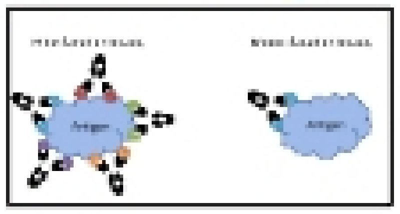
Abs as Drugs

Monday, November 17, 2014
11:58 AM

<u>Lecture Outline</u>
• mAbs (made/modified)
• clinical Abs (autoimmunity/cancer)
• limitations

<u>Learning Objectives</u>
• mAb
• hybridomas & how they make mAbs
• Ab engineering, Ab derivatives as therapy
• clinical mAbs to target autoimmunity & cancer
• limitations of mAbs & solutions

B-CELL ACTIVATION - meets Ag, differentiates w/CD4 help, made into Ab-secreting plasma cells



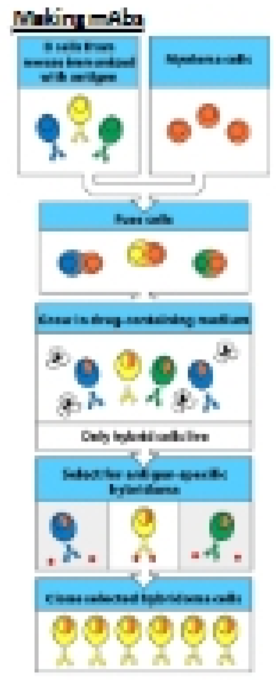
*Ags may be very complex with multiple epitopes

pAbs - binds 2+ epitopes on Ag
mAb - binds 1 epitope on Ag

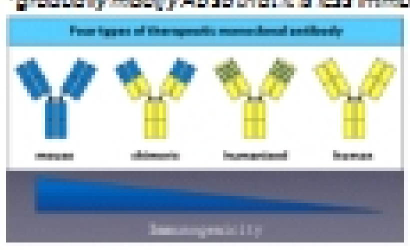
<u>Making mAbs</u>
1) mouse plasma B-cells (immunized with Ag) + myelomas
2) PEG fusion (most don't fuse)
3) only hybridomas survive:
   - <u>myeloma</u>: sensitive to drug (die)
   - <u>B-cells</u>: NOT sensitive to drug, but short-lived (die)
4) multiplication (of Ag-positive hybridoma)

MYELOMA - immortalized cancer cell line
HYBRIDOMA - fusion of plasma B-cell + myeloma

<u>Making mAbs</u>



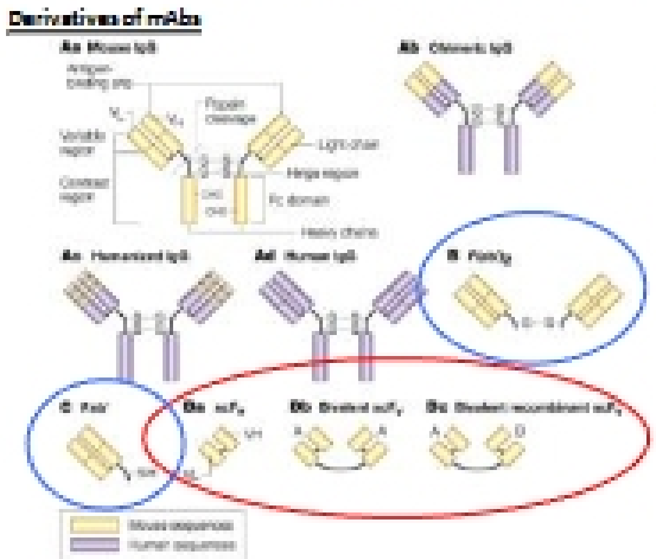
<u>Ab Engineering</u>
gradually modify Ab so that it is less immunogenic in the body



MOUSE - highly immunogenic
CHIMERIC - variable (mouse) + constant (human)
HUMANIZED - CDR1/2/3 loops (mouse) + rest (human)
HUMAN - cannot start with mouse Ab

XENOMOUSE - genetically modified mouse that has human Ab genes & creates human Abs

<u>Derivatives of mAbs</u>



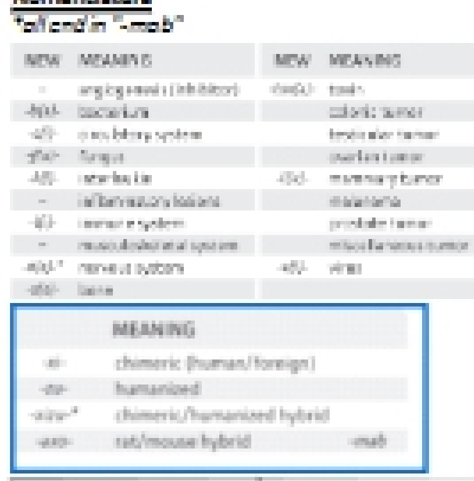
<u>Typical Abs</u>: long half-life
<u>Single-chain Abs</u>: much shorter half-life

can make each chain different in specificity

no Fc portions
(no immune-activating potential)

only variable regions

<u>Nomenclature</u>
all end in "-mab"

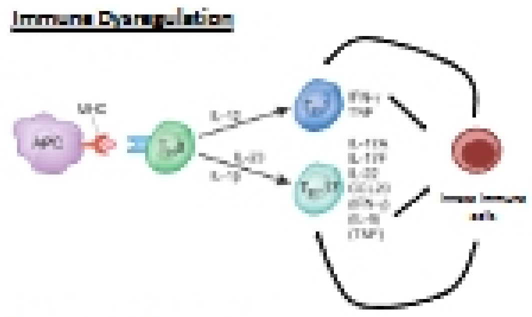


NEW	MEANING	NEW	MEANING
-	angiogenesis (inhibitor)	-tox(a)-	toxin
-b(a)-	bacterium		colonic tumor
-c(i)-	circulatory system		testicular tumor
-f(u)-	fungus		ovarian tumor
-k(i)-	interleukin	-t(u)-	mammary tumor
-	inflammatory lesions		melanoma
-l(i)-	immune system		prostate tumor
-	musculoskeletal system		miscellaneous tumor
-n(e)-*	nervous system	-v(i)-	viral
-s(o)-	bone		

	MEANING	
-xi-	chimeric (human/foreign)	
-zu-	humanized	
-xizu-*	chimeric/humanized hybrid	
-axo-	rat/mouse hybrid	-mab

Herceptin (trastuzumab)	tras-tu(tumor)-zu(humanized)-mab
Remicade (infliximab)	inf-li(immune)-xi(chimeric)-mab

<u>Immune Dysregulation</u>



<u>Autoimmune Diseases</u>
- Crohn's
- RA
- MS
- Lupus
- Psoriasis
- Ankylosing Spondylitis

<u>Autoimmune Targets</u>

	Example Target	Autoimmune Disease	Purpose
Ligand Blockade	TNF	- Psoriasis - RA - Crohn's - Colitis	↓cytokine environment
Receptor Blockade	IL6-R	- RA	↓cytokine environment
Receptor Downregulation	ICAM1	- Psoriasis	↓recruitment of immune cells to certain tissues
Cell Depletion *(also used in cancer)*	CD52	- MS	kill B/T-cells (via NK/macrophages/B-cells)
Signal Induction *(less common)*	CD3	- DM1	targeting Abs to induce signal

<u>Cancer Targets</u>

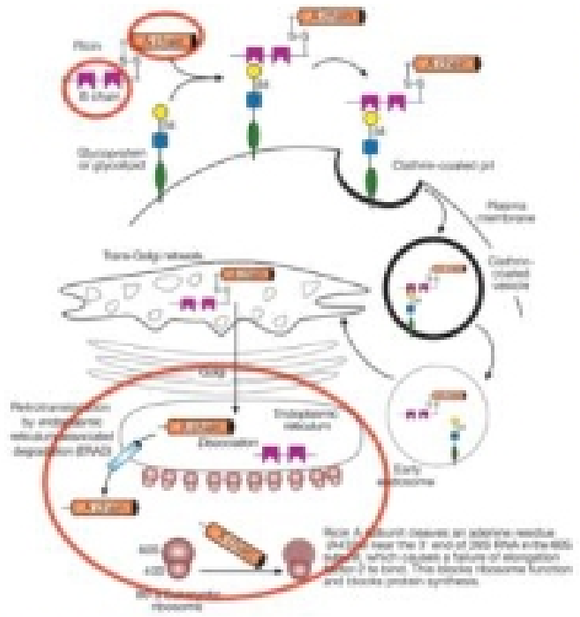
	Example Target	Cancer	Purpose
Ligand Blockage (Angiogenesis Inhibition)	VEGF	- colorectal - lung - renal	- ANTI-VEGF blocks angiogenesis
Receptor Blockage (GF Inhibition)	Her2	- breast	- HERCEPTIN blocks growth
Immunoconjugates (radionucleotide, chemo, toxin)	Abs	- most	- conjugated Abs kill cancer cells
Immunomodulatory			

ANGIOGENESIS - growth of blood vessels to provide O_2 & nutrients to tumor
   VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) - secreted by tumors, ligand that causes angiogenesis
      ANTI-VEGF - blocks angiogenesis (colorectal, lung, renal); may cause problems with wound healing

HER2 - receptor in breast cancer
   HERCEPTIN - blocks dimerization of Her2, blocking signal that induces growth

GUANYLYL CYCLASE C (GCC) - target in colon cancer cells; tissue-specific biomarker
   GUCY2C - gene that expresses GCC enzyme; rapidly internalized into lysosomes
      Anti-GCCAB:RICIN-A - kills GUCY2C

<u>Bacterial/Plant Toxins</u>



*bacterial/plant toxins are highly effective

B-CHAIN - receptor (for glycoprotein on target cell)
A-CHAIN (RICIN) - toxin; blocks protein synth (ribosomal inhibitor)

1) A+B enters cell
2) A & B split
3) A blocks protein synth (ribosomal inhibitor)

**can replace B-chain with Anti-CD22 Ab & bind it to A-chain to kill CD22+ BC

Limitations of Ab Therapy

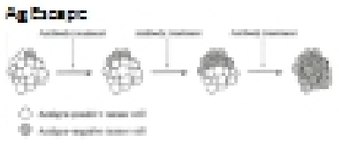
*Abs are not like typical drugs (manufacturing, PK/PD/tolerance, drug linkers)

- manufacturing	more expensive/difficult to make
- PK	eliminated quickly.. need more doses
- linkers	Ab:drug linkers may cleave in circulation (rather than in lysosome)
- anti-toxin Abs	mount anti-toxin Ab response that can clear drug (limits dose)/need to make them human/humanized)
- anti-Ab Abs	even humanized Abs can be immunogenic (body creates Abs for Ag binding sites - drug:Ab receptors)
- targeting self-Ags	when treating autoimmune diseases & cancers, we are targeting self-Ags
- infections	limiting cytokines causes ↑ risk of infection
- Ag escape	continuous targeting of 1 Ag can lead to tumors with only the Ag that we can't target

Linker

Anti-Ab Abs

Ag Escape



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