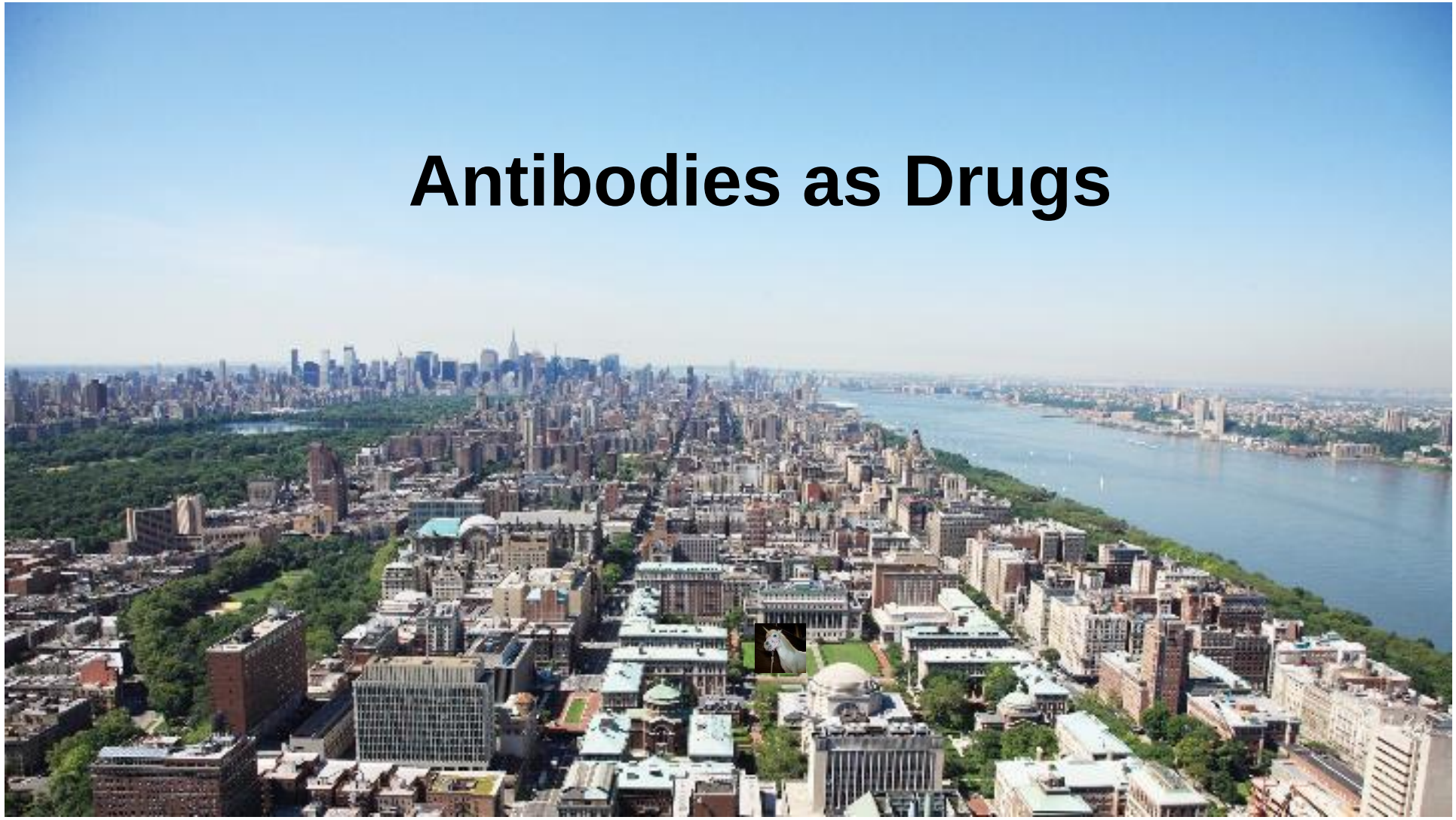
Antibodies as Drugs



Charles G. Drake MD / PhD
Director GU Medical Oncology
Co-Director: Immunotherapy Program
Associate Director for Clinical Research
Professor of Oncology and Urology
Herbert Irving Cancer Center at Columbia University

Columbia University Medical Center
Herbert Irving Comprehensive Cancer Center

NewYork-Presbyterian

Complete Disclosure

- Consulting:
  Bayer, BMS, Compugen, F-Star, Genocea, Janssen, Kleo, Merck, Merck-Serono, Pfizer, Pierre Fabre, Roche / Genentech, Shattuck Labs, Tizona, Urogen, Werewolf

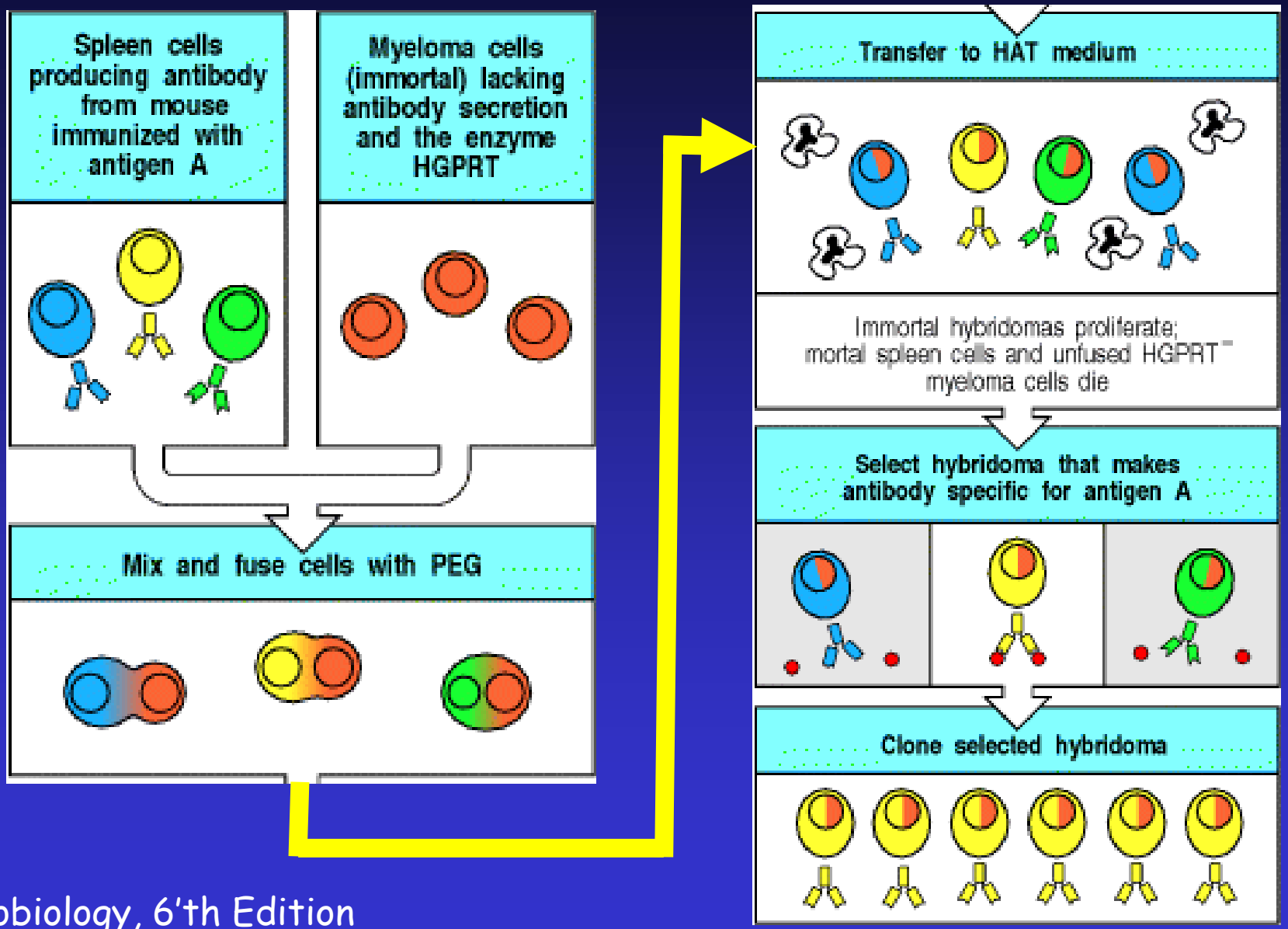
- Patents (held by Johns Hopkins University)
  BMS, Janssen

- Options
  Compugen, Harpoon, Kleo, Tizona, Werewolf

Four Things To Learn (Objectives)

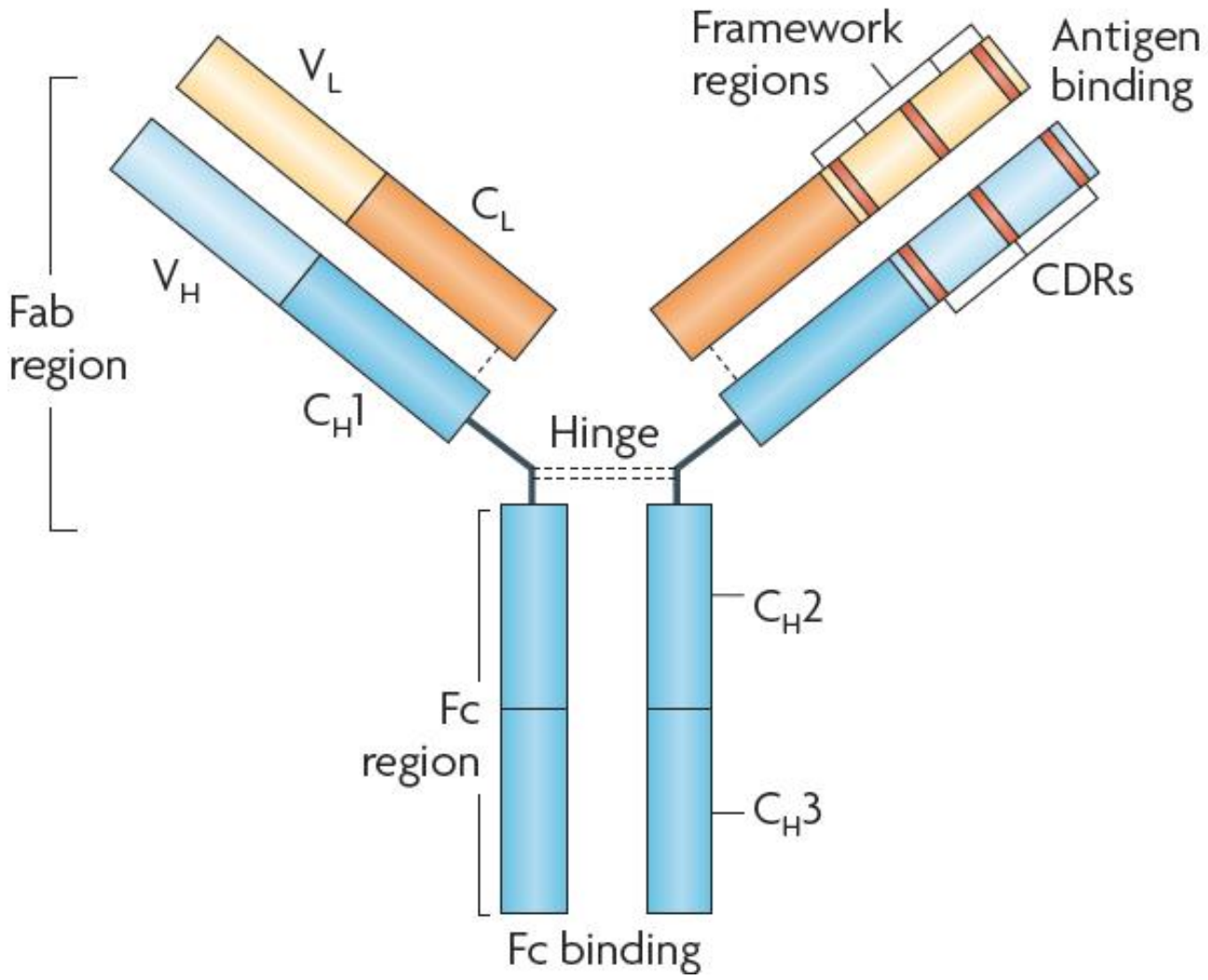
- Briefly review how monoclonal antibodies are generated
- Understand the **FOUR** basic Monoclonal Antibody (Mab) Types in the Clinic
- List the **FOUR** Major Mechanisms of Action of Mab clinically
- Know the Differences Between the **FOUR** IgG Types in humans
- List the **FOUR** Fc Gamma Receptors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

Where DID monoclonal antibodies come from?



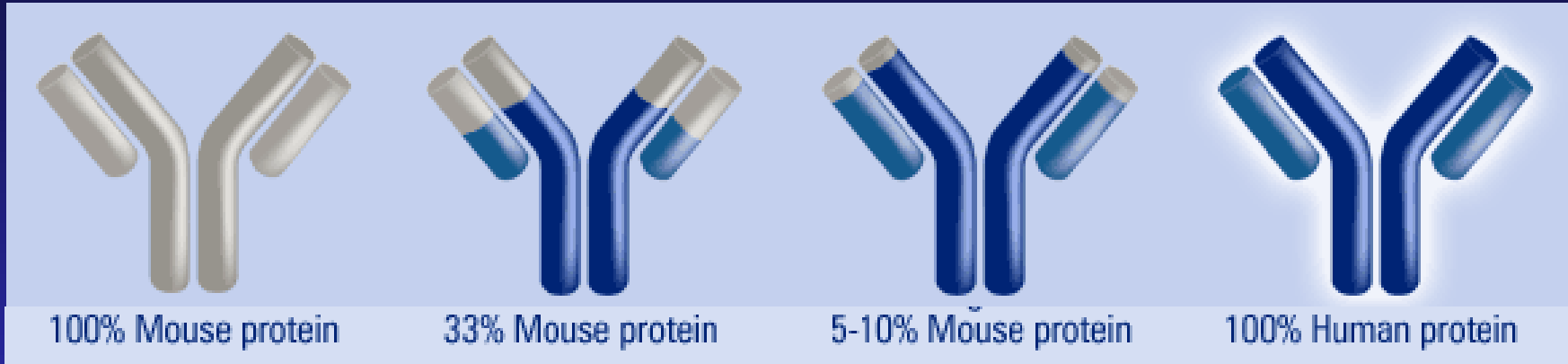
Janeway's Immunobiology, 6'th Edition

Antibody Structure



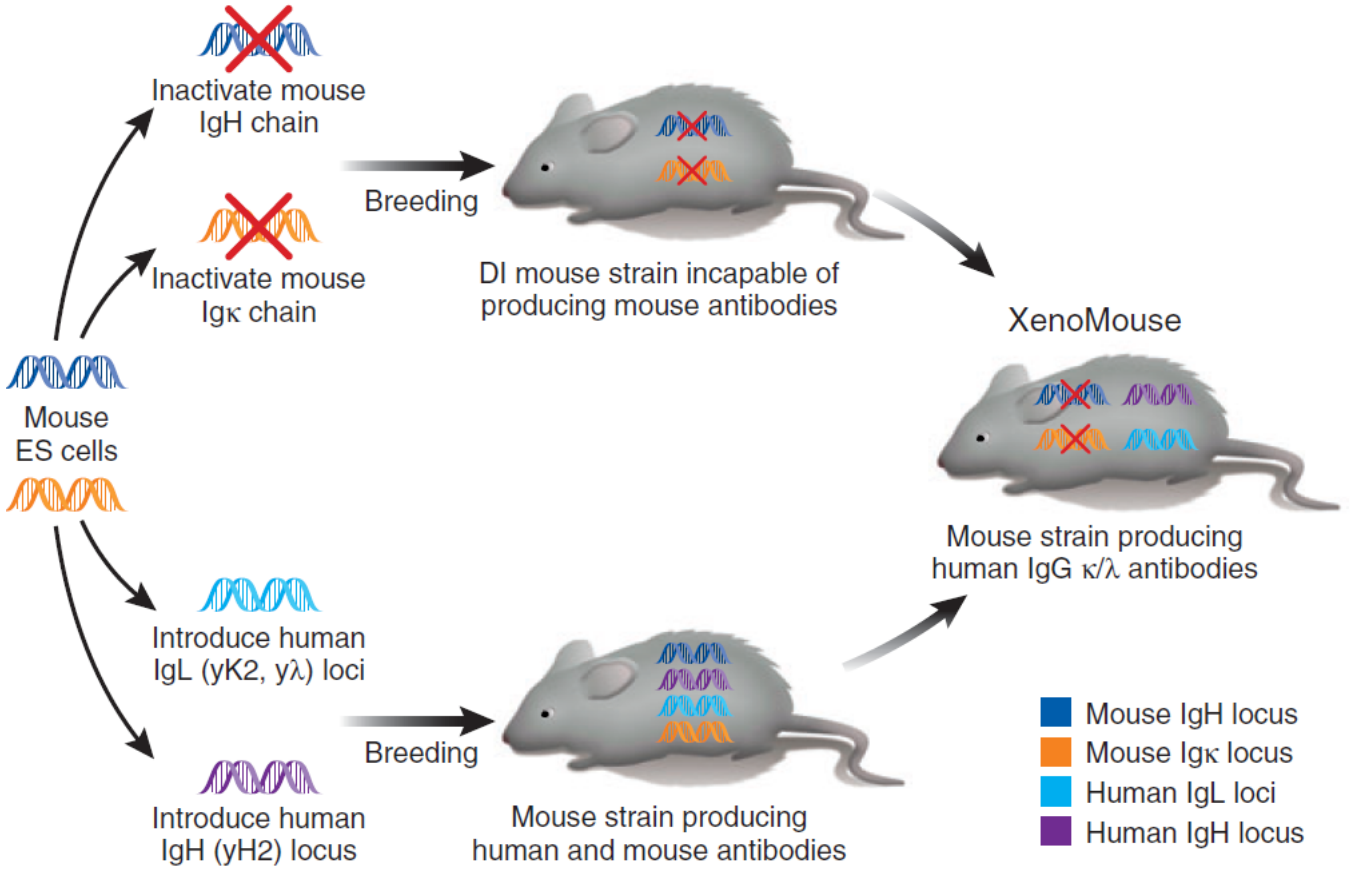
Hansel et. al, *Nature Rev Drug Discovery*, 2010: 9:325.

4 Kinds of Monoclonal Antibodies



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

A Mouse that Produces Fully Human Antibodies

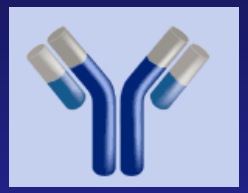


Jakobovits A. et al, *Nature Biotechnology*, 2007: 25:1134-1143.

Monoclonal Antibodies in Cancer
Rixuximab as an Example

FIRST monoclonal antibody approved for cancer treatment (1997)

A chimeric antibody



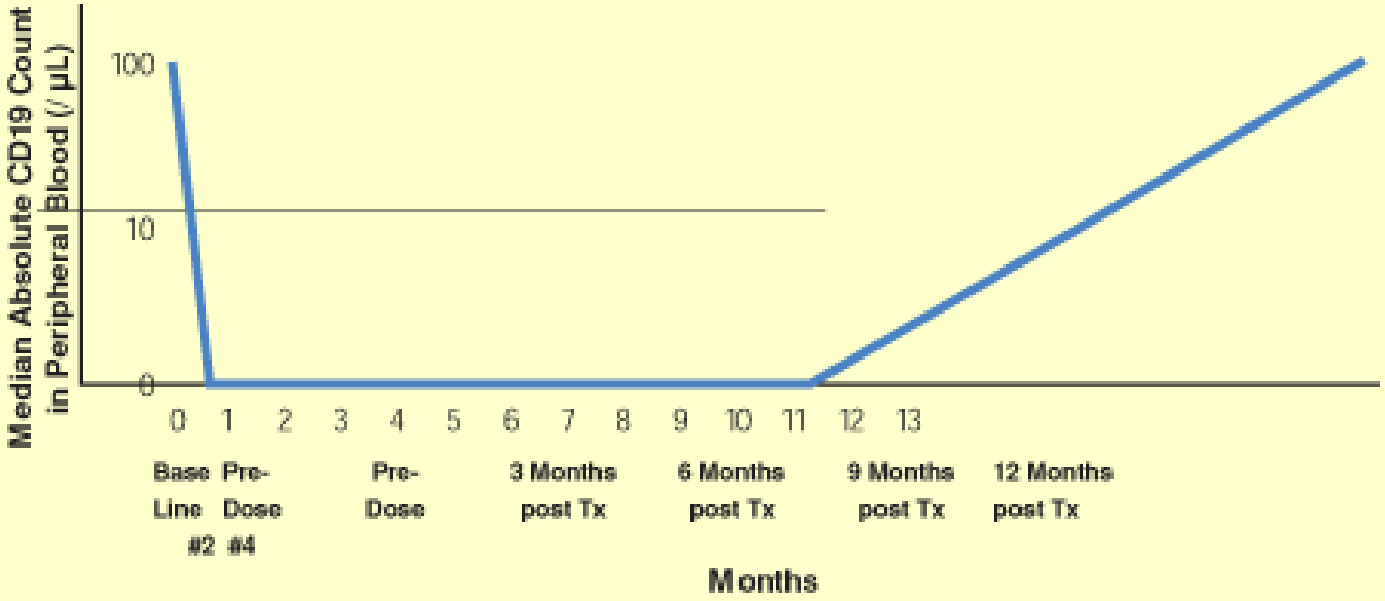
Approved For CD20+ Non-Hodgkin's Lymphoma (NHL)

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

Approved for Rheumatoid Arthritis (2006)

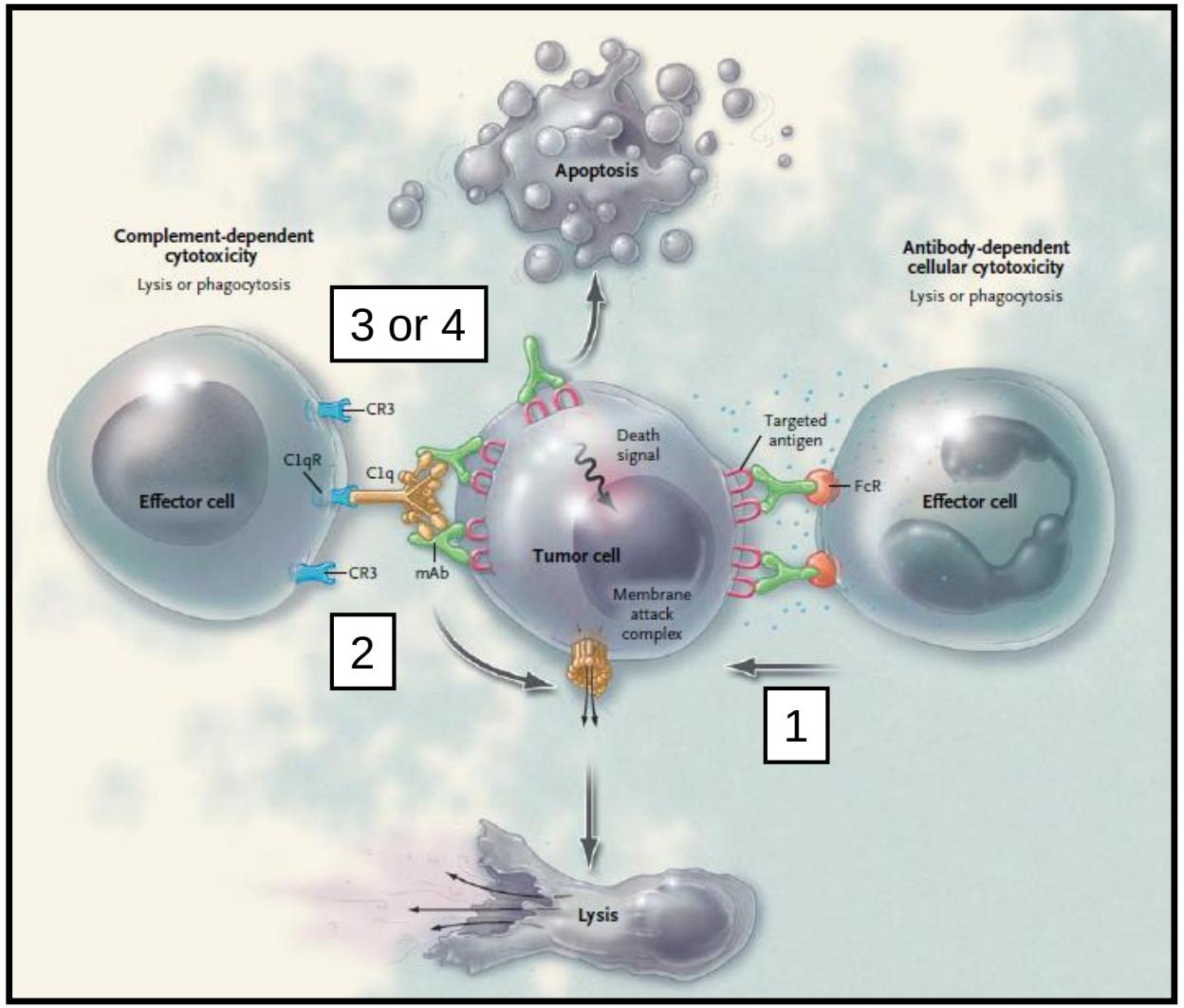
- **With methotrexate if anti-TNF therapy fails**

Rituximab Durably Depletes CD20+ Cells



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

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

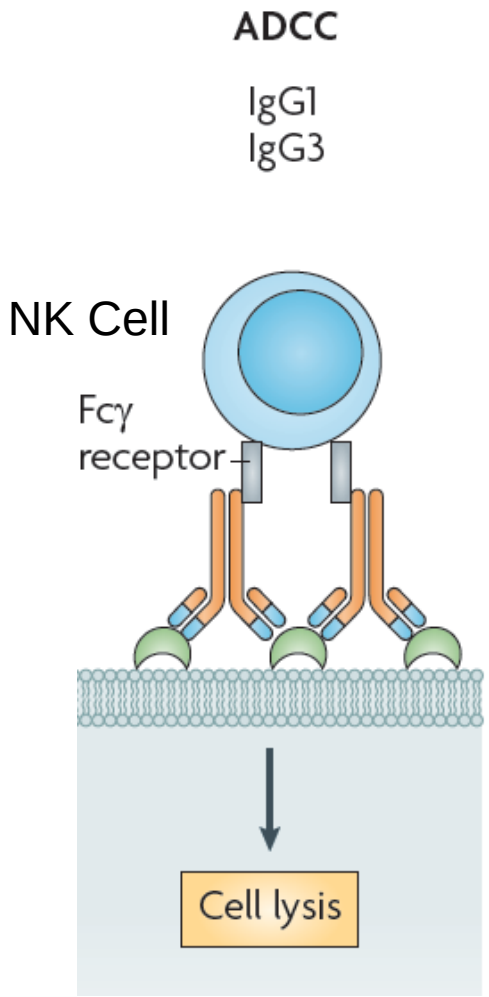


Mechanisms Of Action

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

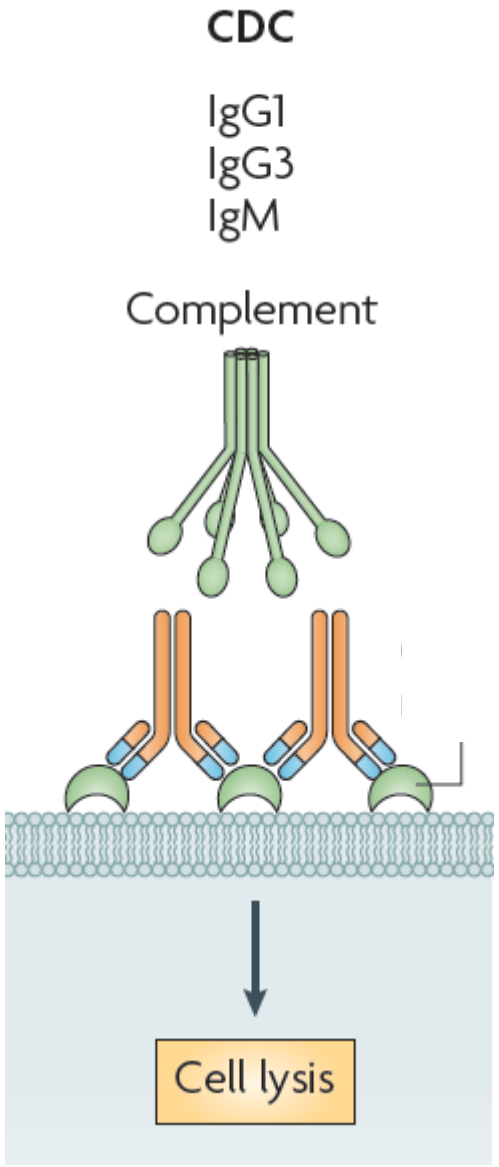
Rotschild et al, *NEJM* 2012

Antibody Dependent Cellular Cytotoxicity (ADCC)



a) Mediated 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 increasing glycosylation of Fc
    c) Increased ADCC when antibodies **lack fucosylation**

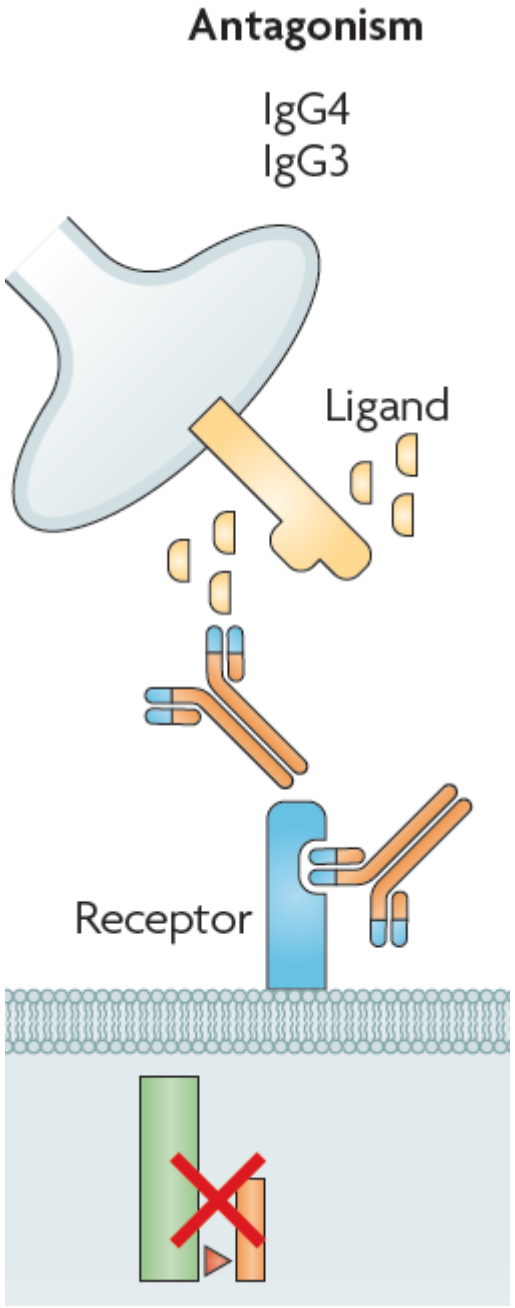
Hansel et. al, *Nature Rev Drug Discovery*, 2010: 9:325.



Complement Dependent Cytotoxicity (CDC)

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

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



Antagonist (blocking)

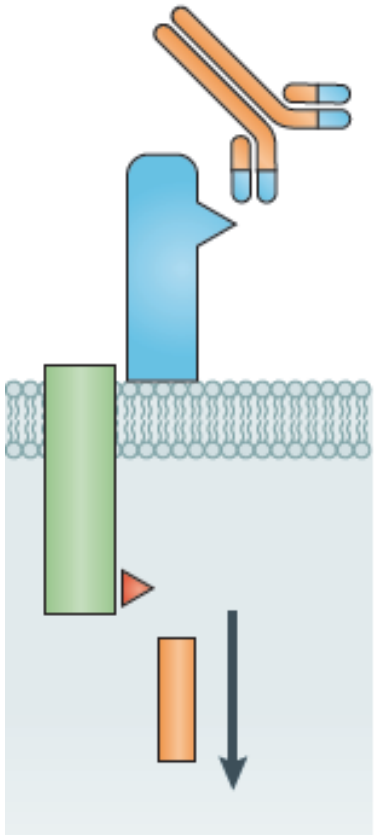
a) Can block EITHER a receptor OR a ligand

b) Ligand may be soluble (like TNFα, VEGF)

   a) Fc function not desirable, usually IgG4

   b) Other Ig subtypes can be engineered to minimize ADCC

c) Many / most Immune Checkpoint Abs = IgG4 (blockers)

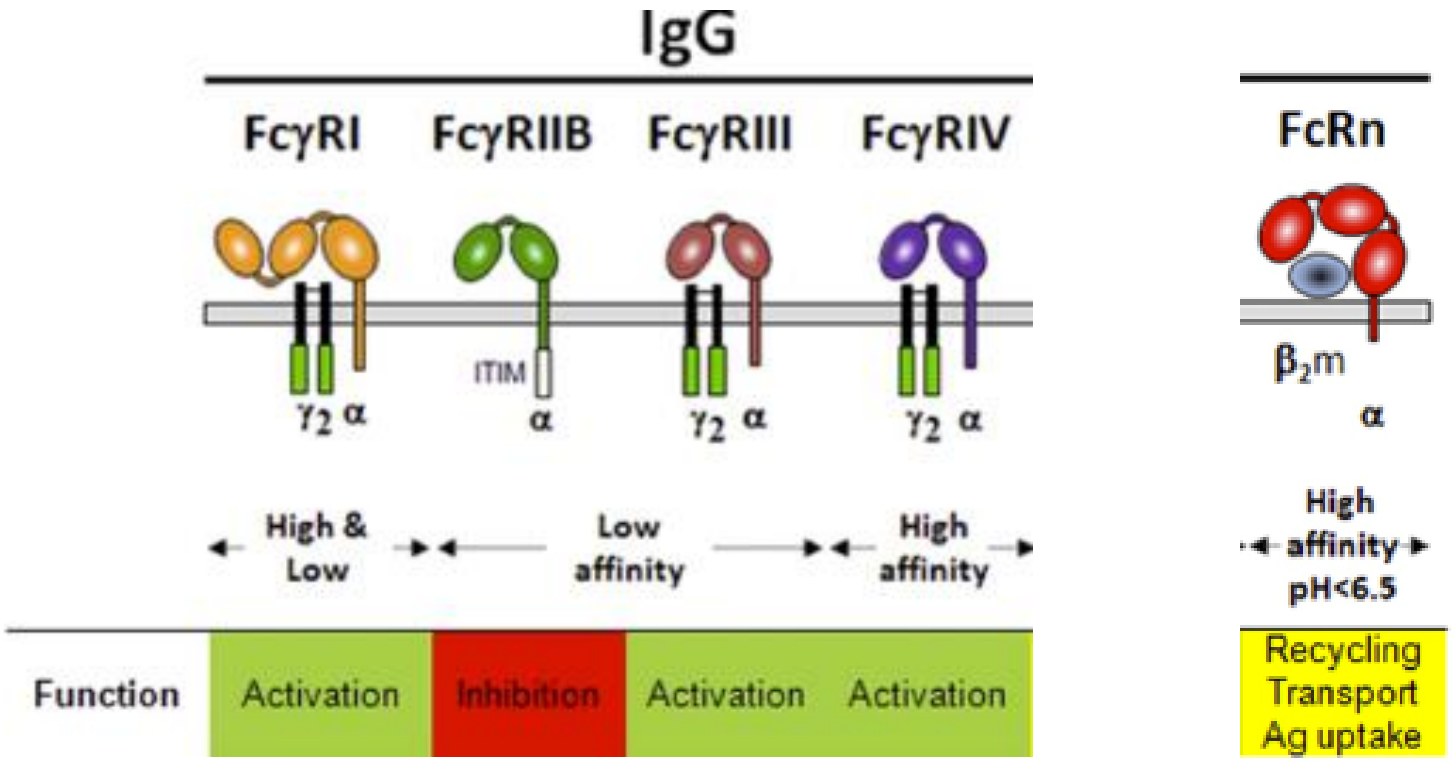


Agonist (Signalling)

a) Activating antibodies are in development for cancer immunotherapy
b) Examples include anti-CD40 and anti-4-1BB
c) Usually require cross linking for function

Exception = “superagonists”

There are FOUR Major Fc Gamma 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

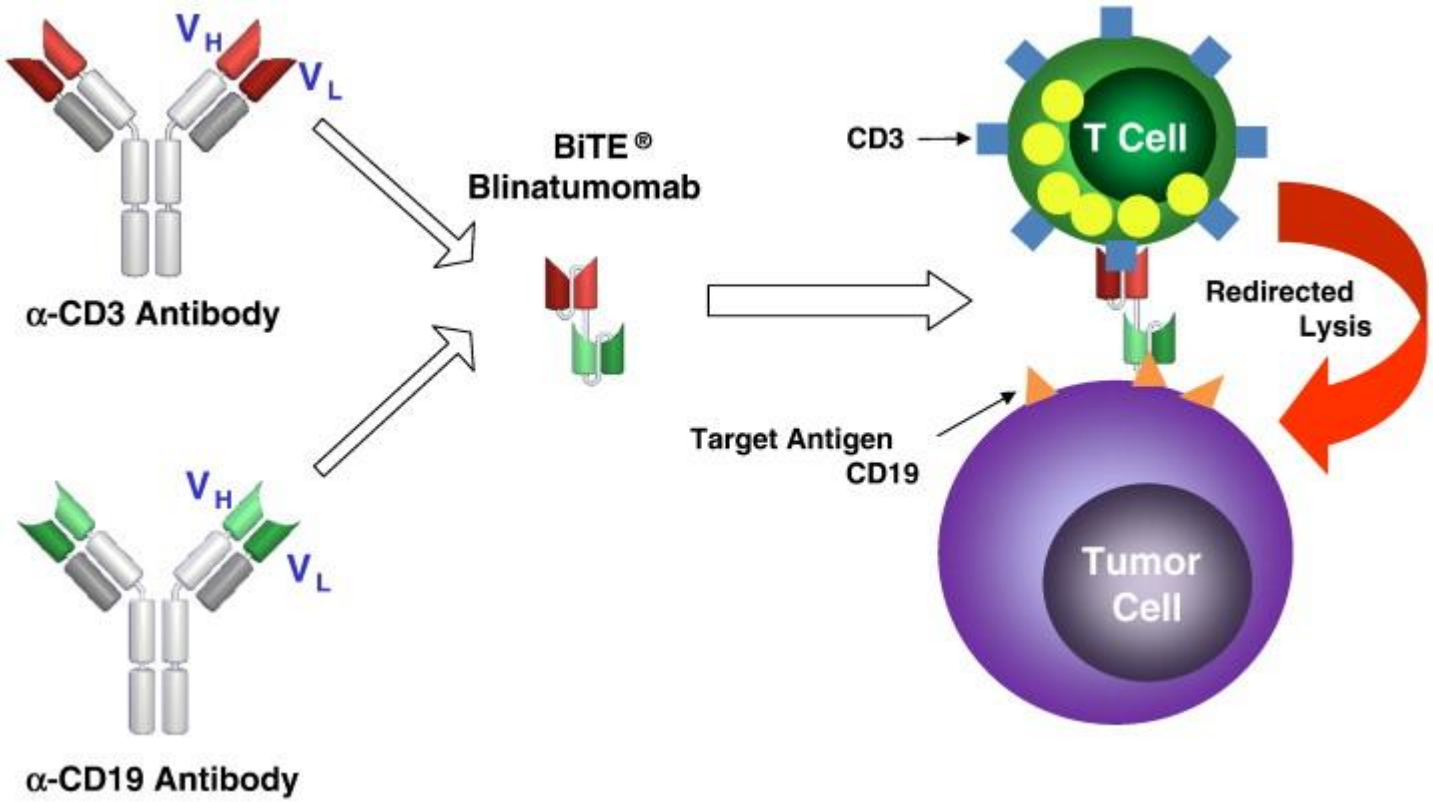
- For any IgG, Can modify hinge region to increase half-life

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

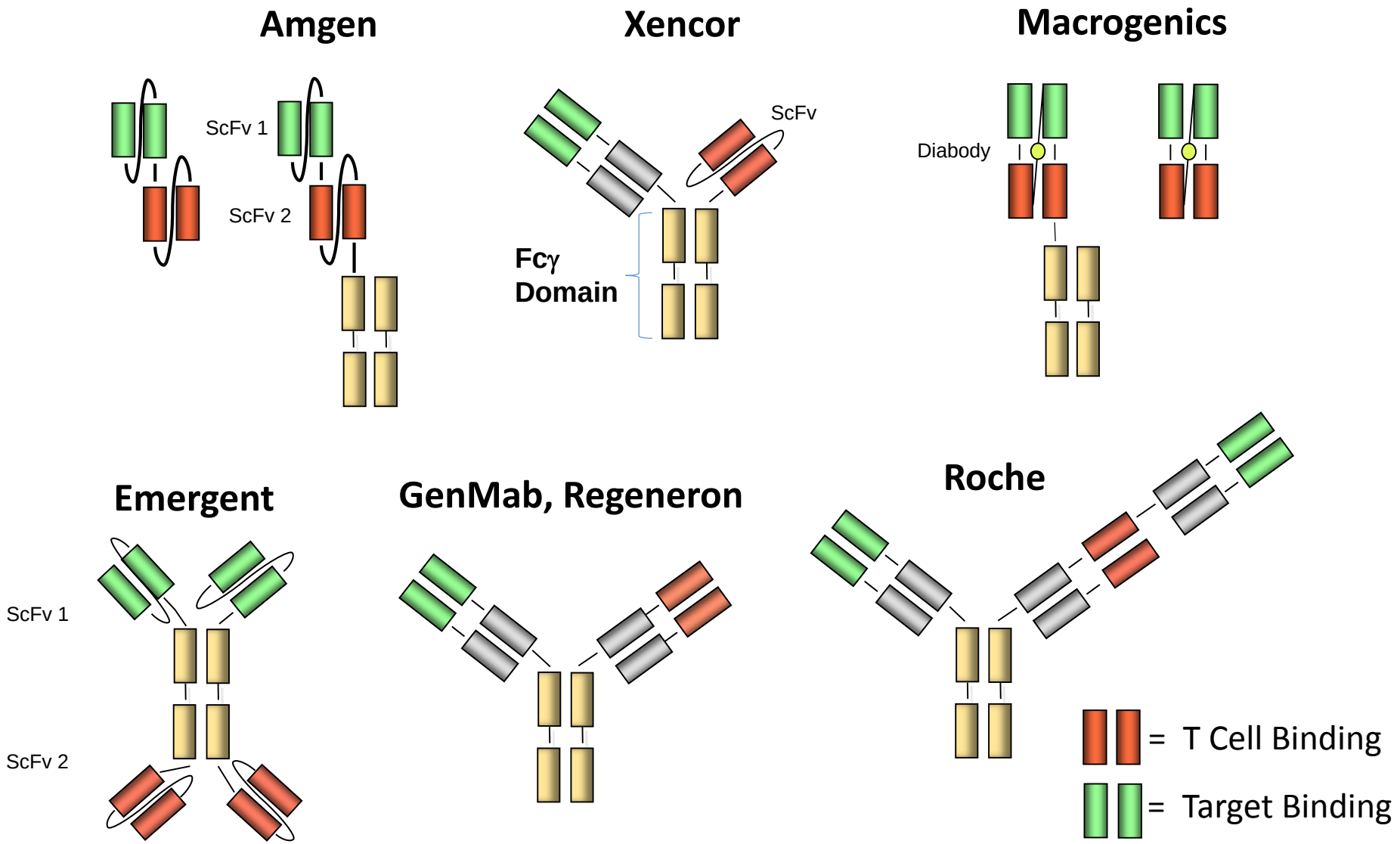
  Bind less strongly to FcRN = SHORTER half life

Modified Antibodies

1. Single-Chain Dual Specificity (BiTE)

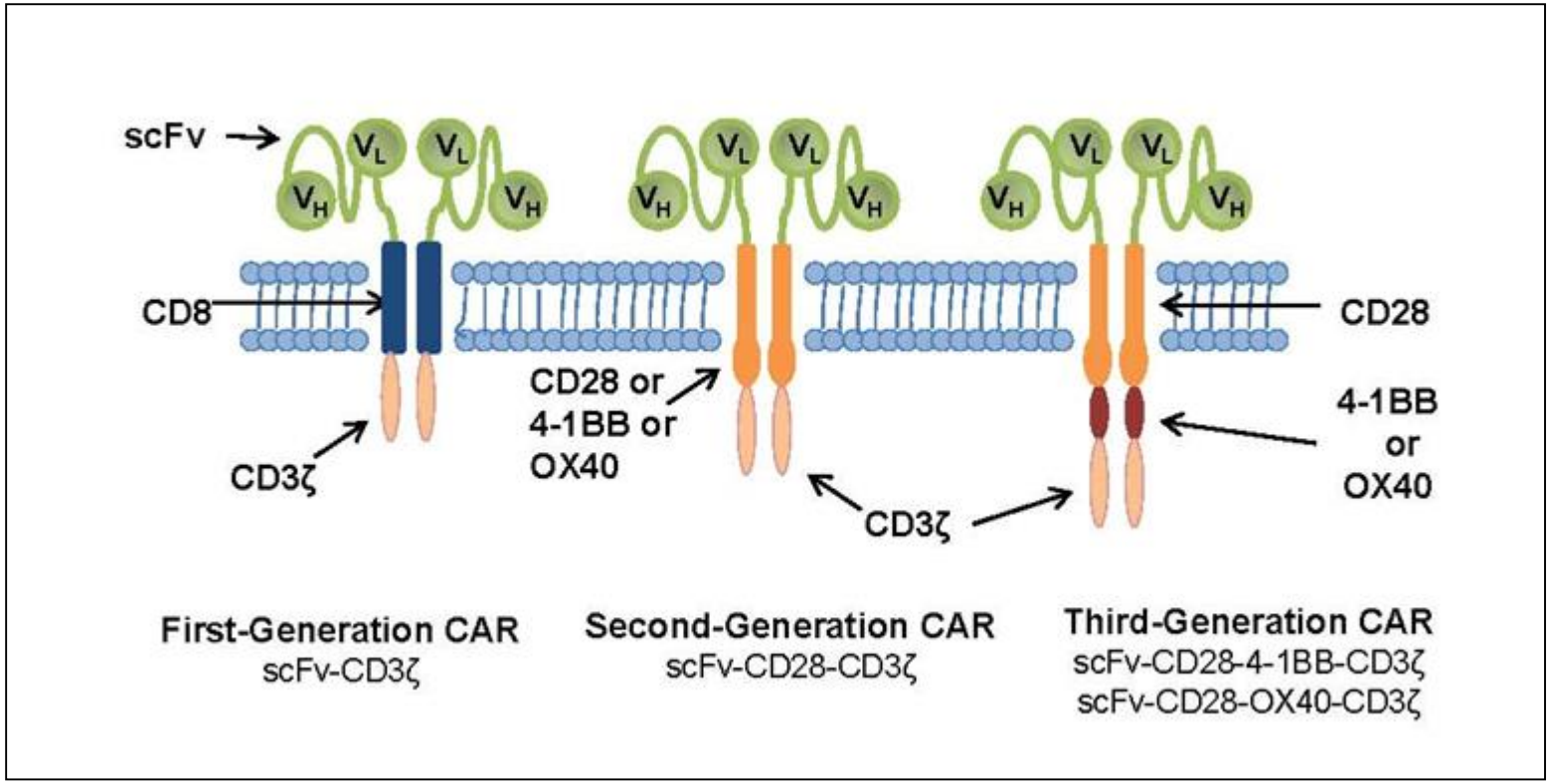


2. Additional T Cell-engaging Antibodies in Development (not complete)

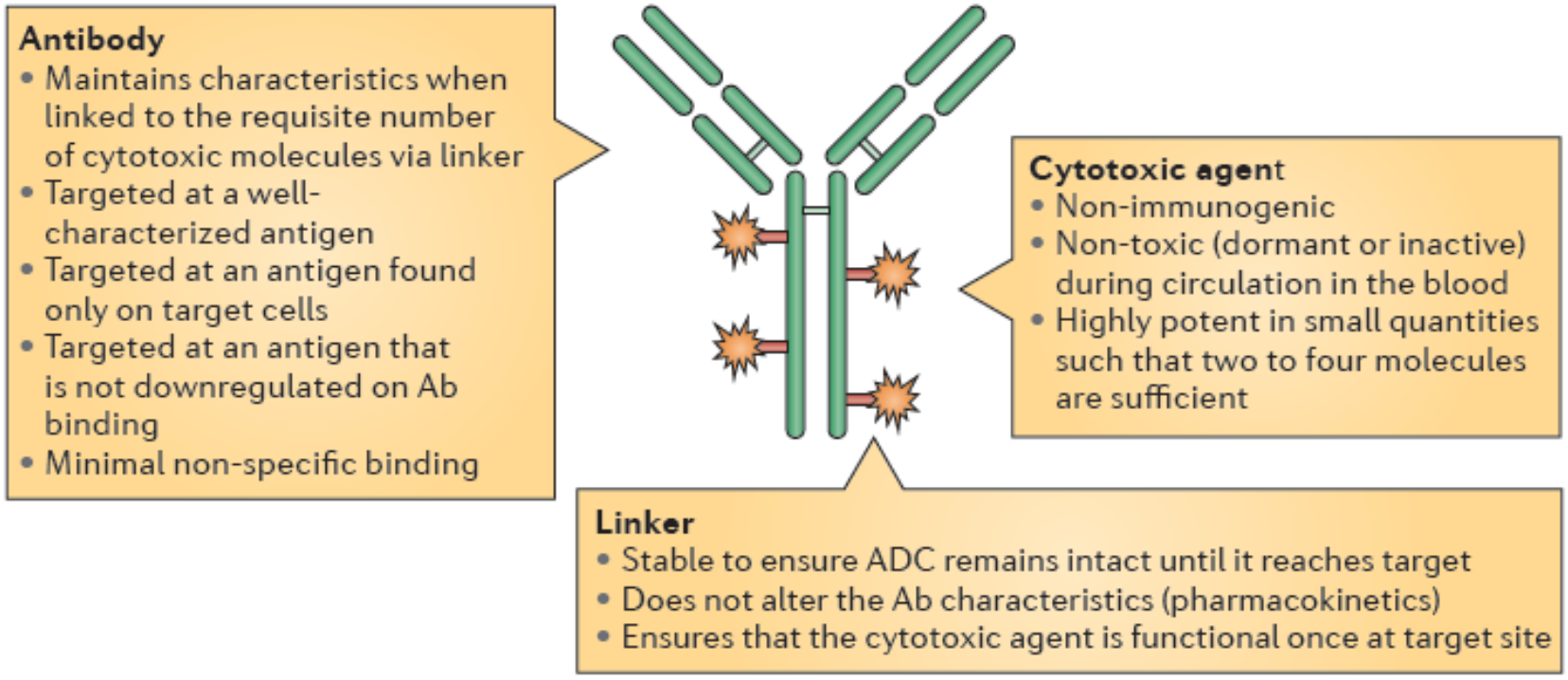


Slide Courtesy of Dr. Patrick Baeuerle

3. Chimeric Antigen Receptors

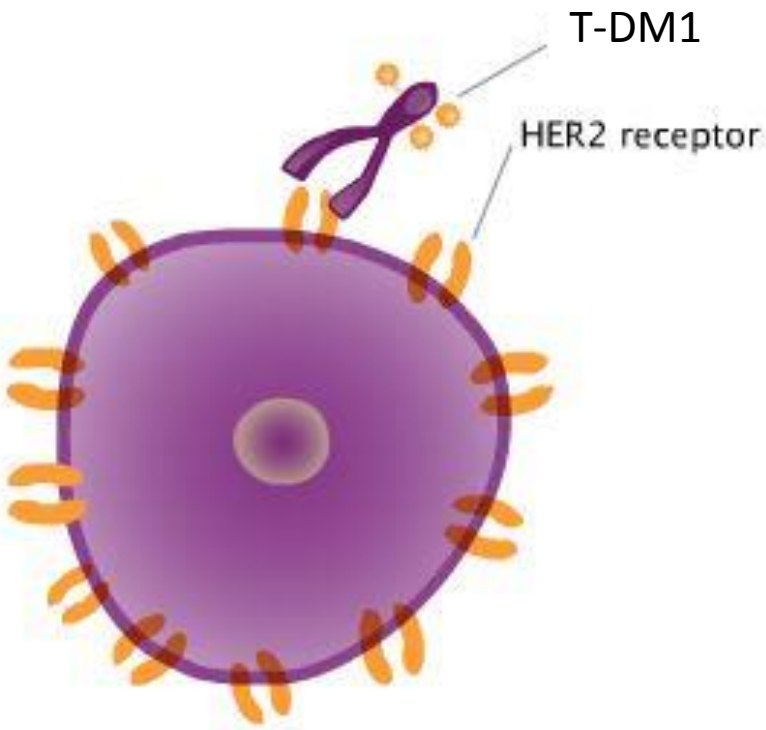


4/ Antibody Drug Congugates (ADC)

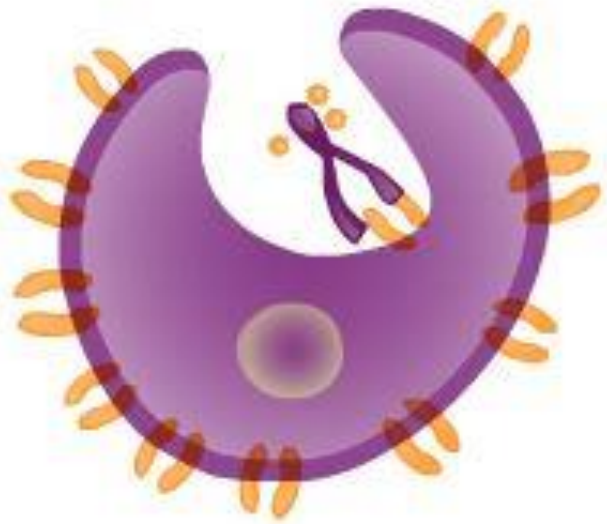


Zolot et. al. Nat Rev Drug Disc 2013:12:259

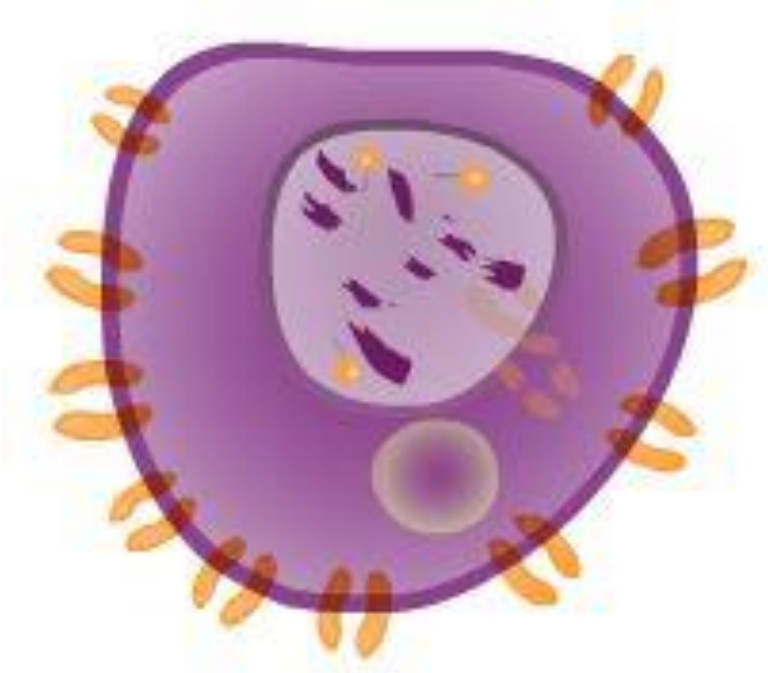
1: Binding



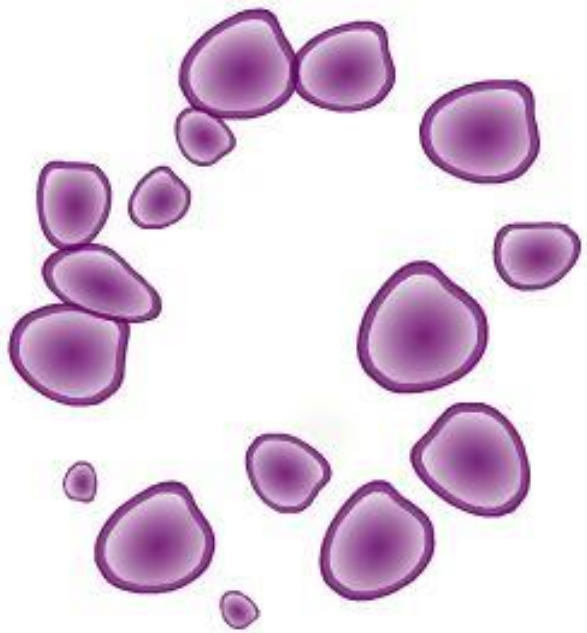
2: Internalization



3: Dissociation



4: Target Cell Lysis



Examples

Ipilimumab (Anti-CTLA-4)

“u” = Fully Human

IgG1 with modified hinge region

Blocker (antagonist)

FDA approved in Melanoma, in combination in RCC, SCLC

Pop Quiz:

What’s wrong with this picture?

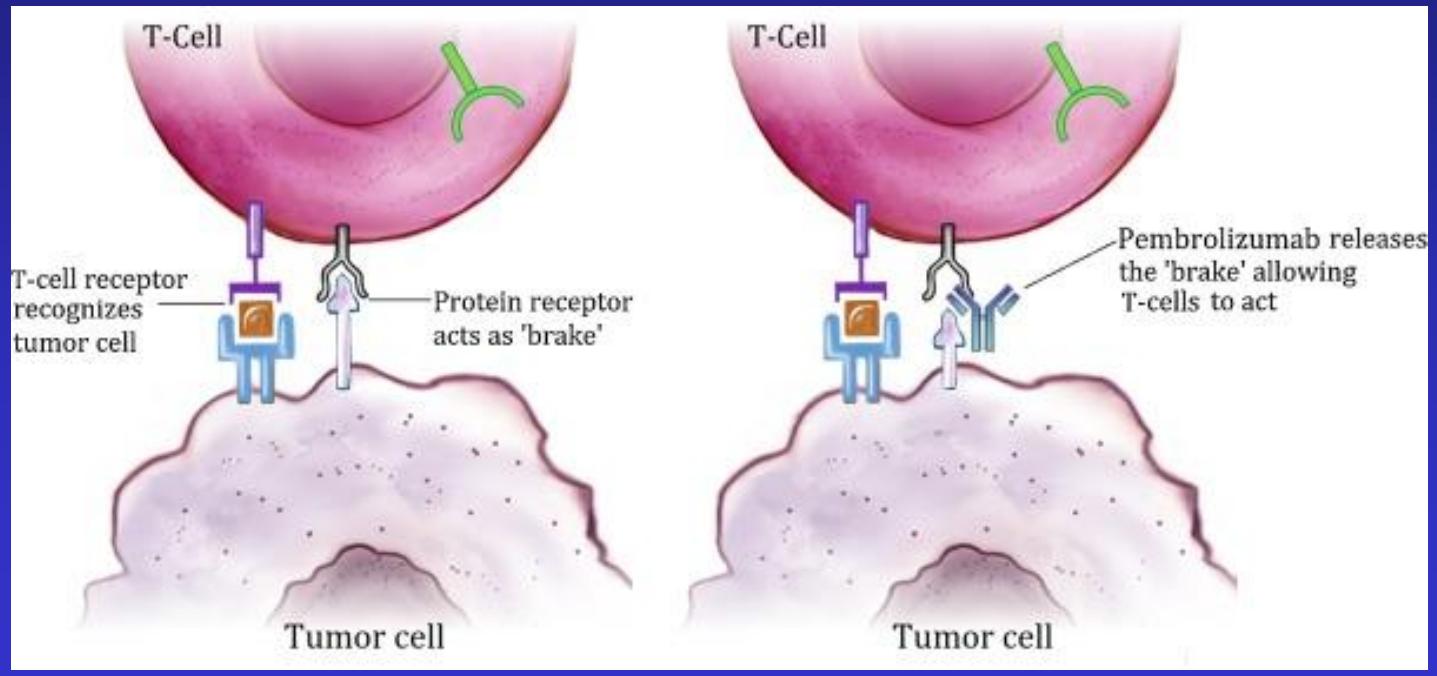
Pembrolizumab (Anti-PD-1)

“zu” = Humanized

IgG4 with modified hinge region

Antagonist

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



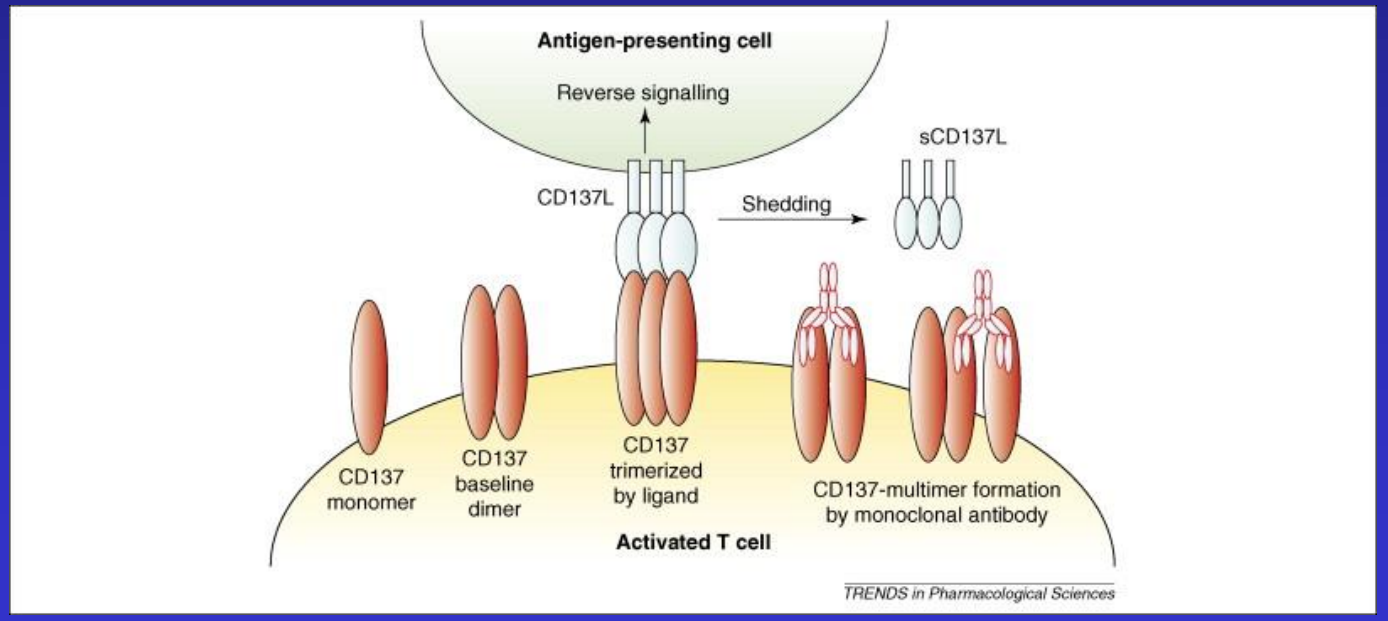
Urelumab (Anti-4-1BB)

“u” = Fully Human

IgG4

Agonist

In Phase I / II

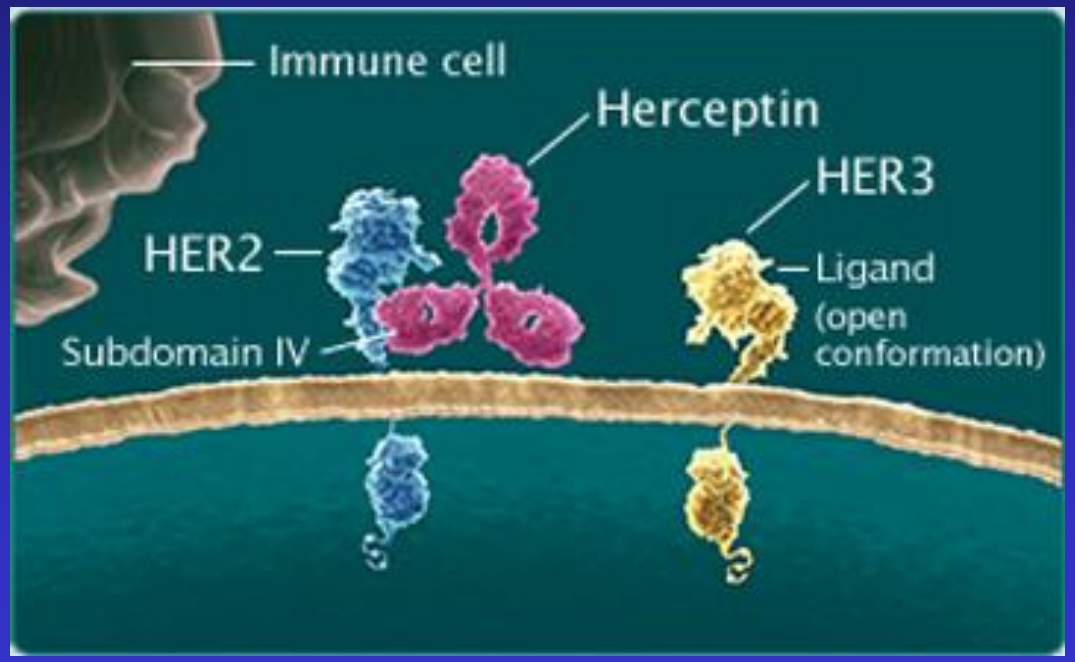


Trastuzumab (Herceptin)

“zu” = Humanized

IgG1

MOA = prevent dimerization / ADCC

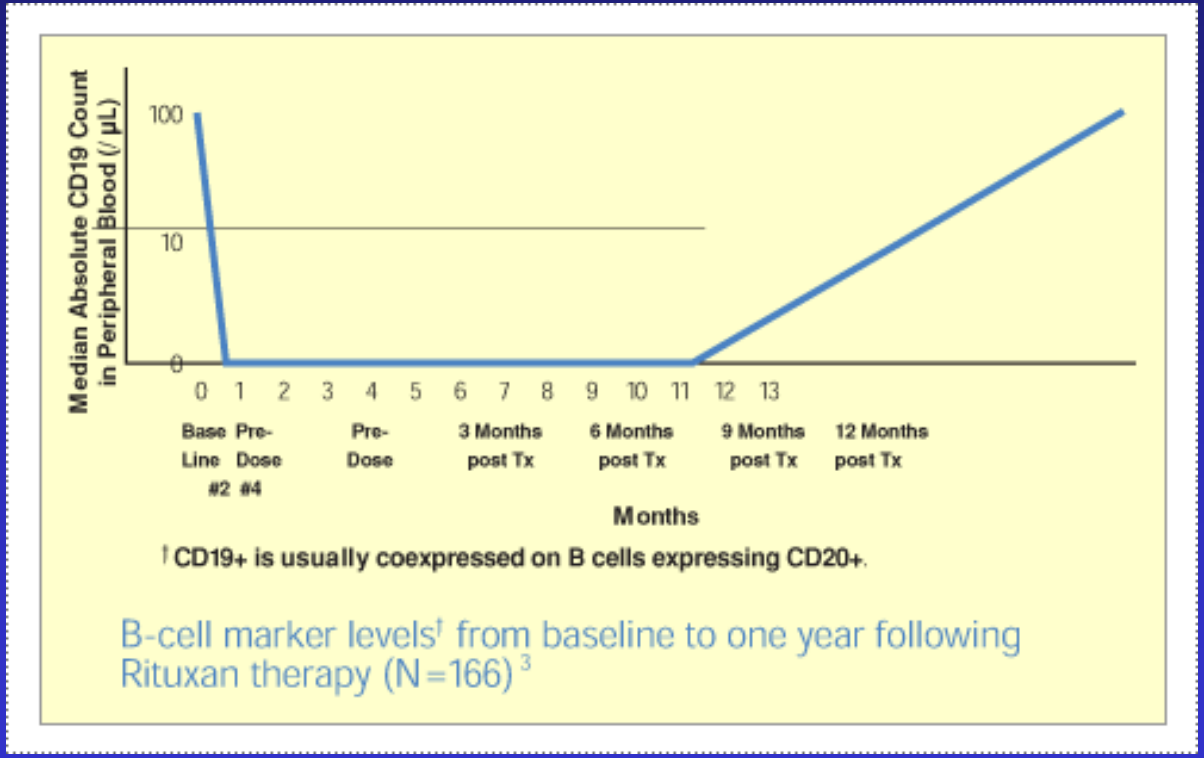


Rituximab (Rituxan)

“xi” = Chimeric

First Monoclonal Antibody Approve to Treat Cancer (1997)

IgG1 (ADCC)



Summary

- Monoclonal Antibodies = Drugs
- Prominent in Cancer Immunotherapy and Rheumatology
- Engineered Modifications to Fc Region affect multiple properties, especially half life
- Many T-cell engaging constructs in development
- ADC on the rise (improved linker technology)

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.

cgd2139@Columbia.edu