Outline of Targeted Cancer Treatments

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Introduction

Treatments that **TARGET** specific proteins, processes, and pathways

Which for the purpose of this presentation are:

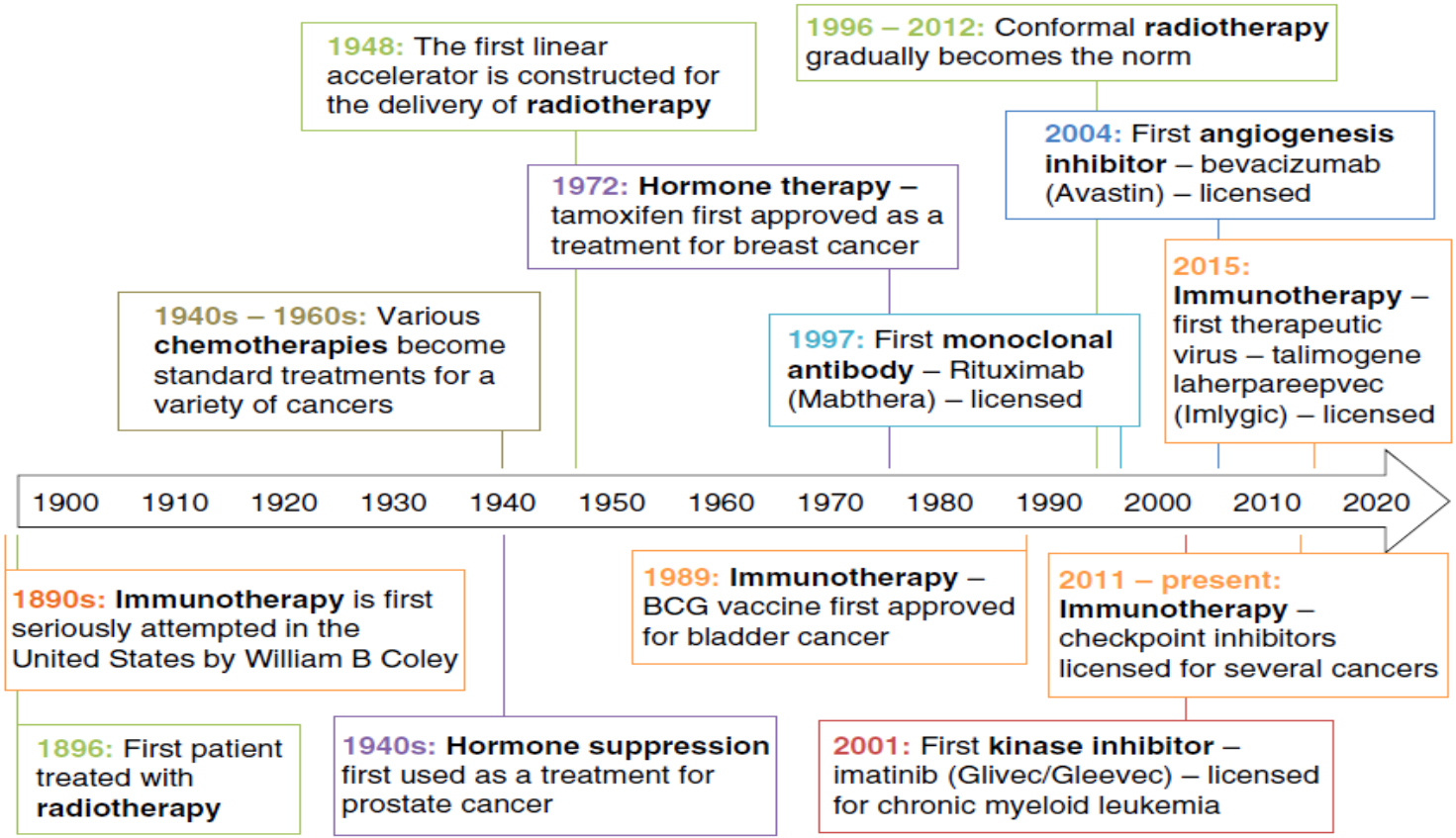
1. Target proteins on the surface of cancer cells
2. Block faulty or overactive enzymes in the cell cytoplasm
3. Target the patients' immune system
4. Create or boost a cancer fighting immune response

Introduction

- Mutated gene -> Mutated Protein -> Tumorigenesis
- Ideal target: specific to cancer cells
- More precise than chemotherapy
- No uniformly agreed definition

- Broadly two types

1. Small molecules
2. Monoclonal Antibodies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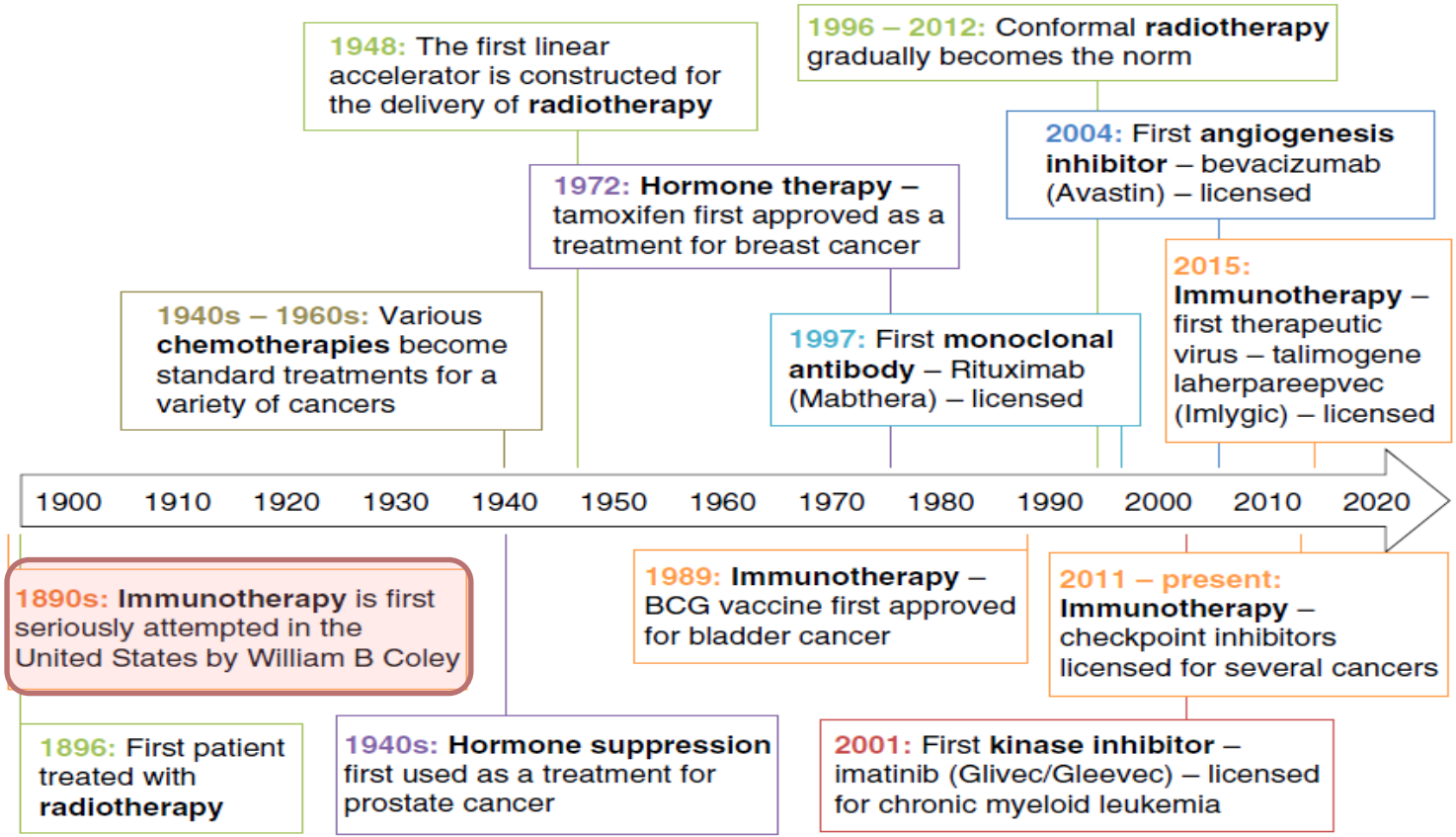
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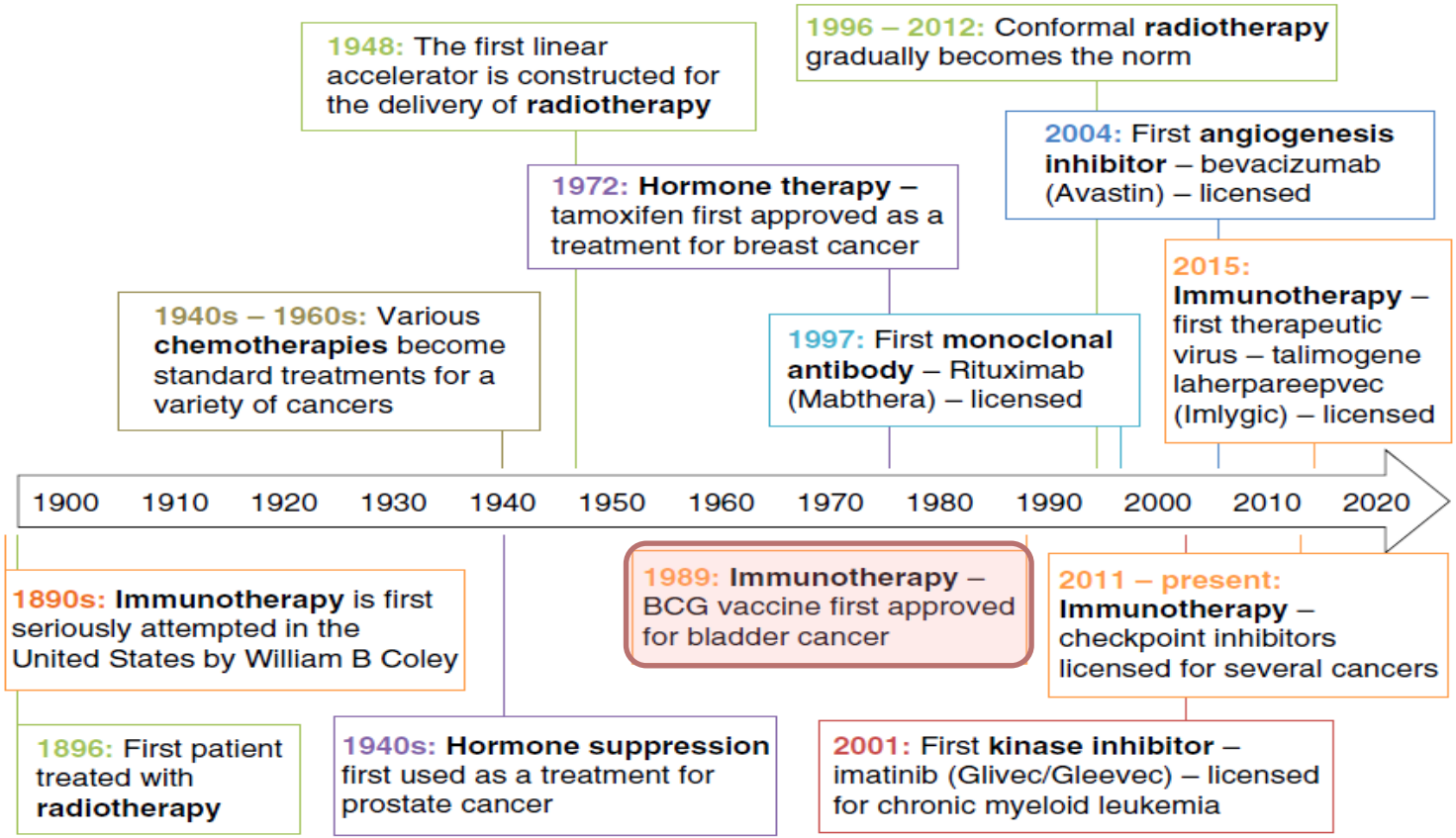
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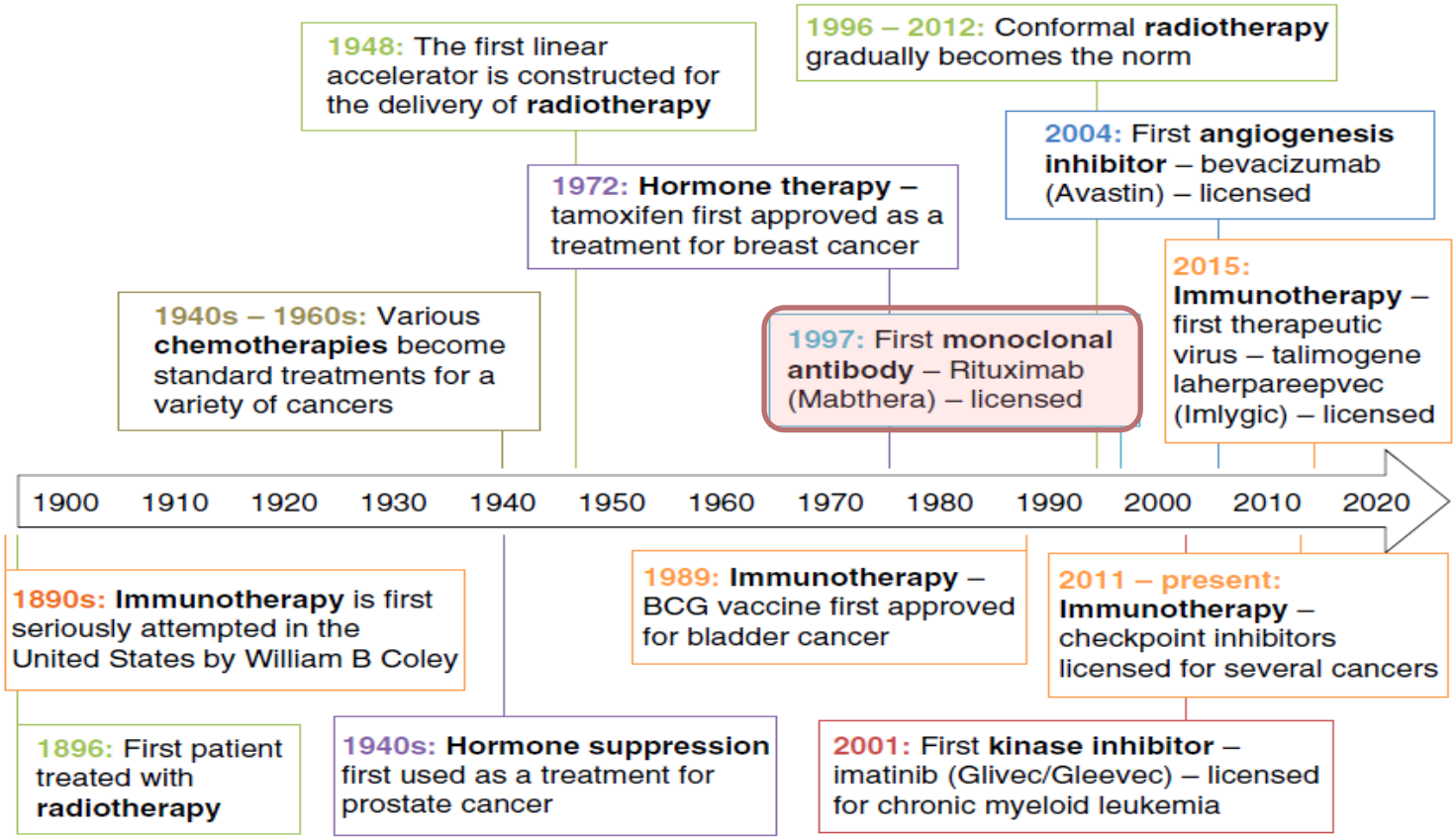
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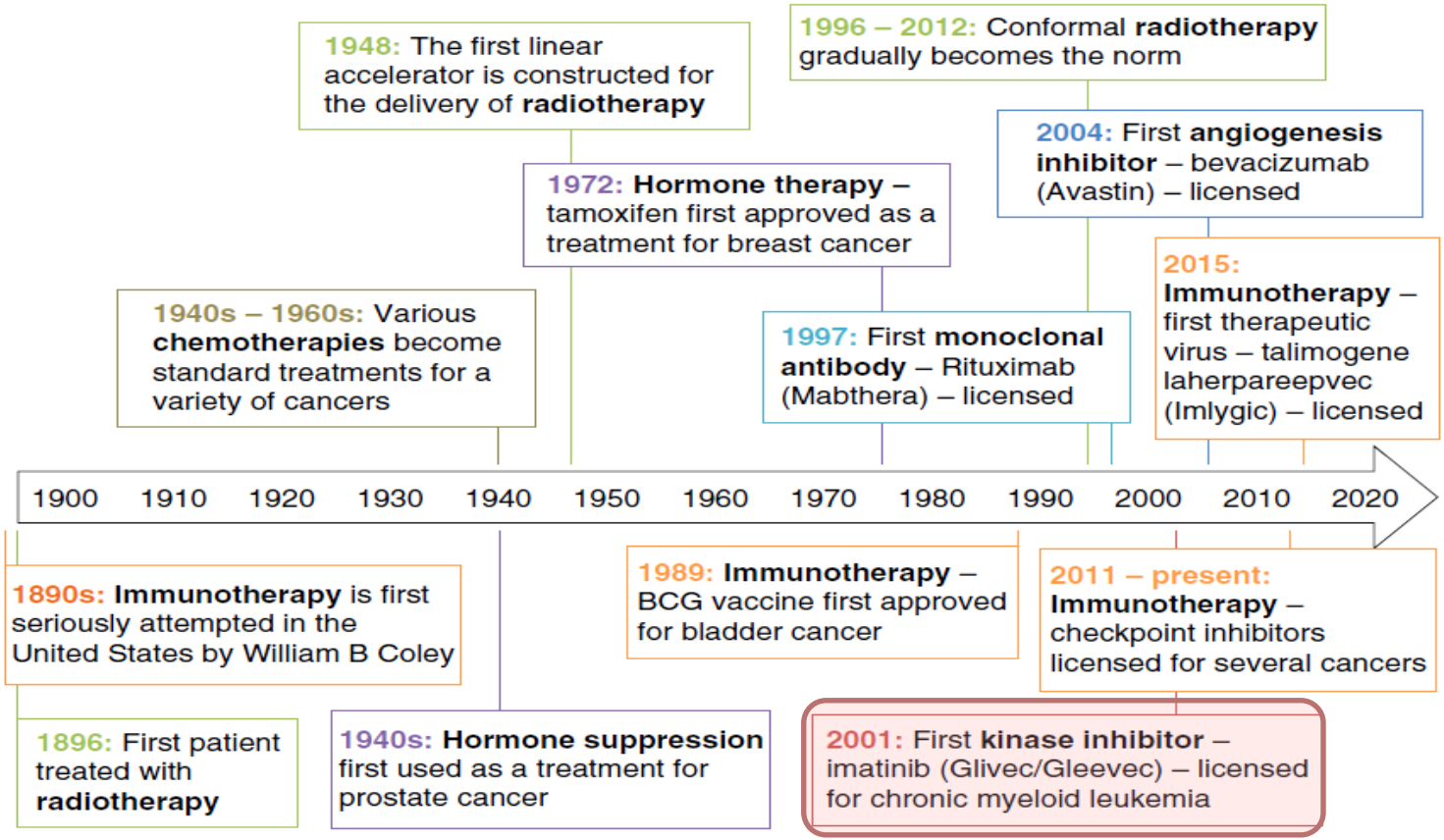
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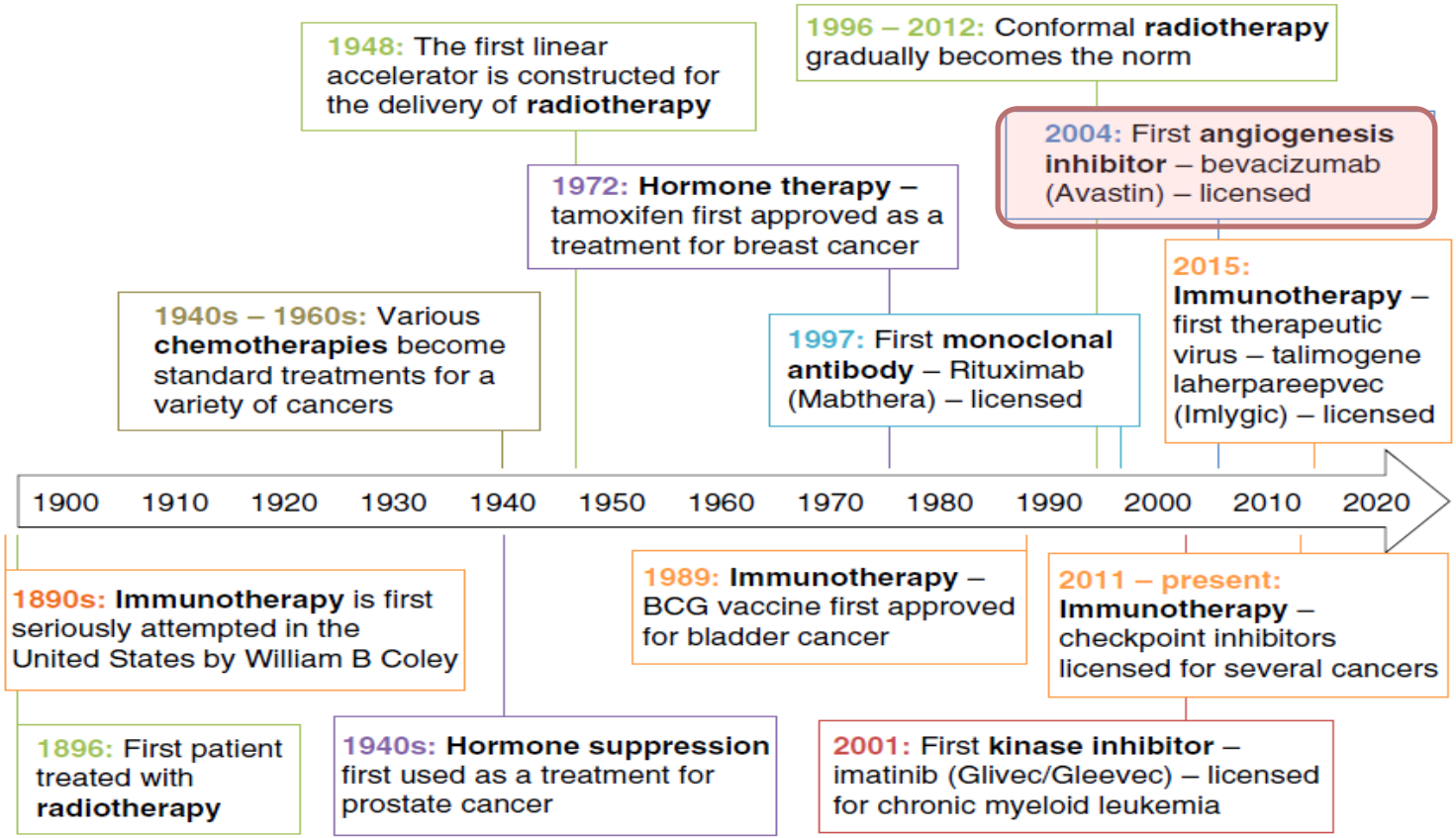
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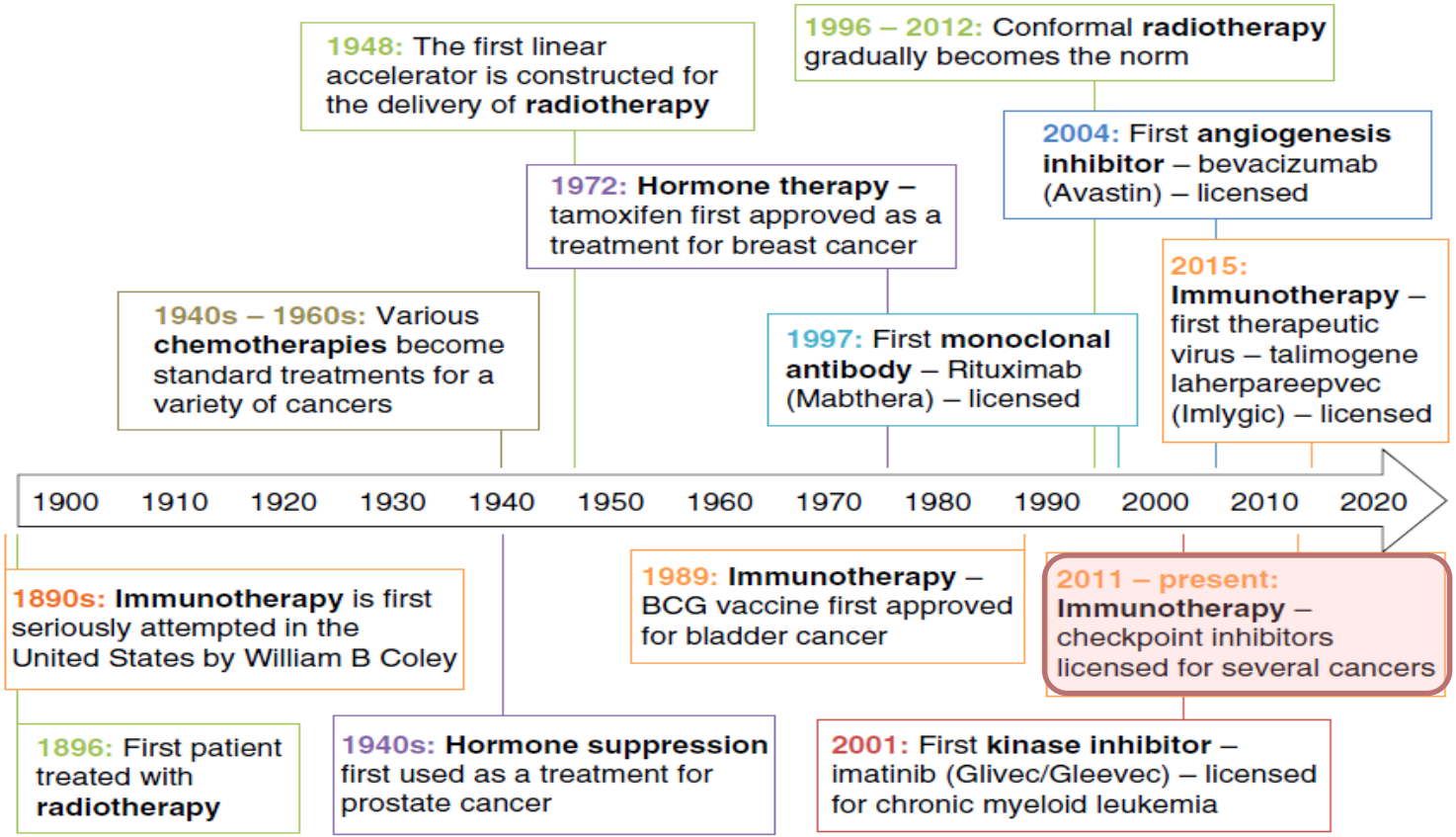
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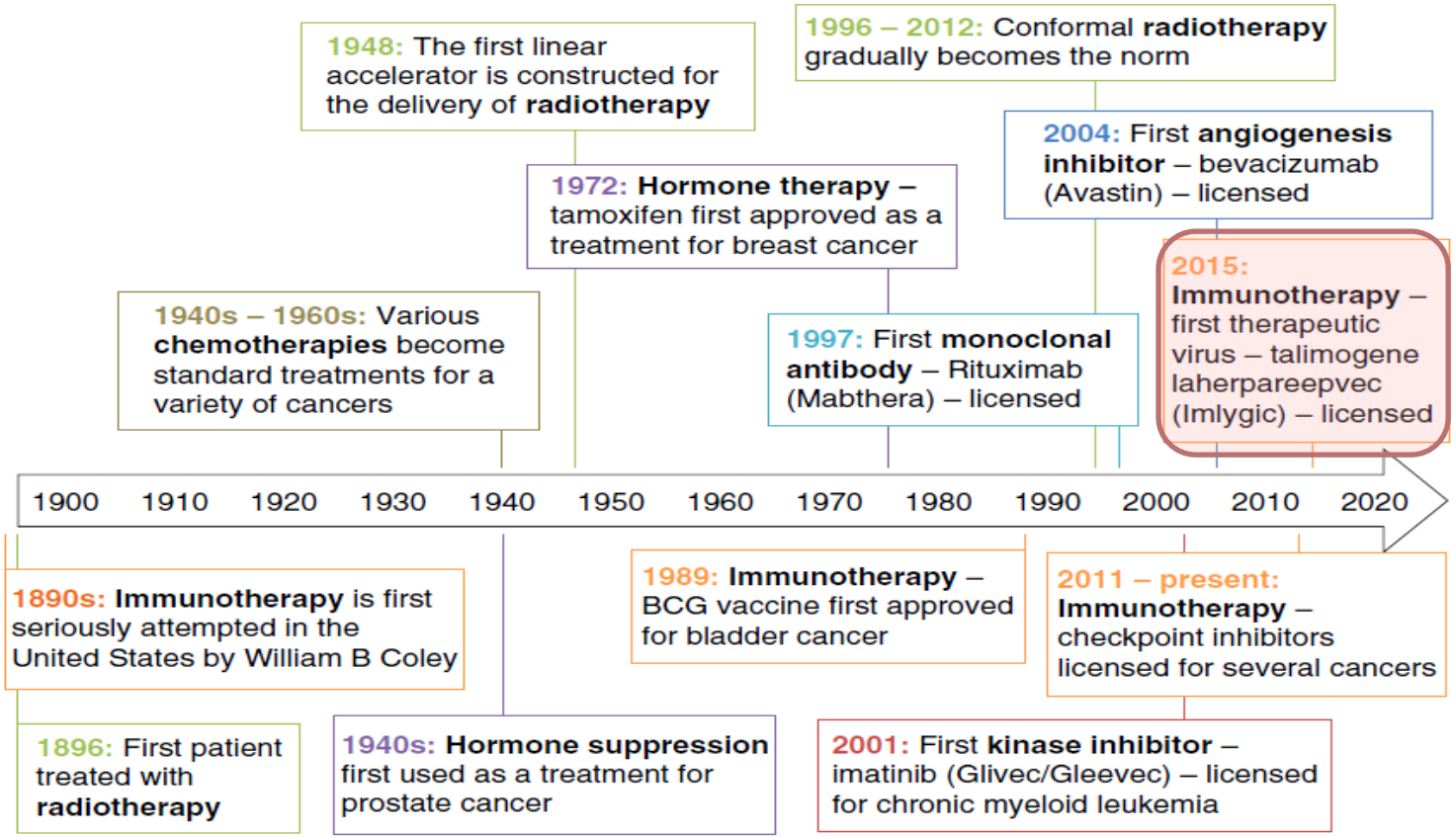
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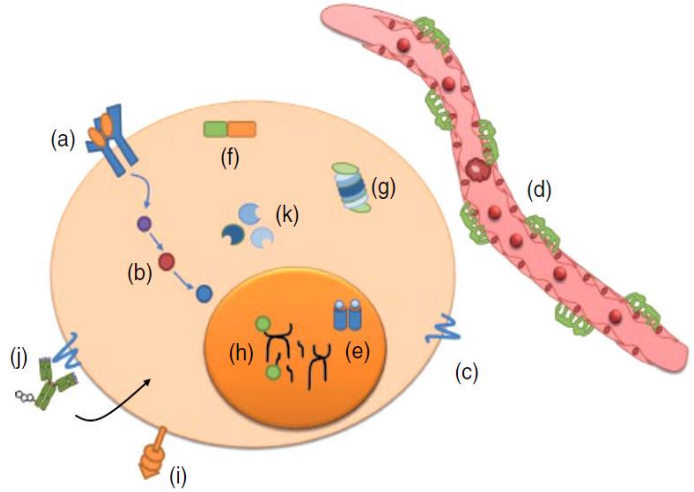
Targets of Targeted Cancer Treatments



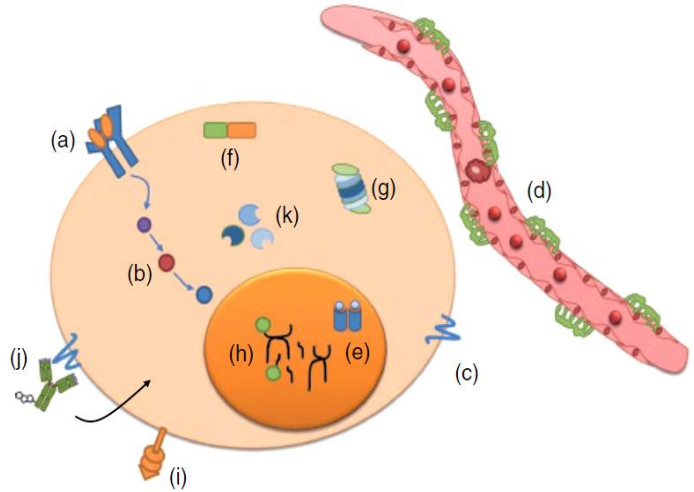
a. Target Cell Surface Proteins known as growth factor receptors

b. Get inside cancer cells and block kinases

c. Target CD antigens

d. Block angiogenesis

Targets of Targeted Cancer Treatments



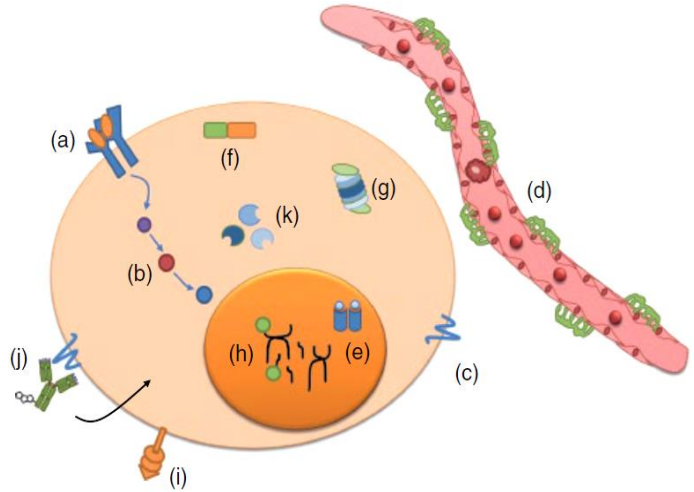
e. Block hormone receptors in nucleus or cytoplasm

f. Block fusion proteins

g. Block proteasomes

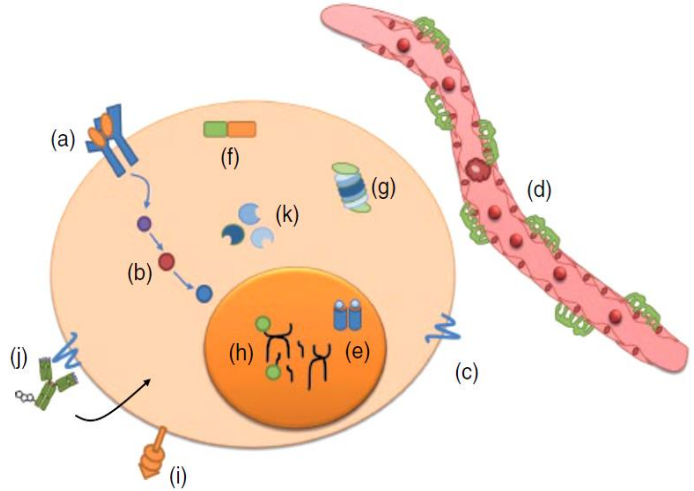
h. Take advantage of some cancer cells' inability to accurately repair DNA damage

Targets of Targeted Cancer Treatments



i. Overcome cancers' ability to suppress the patients' immune system. These treatments create or trigger an immune response against cancer cells and they are called **IMMUNOTHERAPIES.**

Targets of Targeted Cancer Treatments



j. Deliver chemotherapy, radiotherapy, or toxins directly to cancer cells

k. Overcome cancer cells resistance to apoptosis

Should All Antibody-based Cancer Treatments Be Classed As Immunotherapies

- Perpetual area of confusion

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- Some monoclonal antibodies directly bind to the cancer cells to kill them
- Because they're targeting specific receptors in the cells, these monoclonal antibodies are referred to as targeted therapies
- Trastuzumab: attaches to a protein HER2
- Rituximab: attaches to a protein CD20

Should All Antibody-based Cancer Treatments Be Classed As Immunotherapies

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- Trastuzumab: attaches to a protein HER2
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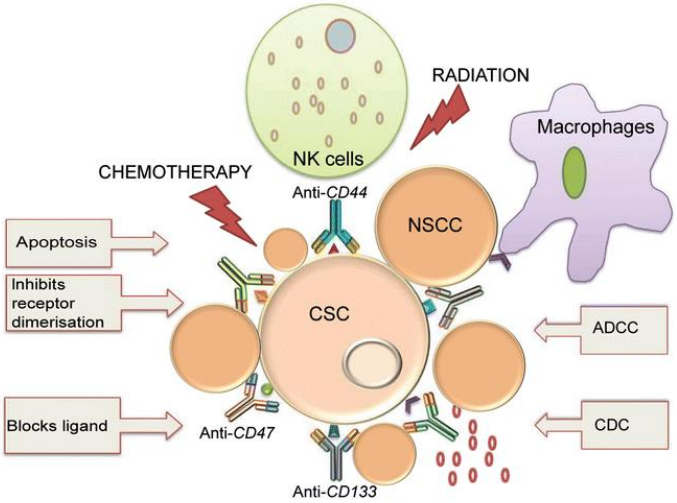
- Other monoclonal antibodies help improve the immune system's response to cancer cells. These drugs are known as immunotherapy
- Nivolumab: attaches to a protein PD-1 found on activated T cells, preventing its attachment to PD-L1 & PD-L2 thereby preventing T cell suppression

How do Monoclonal Antibodies Induce Cytotoxicity in Target Cells



ADCC : antibody dependant cellular cytotoxicity
CDC: complement mediated cytotoxicity
NK cells: natural Killer cells
CSC: cancer stem cell
NSCC: non stem cancer cell

Antibody-dependent cell-mediated cytotoxicity (ADCC)

An effector cell (eg, natural killer [NK] cells, monocytes, macrophages) recognizes the antibody bound to the target cell through Fc receptors and destroys the target cell

Complement-dependent cytotoxicity (CDC)

Antibody bound to the target cell activates the complement cascade via the classical pathway, ultimately leading to the formation of the membrane attack complex and lysis of the cell

Direct killing

Binding of antibody to the epitope on target cells leads to transmission of intracellular signals resulting in apoptosis or programmed cell death

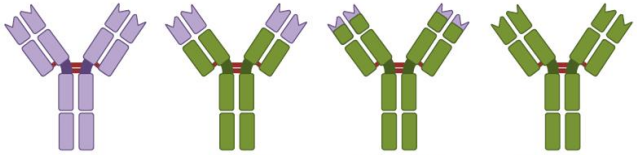
Limitations & Adverse Effects of Antibody Treatment

- Allergy type reactions: antibodies used are foreign to body
- Antibodies are large proteins -> cannot cross cell membrane. Target must be on the cell surface
- Cannot reach all body tissues because of large size
- Digested by gut enzymes and degraded by stomach acid
- Poor penetration and heterogeneous distribution in solid tumors
- Target proteins also present on healthy cells: adverse effects

Nomenclature of mAbs

Flowchart of How Monoclonal Antibodies Are Named

1. Prefix unique to drug				
2. Target/ disease class	-tu-, -t- = tumor	-li-, -l- = immunomodulator	-ki-, -k- = interleukins	-ne-, -n- = neurons as target
	-so-, -s- = bone	-ci-, -c- = circulatory system	-vi-, -v- = antiviral	-ba-, -b- = bacterial
	-gro-, -gr- = growth factor	-tox-, -toxa- = toxin	-fu-, -f- = fungus	
3. Antibody source	-o- = mouse (100% foreign)	-xi- = chimeric (~75% human/~25% foreign)	-zu- = humanized (~95% human/~5% foreign)	-u- = human = fully human (100% human)
4. Suffix = mab				



mouse	chimeric	humanized	fully human
tositumomab	cetuximab	trastuzumab	panitumumab
ibritumomab	rituximab	bevacizumab	ofatumumab
		pertuzumab	nivolumab
		pembrolizumab	durvalumab
		atezolizumab	

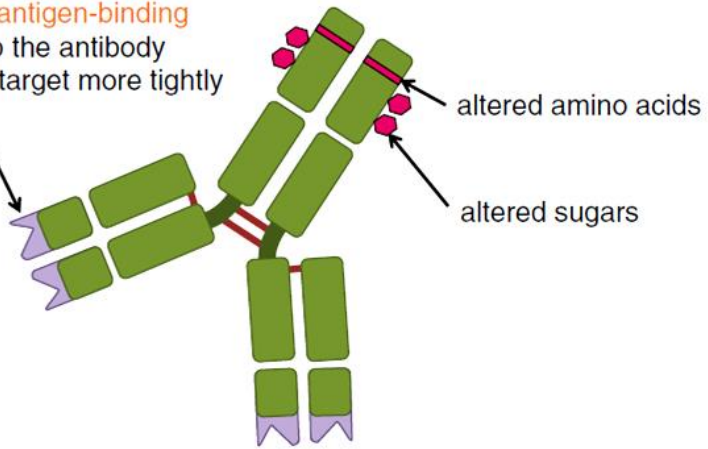
How to Improve Monoclonal Antibody Cancer Treatments

- Making it less foreign: more humanized
- Making slight tweaks: altering the structure
- Creating antibody conjugates
- Complete reconstruction

Making Slight Tweaks

Modifying the back-end of the antibody can make the antibody more visible to white blood cells and more able to attract complement proteins

Altering the antigen-binding site can help the antibody attach to its target more tightly



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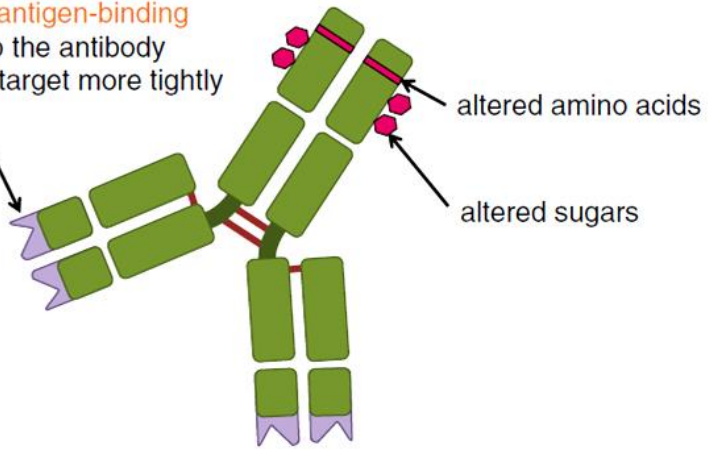
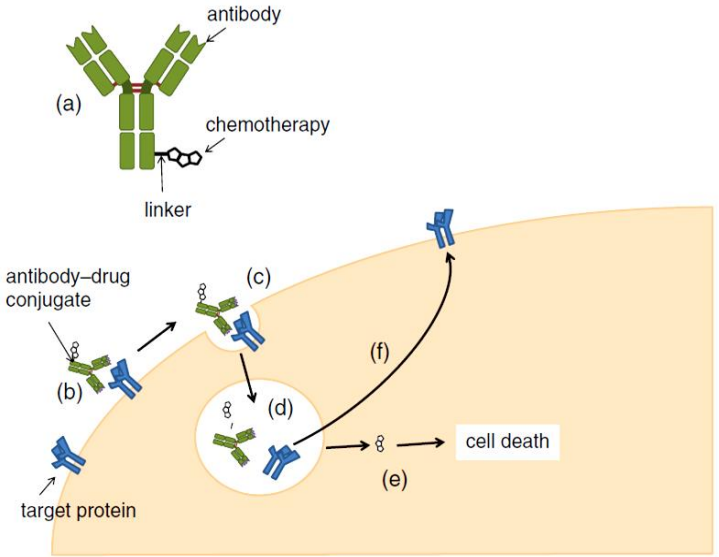


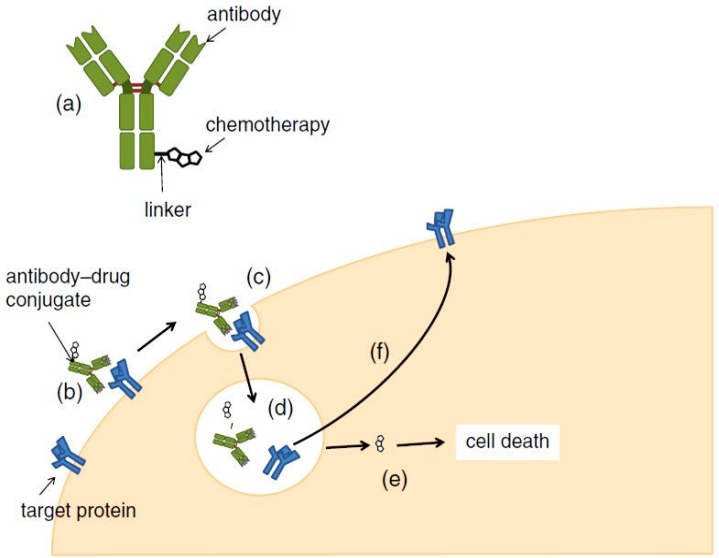
FUCOSYLATION

Creating Antibody Conjugates



a. ADC
b. Attachment
c. Engulfment
d. Biodegradable Linker breakage
e. Release of payload
f. Recycling

Creating Antibody Conjugates



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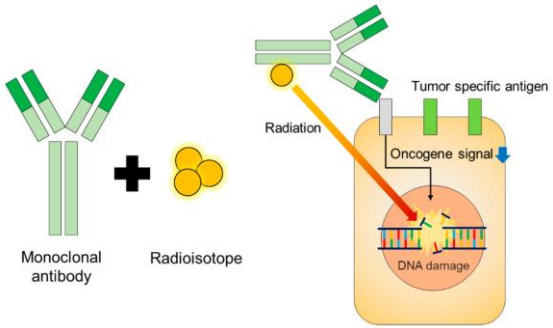
eg

1. Ado-trastuzumab emtansine (Kadcyla®)
2. Brentuximab vedotin (Adcetris®)
3. Gemtuzumab ozogamicin (Mylotarg®)
4. Inotuzumab ozogamicin (Besponsa®)

Creating Antibody Conjugates: Radioimmunoconjugates



- Radioconjugates targeting CD20 on lymphomas have been approved for use

1. Ibritumomab tiuxetan [Zevalin®] using Yttrium-90
2. 131I-tositumomab [Bexxar®]: Approved in US only

- These agents may be especially helpful in bulky tumors or those that are poorly vascularized

- Lutetium Lu 177 dotatate (Lutathera®) is a radiolabeled somatostatin analog for neuroendocrine tumors.

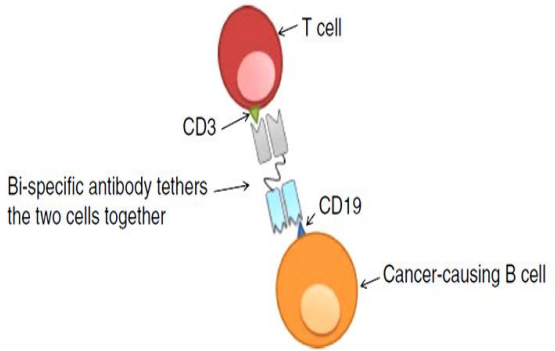
Complete Reconstruction
Concept of Bi-specific Antibodies

- Bispecific antibodies (BsAbs)
  two binding sites directed at
  * two different antigens or
  * different epitopes on the same antigen
  (back to back fusion of Fv)

- Clinical therapeutic effects of BsAbs are superior to those of monoclonal antibodies

- Why NOT join two complete antibodies:

1. Difficult to manufacture
2. Get stuck in vessels (enormous size)



Blinatumomab

The goal of blinatumomab is to draw together the two cell types and compel the T cell to destroy the B cell

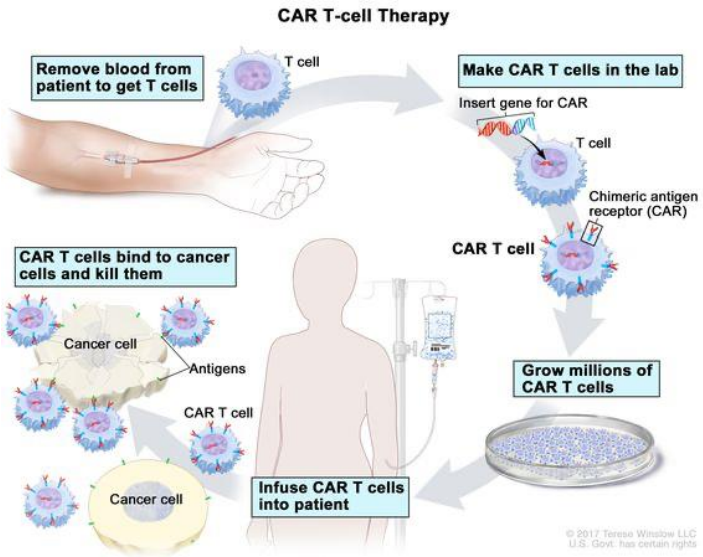
CAR T Cell Therapy

- **Create genetically modified T cells that**

1. Would never otherwise exist in patient
2. Attach to one particular protein on cancer cell
3. Directly activated: further signal not required
4. Leukemia, Lymphoma, Multiple Myeloma

CURRENTLY APPROVED:

- Tisagenlecleucel (Kymriah)
- Axicabtagene ciloleucel (Yescarta)
- Brexucabtagene autoleucel (Tecartus)
- Lisocabtagene maraleucel (Breyanzi)
- Idecabtagene vicleucel (Abecma)
- Ciltacabtegene autoleucel (Carvykti)



Generics, Biologics, Biosimilars

- Generics: manufactured through chemical synthesis
- Biologics: one or more active principles produced or derived from a biologic source
- Biosimilars: Biosimilars are medicines manufactured through biotechnology and which have demonstrated their equivalence in quality, efficacy and safety to the reference product
- Biologics: goal of trials is to ascertain the clinical efficacy of the product.
- With biosimilars the goal is to demonstrate that the product is comparable to the reference biologic product in terms of its pharmacokinetics, pharmacodynamics, safety and immunogenicity

Originator development

Main objective to demonstrate product efficacy

CLINICAL

PK/PD

PRE-CLINICAL

ANALYTICAL

CLINICAL

PK/PD

PRE-CLINICAL

ANALYTICAL

Biosimilar development

Main objective to determine comparable pharmacokinetic, pharmacodynamic, safety and immunogenicity against the reference product

mAbs: Practical Tips

- Not metabolized via cytochrome p450: No drug interaction
- No renal or hepatic metabolism/elimination; therefore no dose adjustments necessary
- Metabolized by Reticuloendothelial system
- Ado-trastuzumab emtansine is classified as an irritant
- Other monoclonal antibodies are classified as non-vesicants and non- irritants
- Low emetogenicity

Small Molecules

- The two main approaches of specific molecular targeting available for use in clinical practice are small molecule agents and monoclonal antibodies (mAbs)

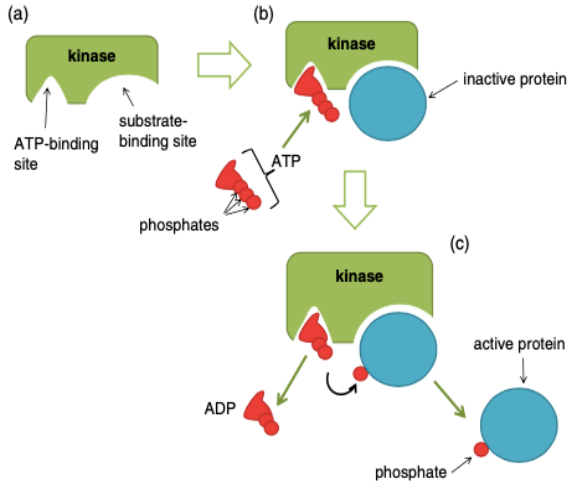
- mAbs: large molecular weight proteins of around 150kDa
- Small molecule: much smaller in size (≤500Da), translocate through plasma membranes

- Cancer is a “miscommunication” disease, initiation and further progression of cancer relies on over activation of various extrinsic and intracellular signalling pathways.

Small Molecules

- Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor
- Vascular Endothelial Growth Factor (VEGF) Receptor
- Mitogen-Activated Protein Kinase (MAPK)
- Anaplastic Lymphoma Kinase (ALK)
- B-Cell Receptor-ABL (BCR-ABL)
- Isocitrate Dehydrogenase and Ten-Eleven Translocation
- Bruton Tyrosine Kinase (BTK)
- Janus Kinase/Signal Transducer and Activator of Transcription (JAK STAT)
- FMS-Like Tyrosine Kinase 3 (FLT 3)
- Type I and Type II Tyrosine Kinase Inhibitors (TKI)

Kinases are Catalysts that Attach Phosphates to other Proteins

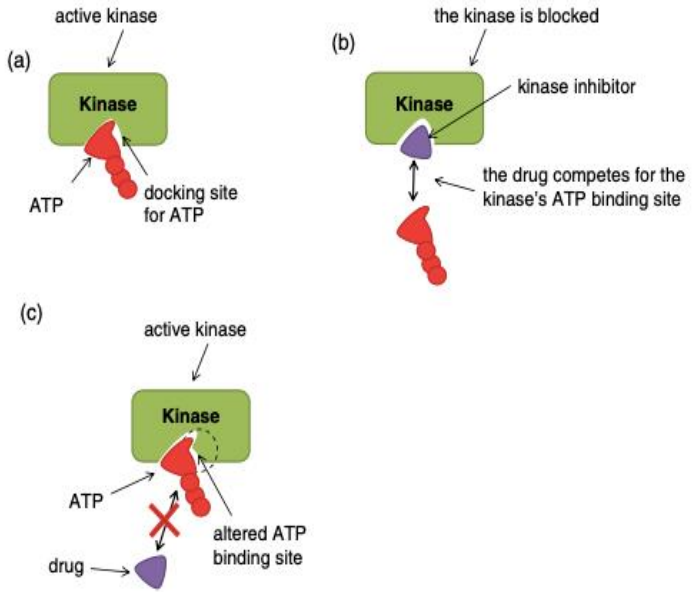


a. Docking sites for both ATP & substrates

b. Both ATP & substrate dock with kinase

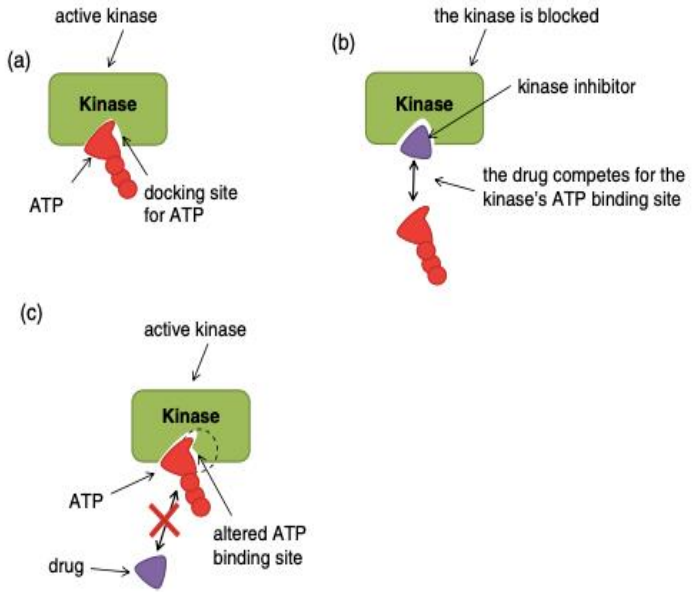
c. One phosphate transferred from ATP to substrate by kinase activating it

Most Kinase Inhibitors Work By Mimicking the shape of ATP



Most Kinase Inhibitors Work By Mimicking the shape of ATP

All kinases have a binding site for ATP. When the kinase is activated, the ATP binding site becomes accessible and ATP enters.
The kinase is then able to phosphorylate its targets



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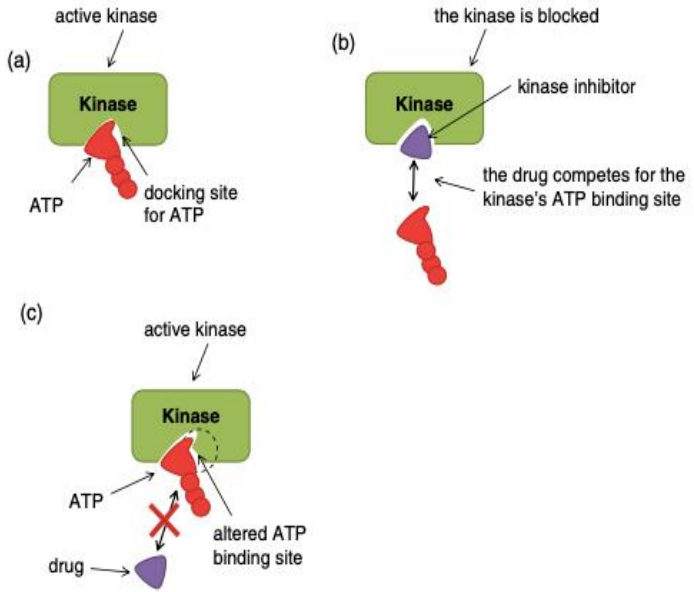
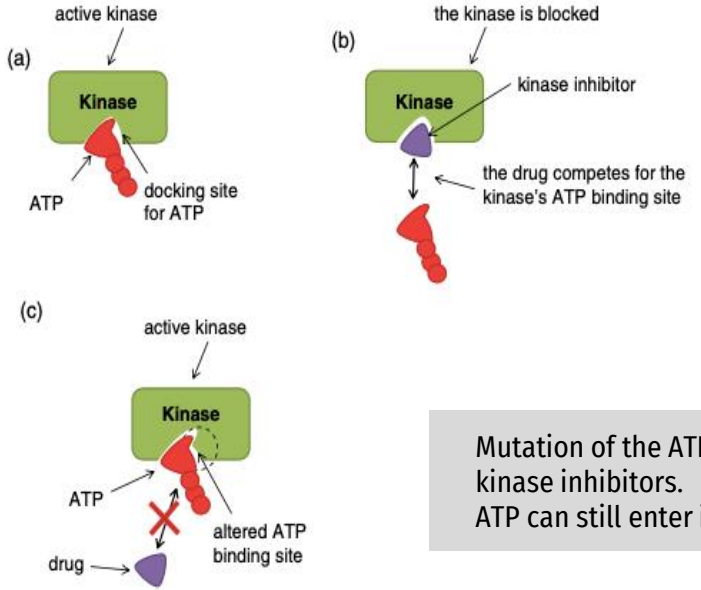


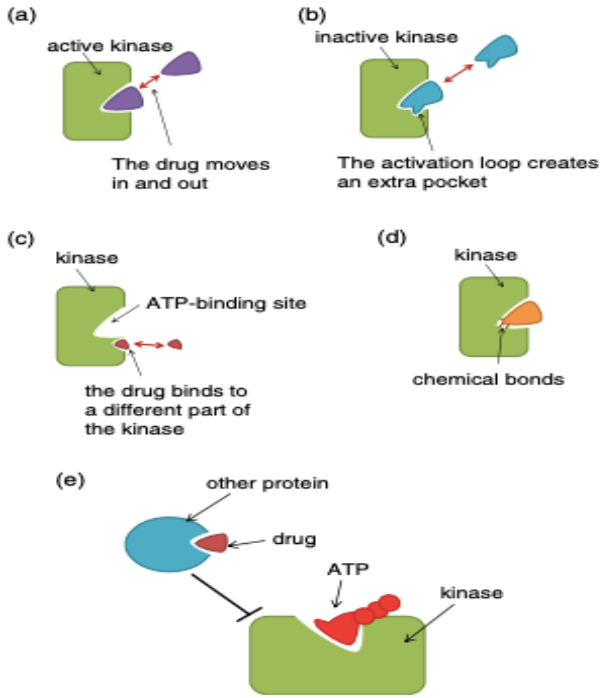
Kinases can be blocked by drugs that mimic the shape of ATP & that compete with ATP for the kinase' ATP binding site

Most Kinase Inhibitors Work By Mimicking the shape of ATP



Mutation of the ATP binding site leads to resistance to kinase inhibitors.
ATP can still enter its binding site though

The 4 Classes of Kinase Inhibitors & the Indirect Inhibitor

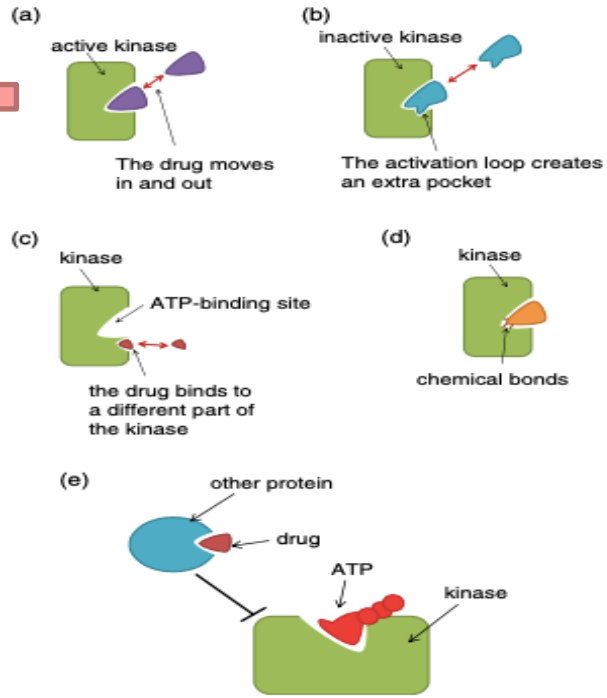


The 4 Classes of kinase Inhibitors & the Indirect Inhibitor

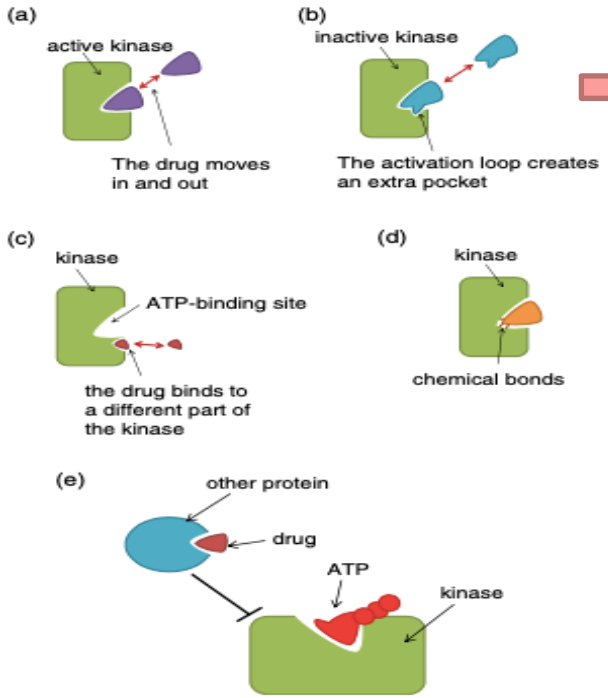
Type 1 Kinase Inhibitor

Reversible
Competes with ATP
Low Selectivity

Gefitinib
Erlotinib
Sunitinib



The 4 Classes of kinase Inhibitors & the Indirect Inhibitor

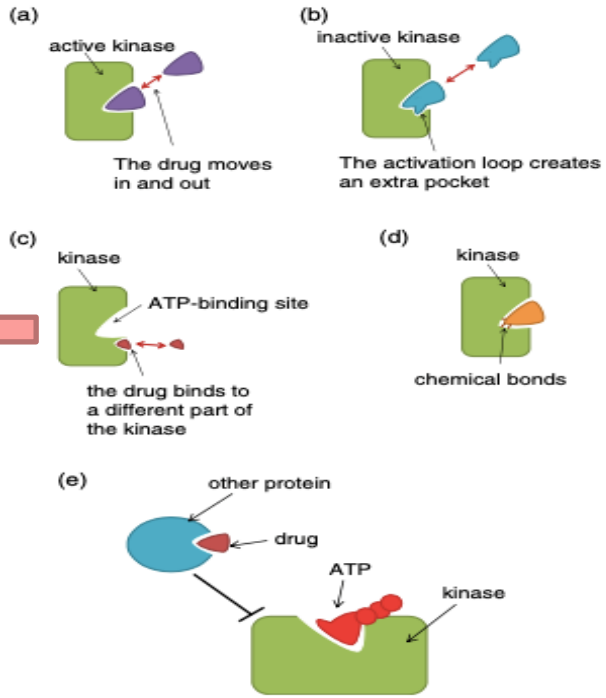


Type 2 Kinase Inhibitor

Reversible
Doesn't Competes with ATP
Medium Selectivity

Imatinib
Nilotinib
Sorafenib

The 4 Classes of kinase Inhibitors & the Indirect Inhibitor

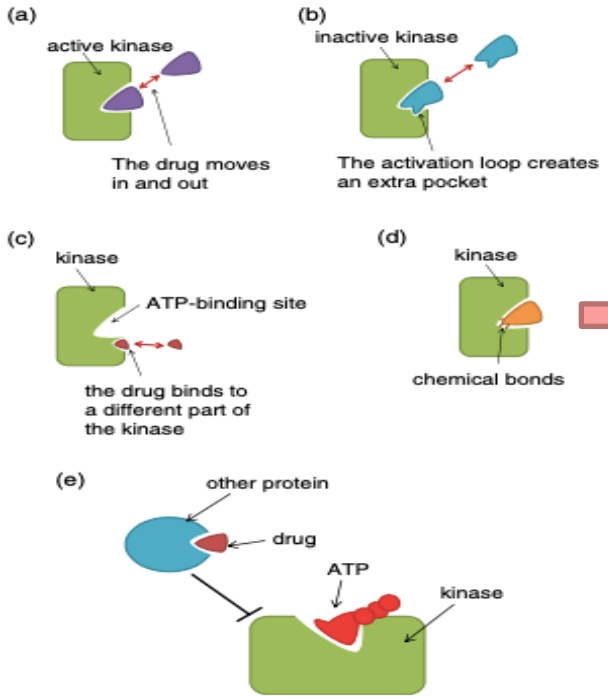


Allosteric Inhibitors

Reversible
Site away from ATP site
Do not compete with ATP
High selectivity

Trametinib
Cobemitinib
Selumetinib

The 4 Classes of kinase Inhibitors & the Indirect Inhibitor

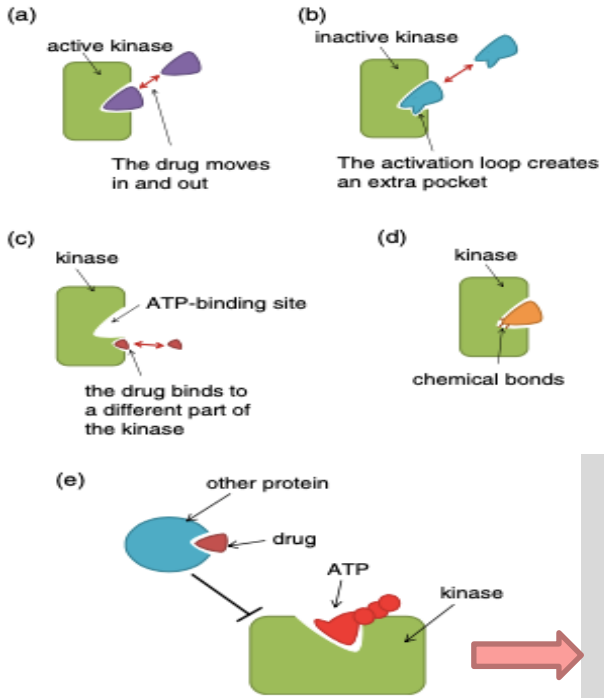


Covalent Inhibitors

Irreversible Binding
Competes with ATP
Low Selectivity

Afatinib
Dacomitinib
Neratinib

The 4 Classes of kinase Inhibitors & the Indirect Inhibitor



Indirect Inhibitor

No physical interaction with Kinase
Work via another Protein

Rapalogues

Common Targets of Kinase Inhibitors

Kinases are very popular with drug companies

1. Lots of kinases are implicated in cancer
2. Companies have become very adept at creating such drugs

- Multitude of drugs commercially available
- May be grouped into 3 category of kinases that have gone wrong

Cat 1.
Overactive Because of Abnormally High Levels or Faulty Gene Mutations

- B-Raf, EGFR, ALK, Bcr-Abl, JAK2, Her-2, FLT-3, KIT, PI3K, AKT, MET, RET
- Powerful, Oncogenic

Cat 1.
Overactive Because of Abnormally High Levels or Faulty Gene Mutations

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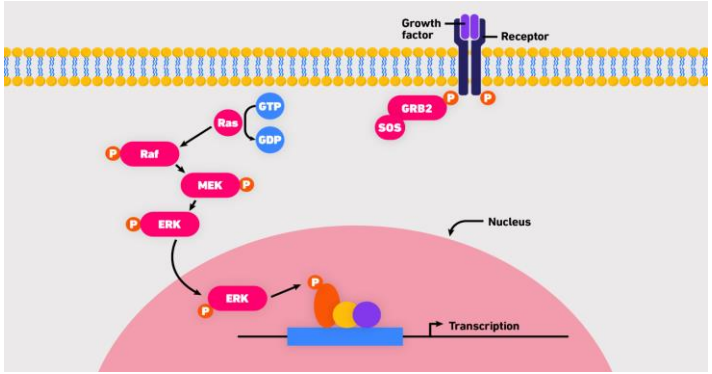
Oncogene Addiction

The cell cannot survive without faulty kinases' activity

Cat 2.
Kinases overactive because of Mutation Affecting another Protein but Kinases themselves are not abnormal

- K-ras, N-ras, H-ras
- Useful drugs when protein at fault is not targetable



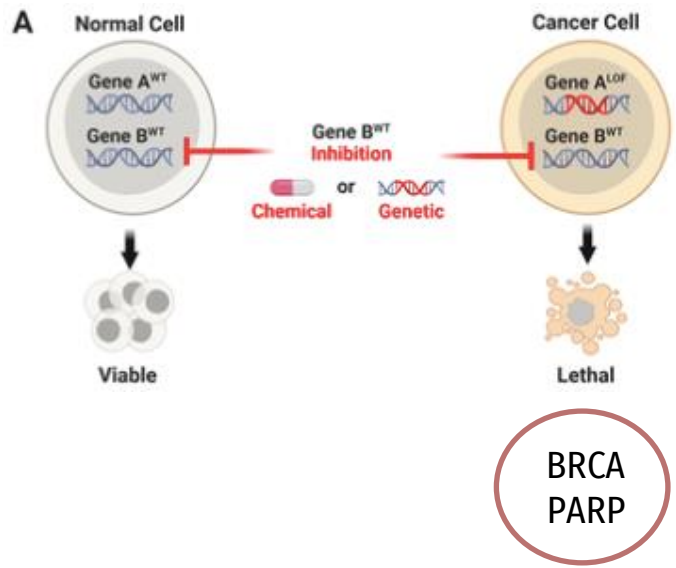
- Ras isn't a kinase, few drugs launched recently
- Ras proteins force cells to multiply via activating kinases
- By blocking these kinases, you can kill cancer cells with faulty Ras proteins (Synthetic Lethality)

Synthetic Lethality

Lethal combination of a mutation in one protein, and a drug that targets another protein

Describes a situation in which mutations in two genes together result in cell death, but a mutation in either gene alone does not.

Cancer cells that only have one mutated gene in a specific pair of genes can depend on the normal partner gene for survival. Interfering with the function of the normal partner gene may cause cancer cells to die



Cat 3.
Kinases found in/on non-cancer cells in the cancer's microenvironment

- VEGF, PDGF, FGF receptors

- They are growth factor receptors found on the surface of endothelial cells that line the blood vessels, necessary for tumor angiogenesis

Useful Properties of Kinase Inhibitors in Cancer Treatment

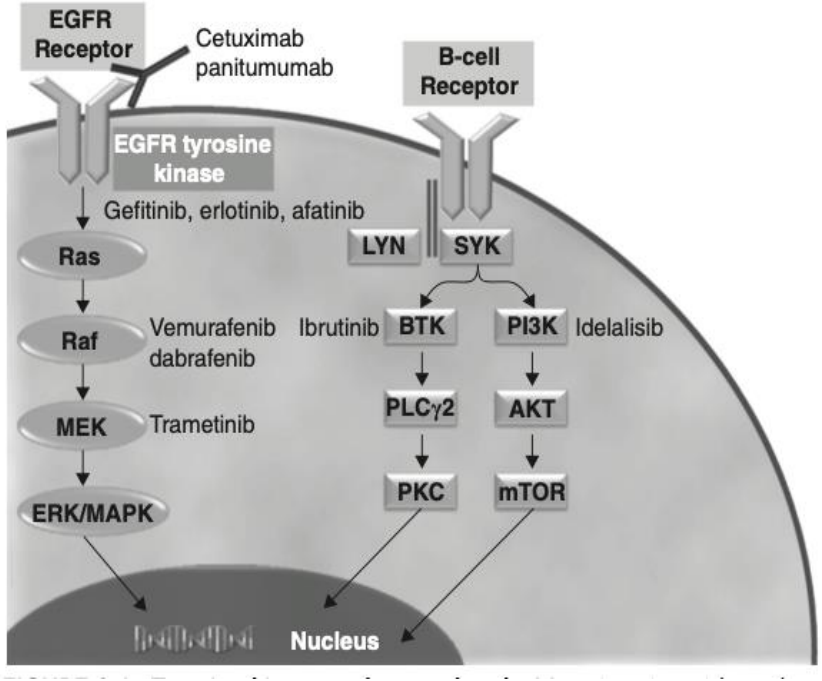
- Kinase inhibitors can block kinases that are driving the growth and survival of cancer cells
- Small size -> Cross cell membrane, inaccessible to Mab -> Block intracellular kinases
- kinase inhibitors can travel around the body and through our organs and tissues much more easily than mAbs. (Can cross blood-brain barrier)
- Chemical compound: can be taken in tablet form
- Can block multiple kinases: more potent

Limitations of Kinase Inhibitors

- Very imprecise compared to antibody treatment (esp. Type 1)
- Drugs target present in healthy cells: greater adverse effects
- Drug resistance (mutations altering shape of ATP-binding site)
- Broken down in body very quickly: daily/ twice daily treatment
- High degree of drug to drug and patient to patient variation: difficult to find optimum dose

Tyrosine Kinase & Monoclonals: Mechanism of Action

Mutations in epidermal growth factor receptor (EGFR) and BRAF lead to hyperstimulation of the EGFR-Ras-Raf-MEK-ERK/MAPK pathway resulting in hyperproliferation, reduced apoptosis, and increased invasiveness/ metastatic potential of cancer cells



The B-cell receptor is activated by both antigen-dependent and antigen- independent signalling. Overactivation of the Src family kinases (Lyn and Syk), BTK, PLCγ2, PI3K, and other signalling molecules and cascades lead to many cellular processes occur such as proliferation, motility, homing, adhesion, chemotaxis, and survival

Take Home

- Monoclonal Antibodies & Kinase Inhibitors

1. Physically very different: Block the same target
2. Hence overlapping set of uses & adverse effects
3. Additionally MABs attract WBCs & generate immune response
4. MABs: large size, cannot cross cell membrane but incredibly precise

Take Home

- Monoclonal Antibodies & Kinase Inhibitors

1. Small size of kinase inhibitors an advantage: penetrates cell cytoplasm
2. Also blocks intracellular targets

3. Blocks many kinases
   Adv: Boost impact on tumor
   Disadv: Adverse effects

Thanks!

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