclonal Antibodies.

Monoclonal antibodies have several potential mechanisms of action, including antibody-dependent cellular cytotoxicity, which involves recruitment of effector cells, mediated by Fcγ receptors; complement-dependent cytotoxicity; and induction of apoptosis. FcR denotes Fc receptor, and mAb monoclonal antibody.

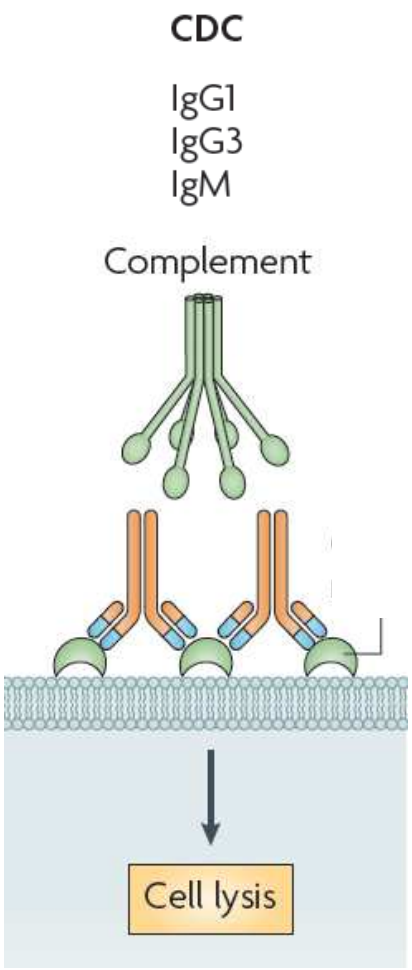
1) ADCC
2) CDCC
3) Antagonist = blocking
4) Agonist = signaling

Rotschild et al, *NEJM* 2012

Antibody Dependent Cellular Cytotoxicity (ADCC)



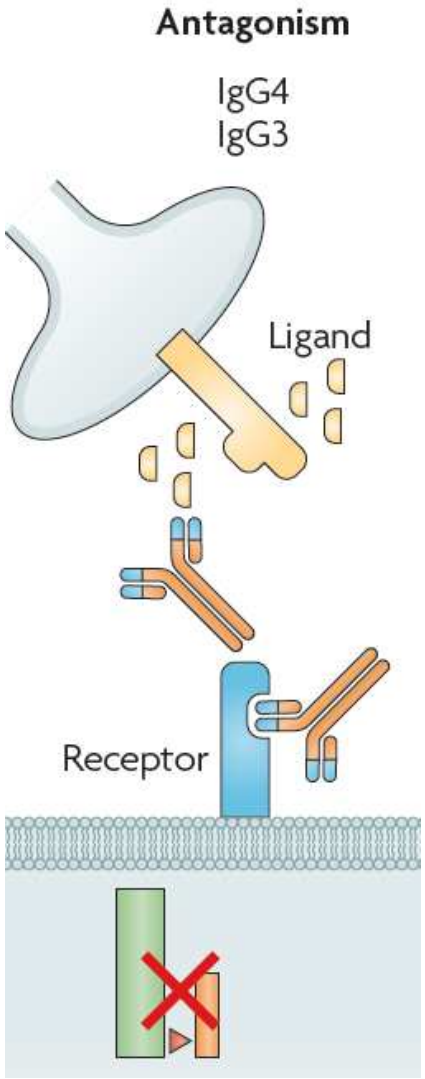
a) Mediated (mostly) by Natural Killer (NK) Cells, Macrophages or Neutrophils
b) Killing requires binding to Fc Gamma Receptor(s) (FcγRIII)
    a) Binding to Fc Gamma Receptors requires glycosylation of the Fc region
    b) Increase ADCC by modifying glycosylation of Fc
    c) Decrease ADCC using antibodies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



Complement Dependent Cytotoxicity (CDC)

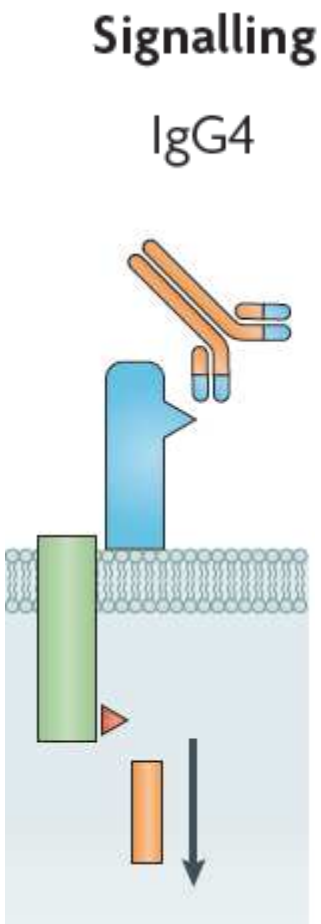
a) Requires antibody cross-linking / proximity
b) Differential effects in humans with polymorphisms in C1Q
c) Monoclonal antibodies rarely engineered to function via CDC

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



Antagonist (blocking)

a) Can block EITHER a receptor OR a ligand
b) Ligand may be soluble (like TNFα)
    a) Fc function not desirable, usually use IgG4
    b) Can eliminate ADC from IgG4 by decreasing Fc glycosylation

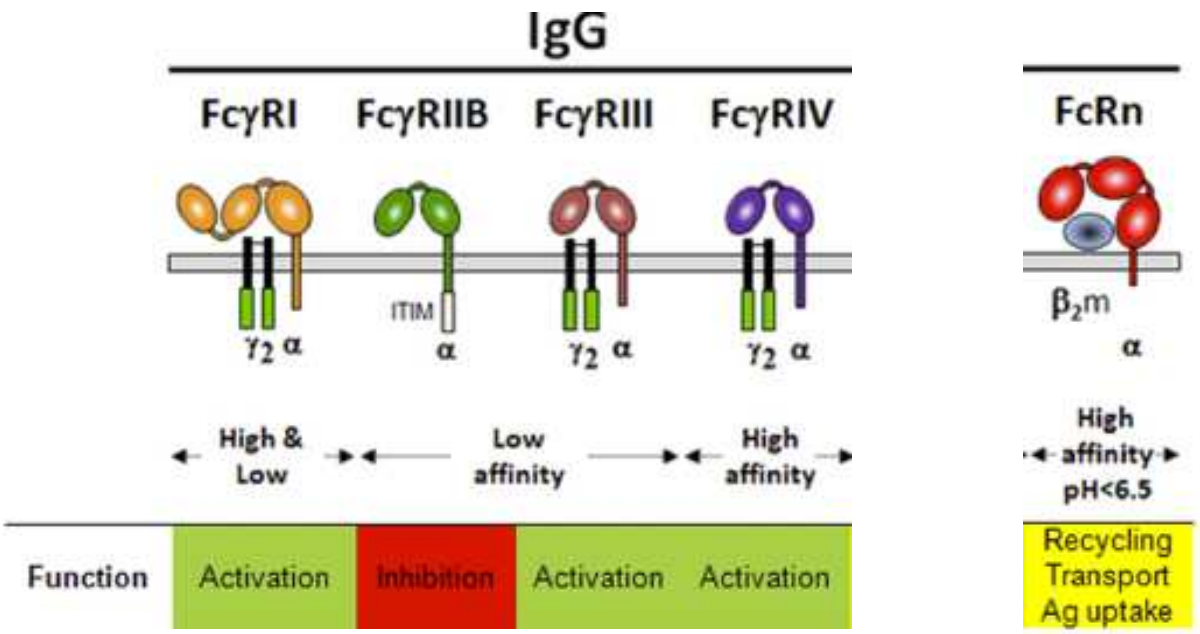


Agonist (Signalling)

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)



Bruhns 2012 Blood 119:5640

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

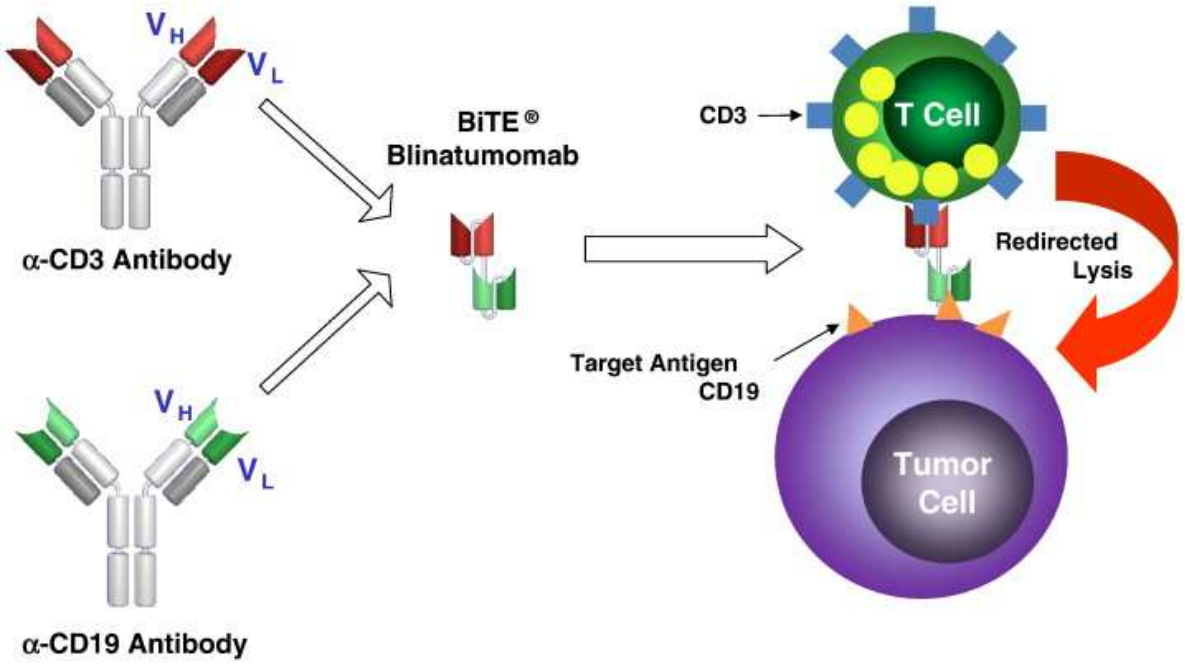
  Bind more strongly to recycling receptor FcRN = more recycling = LONGER half life

  Bind less strongly to FcRN = SHORTER half life

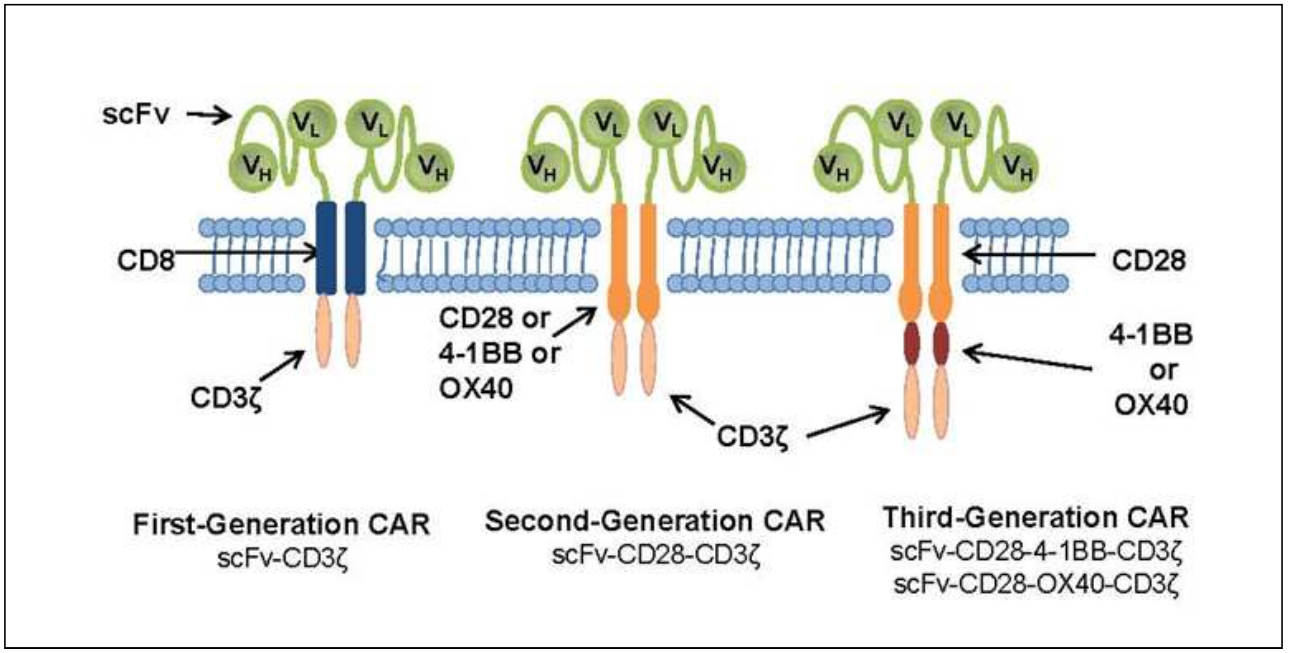
Modified Antibodies

TRAP Molecules (Aflibercept)

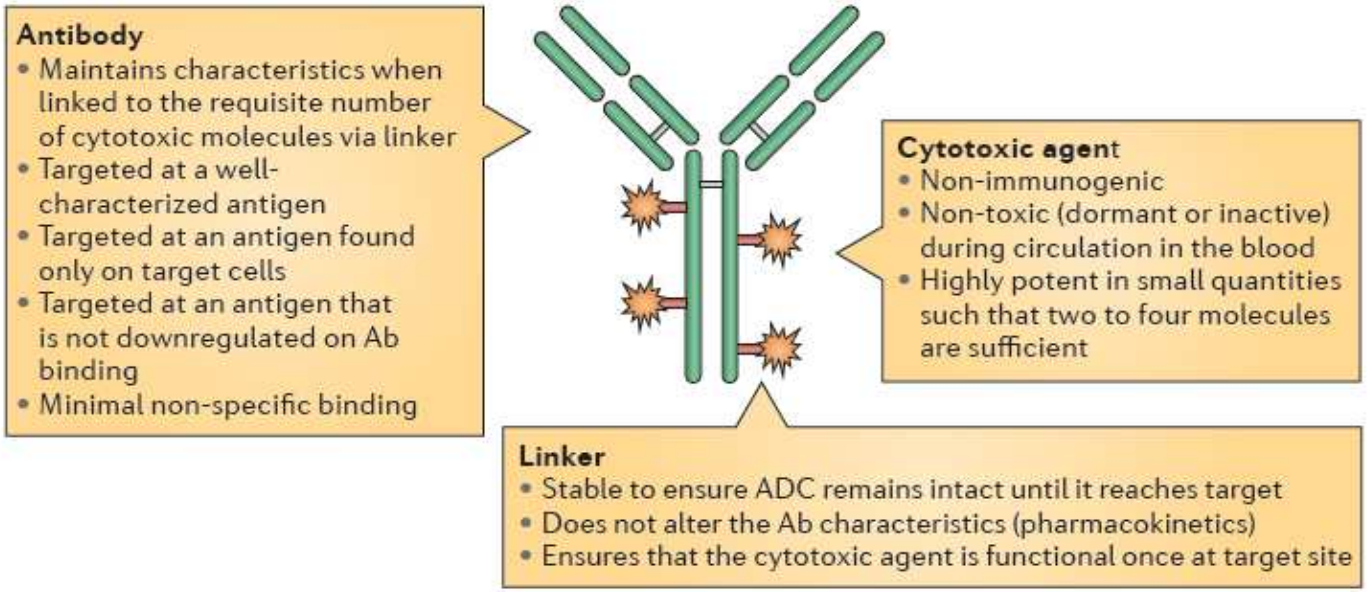
Single-Chain Dual Specificity (BiTE)



Chimeric Antigen Receptors

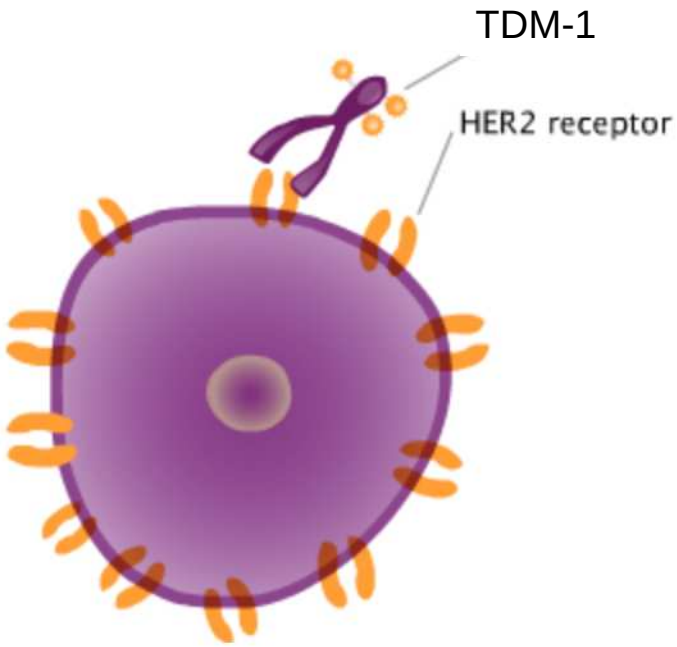


Antibody Drug Congugates (ADC)

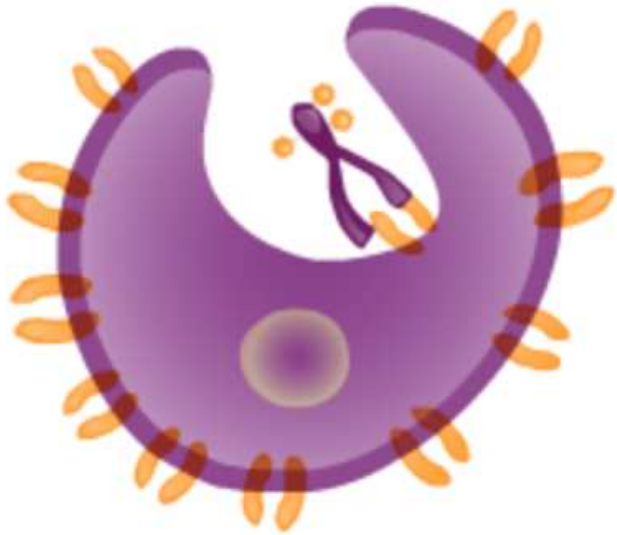


Zolot et. al. Nat Rev Drug Disc 2013:12:259

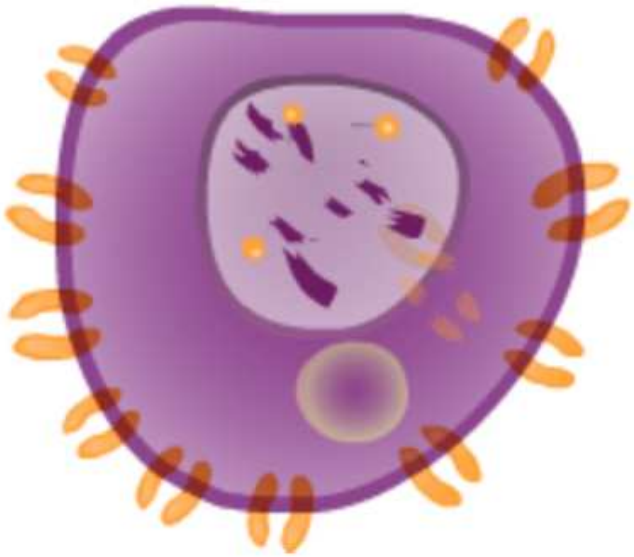
T-DM1 Mechanism of Action
1. Binding



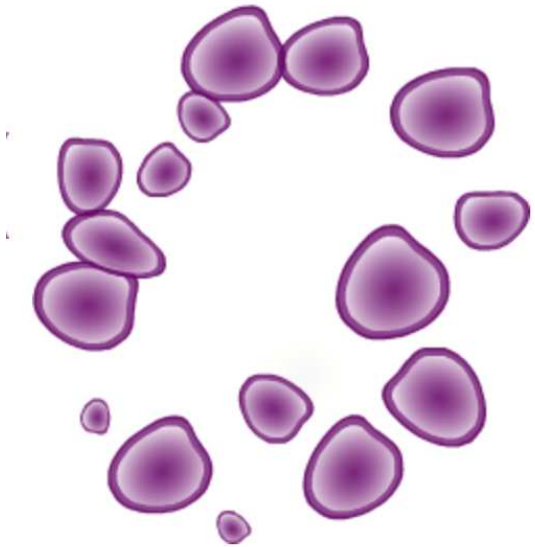
T-DM1 Mechanism of Action
2. Internalization



T-DM1 Mechanism of Action
3. Dissociation



T-DM1 Mechanism of Action
4. Lysis (hopefully)



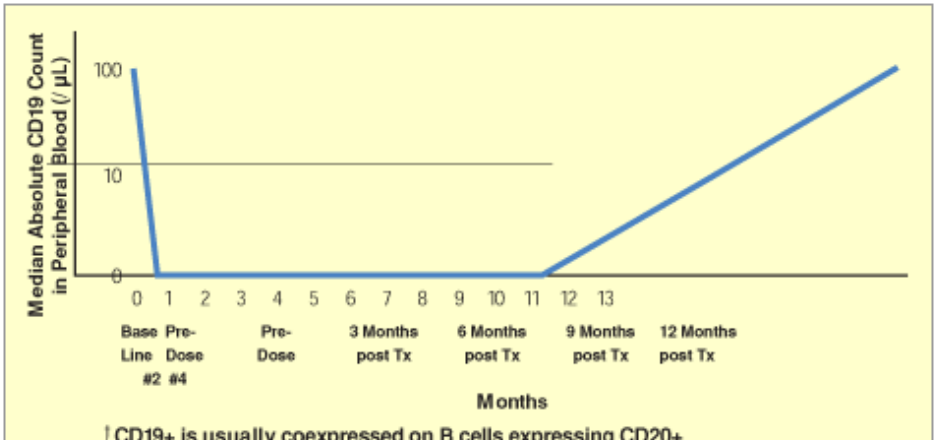
Examples

Rituximab (Rituxan)

"xi" = Chimeric

First Monoclonal Antibody Approve to Treat Cancer (1997)

IgG1 (ADCC)



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

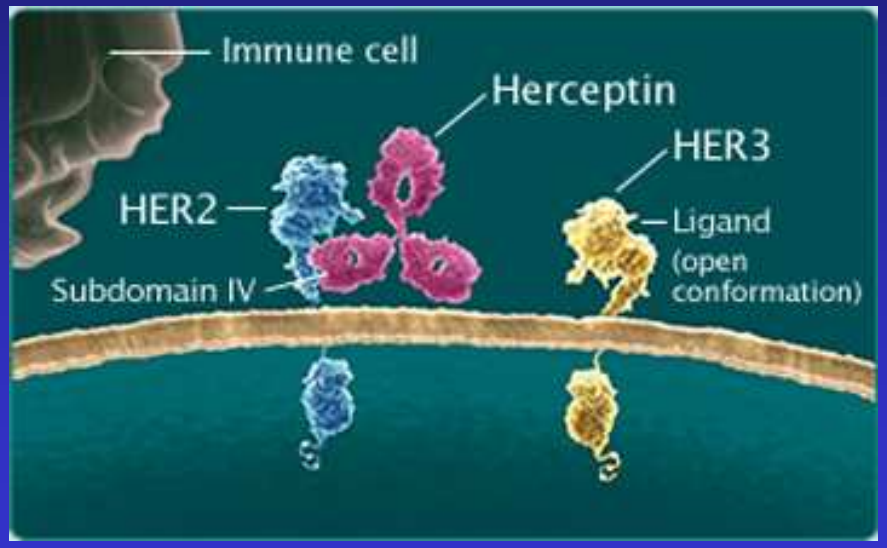
B-cell marker levels† from baseline to one year following Rituxan therapy (N=166) [3]

Trastuzumab (Herceptin)

“zu” = Humanized

IgG1

MOA = prevent dimerization / ADCC



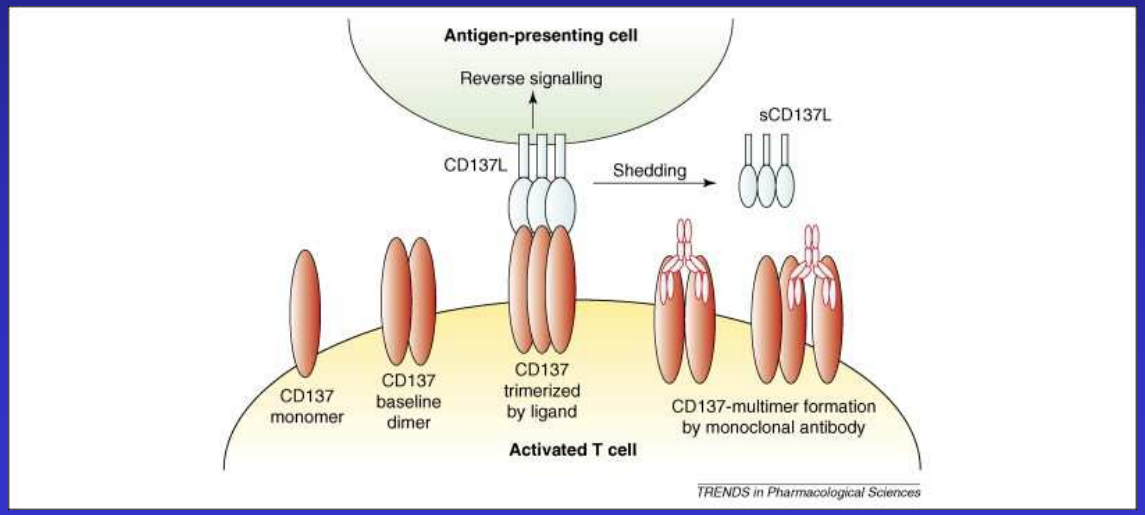
Urelumab (Anti-4-1BB)

“u” = Fully Human

IgG4

Agonist

In Phase I



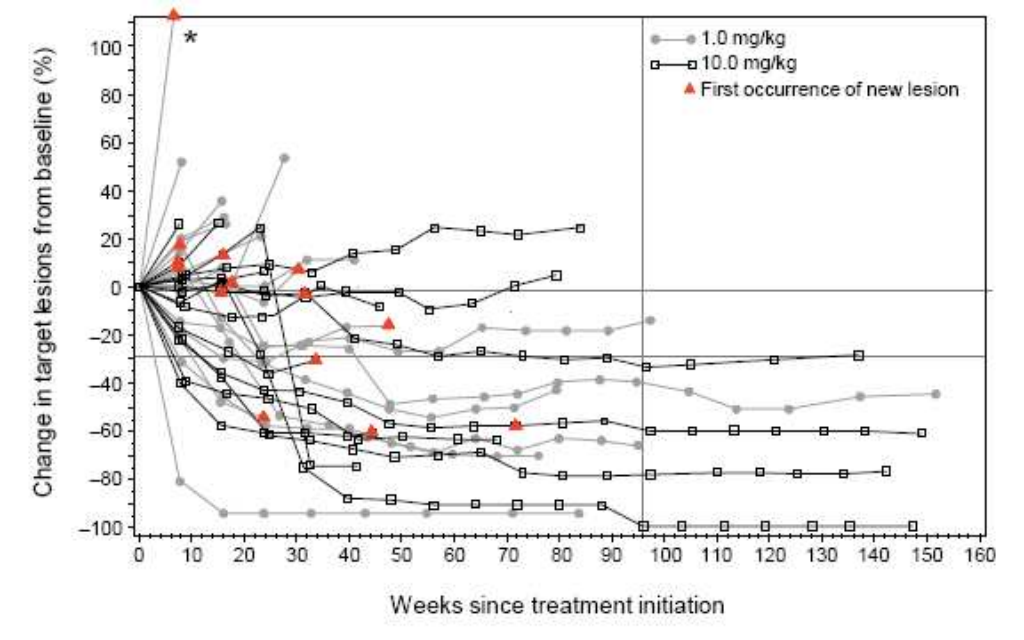
Nivolumab (Anti-PD-1)

"u" = Fully Human

IgG4 with modified hinge region

Antagonist

FDA approved in Melanoma, NSCLC, Phase III in RCC positive



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 pharmokinetic 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 he 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.