Treatment of Cancer – Chemotherapy, Surgery, Radiation and Immunotherapy…

If we only had enough time

1

Cancer

There is a crabgrass illustration – where you find a batch of crabgrass in a beautiful yard… what do you do?

- Cut it – Surgery
- Burn it – Radiation
- Poison it – Chemotherapy

The best approach is to know what caused the crabgrass (it is a kind of grass) and treat it specifically – "Personalized Medicine or Molecular/Targeted Therapy"

2

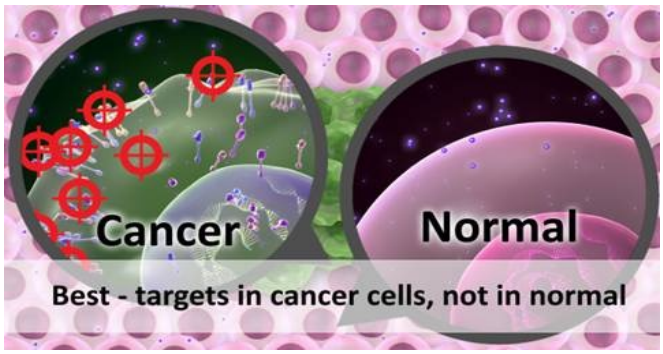
Aim of Therapy

Cure, Control and/or Relieve the symptoms

- **Neoadjuvant chemotherapy**: Before surgery or radiation – to shrink tumor making it more effectively treated or removed
- **Adjuvant chemotherapy**: treated after surgery or radiation – To deal with undetected cells, microtumors…
- **Palliative chemotherapy**: To treat patient and reduce symptoms – improve quality of life, not treat underlying cause or curative

3

Cancer Targets



From National Cancer Institute, US National Institutes of Health.

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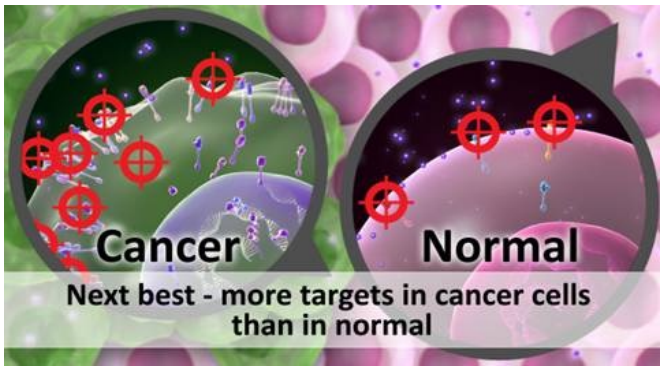
Cancer Targets



From National Cancer Institute, US National Institutes of Health.

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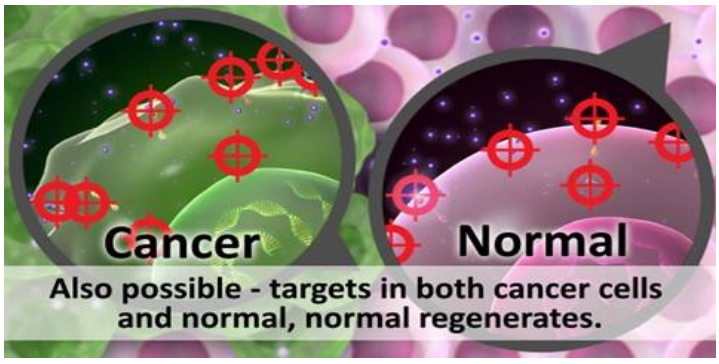
Cancer Targets



From National Cancer Institute, US National Institutes of Health.

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Targets

- The targets currently being used are those that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression.
- The focus is on proteins that are involved in cell signaling pathways, which form a complex communication system that governs basic cellular functions and activities, such as cell division, cell movement, how a cell responds to specific external stimuli, and even cell death.

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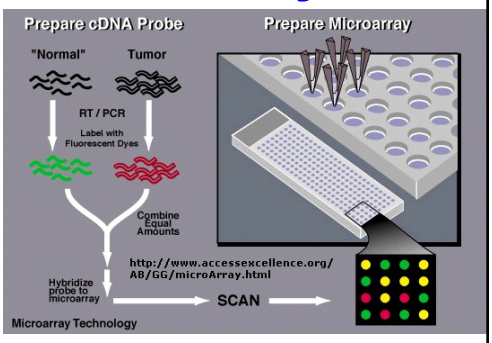
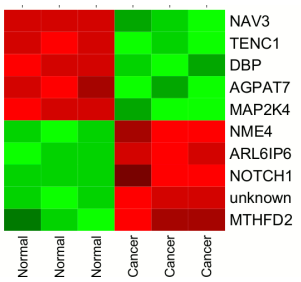
Gene Expression Arrays

- Powerful detection of what proteins (mRNA) is expressed. Like doing thousands of western blots. Can analyze entire genome!
- If a gene is not expressed in either tissue, the spot will appear black. Genes expressed only in tumor tissue will be red, while control only green. Those in both will be a combination
- Heat maps are used to analyze large sets of these data





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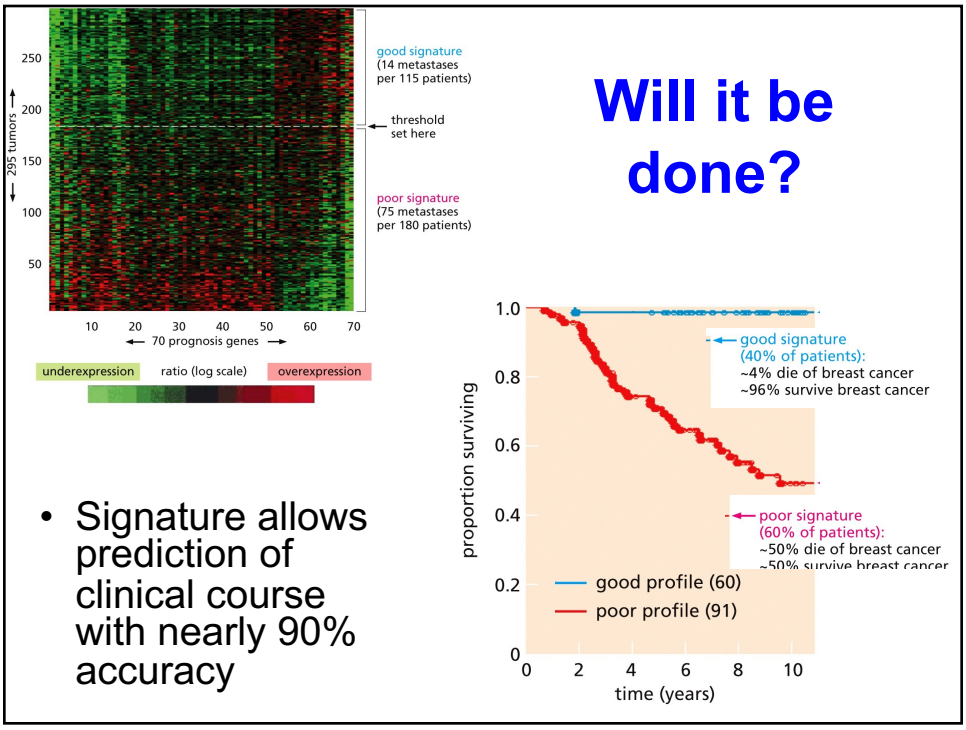

- Signature allows prediction of clinical course with nearly 90% accuracy

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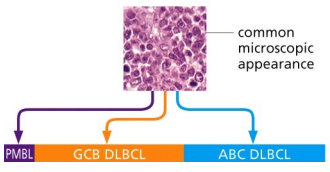
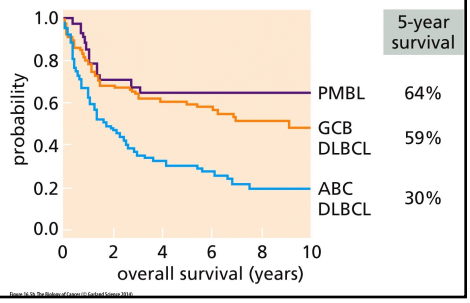
B Cell lymphoma

Common histopathology, yet – some patients die within weeks of diagnosis while others achieve 10-year remission without clinical symptoms.

Three diffuse large B-cell lymphoma (DLBC) diseases each with different clinical outcomes

- Activated B Cell Lymphoma (ABC)
- Primary Mediastinal B-cell lymphoma (PMBC)
- Germinal-center B-cell-like lymphoma (GCB)





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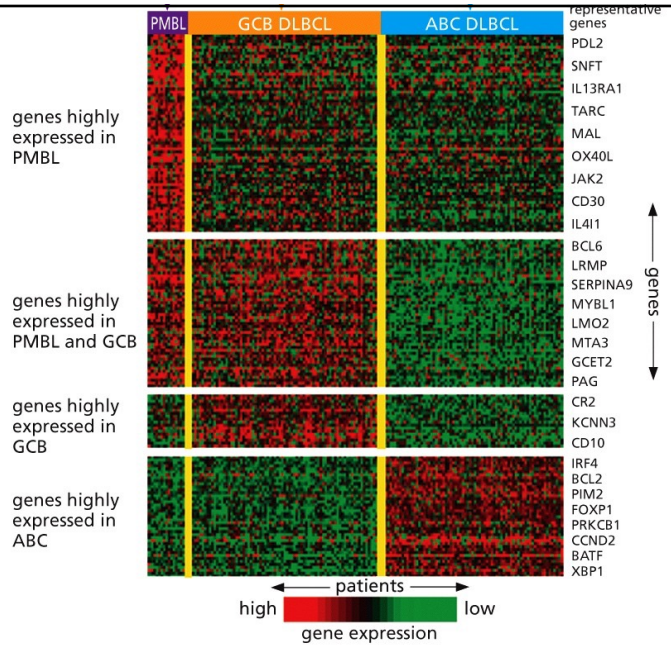

- **Use of microarray helps to divide undistinguishable DLBCL tumors based on expression of oncogenes, tumor suppressor, apoptosis, proteases and EMT genes**

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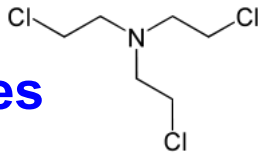
Traditional – most common chemotherapies



WWII mustard gas – origins of several chemotoxins

- 1943 bombing of American warship containing mustard gas in Bari Italy Harbor resulted in loss of bone marrow cells in survivors. Later related studies at Yale (Gilman and Goodman) showed cytoxic effects of the gas killed neoplastic cells sparing most normal tissues.
- Mechanism – alkylation of N on guanine and interstrand cross-links forcing cell into … apoptosis AND block uncoiling/relaxing necessary for replication during cell cycle

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Classification of Chemotherapy Drugs

Categorized into mechanism, structure and relationship to similar drugs. Some drugs fall into more than one category

- **Alkylating Agents** – directly damage DNA
- **Antimetabolites** – alter metabolic function directly and indirectly (altering gene expression)
- **Anti-Tumor Antibiotics** – Altering DNA (not alkylating) to block cell cycle progression
- **Topoisomerase Inhibitors** – Prohibit unraveling of chromosomes for replication during S phase
- **Mitotic Inhibitors** – often plant alkaloids, disrupt mitosis and cell cycle, often by altering cytoskeletal proteins involved in dividing mitotic spindles
- **Corticosteroids** – often glucocorticoids which reduce inflammation involved in support of some cancer types. Also serve to reduce pain, nausea and vomiting as a positive side effect

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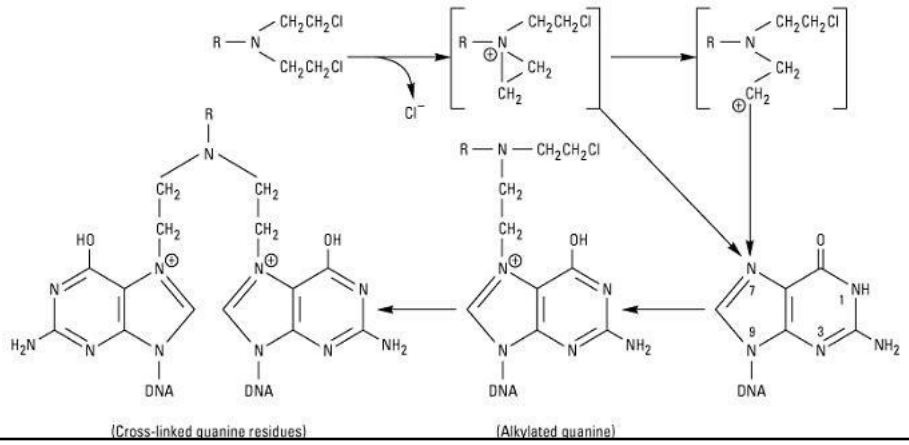
Alkylating Agents

Direct transfer of an alkyl group (R-C_nH_{2n+1}) to DNA – typically a N atom on guanine base leading to cross-linking between strands



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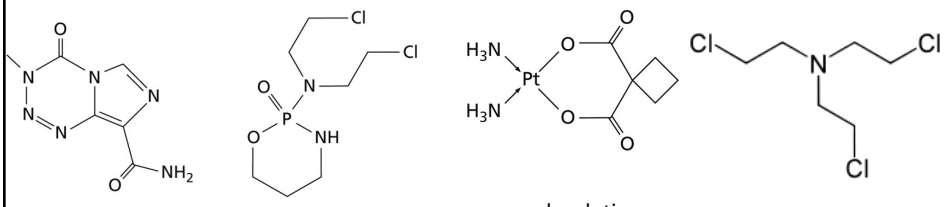
Mechanism of Alkylation

- Alkyl groups forms covalent bonded carbon atom – in DNA to N7 of purines. Form via carbonium ion or carbon radical.
- Nucleophilic alkylation: Organometalic compounds contribute to electron-deficient carbon atoms - often involve halide substituents on a carbon atom.
- Electrophilic alkylation: Alkyl halides with lewis acid catalyst – can react directly with amines (guanine N) to form C-N bonds. Attack on nucleophilic atoms/functional groups include amino, sulfhydrile and nitrogen of guanine



temozolomide | cyclophosphamide | carboplatin

alkylating | alkylating-like | Mustard

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DNA Damage

Because cancer cells (especially short-lived leukocytes) replicate faster, cancer cells are more sensitive to alkylated DNA damage.

- leukemia, lymphoma, Hodgkins disease, multi myeloma, sarcoma, lung, breast and ovary cancer forms.

- Damage activates Checkpoint kinase 1 (Chk1) and ultimately p53 for apoptosis induction
- Mutations of p53 pathway or apoptosis respond poorly to such chemotoxic agents

There is a significant risk for high dose treatments of bone marrow damage. Rare cases, treatment can lead to leukemia.

- Risk after alkylating agents is highest about 5 to 10 years after treatment
- Considered a "second cancer" not a recurrence – Risk is dose dependent (13,175, 3-year survivors were treated and 55 developed secondary bone cancer) Less than a 0.9% risk of developing secondary cancer within 20 years J Natl Cancer Inst 1996 Mar 6;88(5):270-8

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Three Classes of Alkylating agents

- **Classical Agents** – Nitrogen mustards (mechlorethamine, chlorambucil, cyclophosphamide-cytoxan), Nitrosoureas (streptozocin, carmustine, lomustine), Solfonates (busulfan)…
- **Alkylating Like** – Platinum drugs (cisplatin, carboplatin, oxalaplatin) more likely to cause secondary cancer – leukemia (carcinogenic/mutagenic)
- **Nonclassical** – mixed method of action. Includes: *Dacarbazine* – activated by p450 acts as both a purine analoge inhibiting DNA synthesis, alkalyates and interacts with –SH. *Procarbazine* crosses CNS barrier, inhibits DNA synthesis, RNA and protein synthesis, alkylates and is a monoamine oxidase inhibitor…

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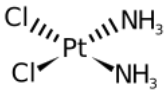
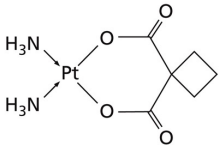
Cisplatin – The Penicillin of Cancer

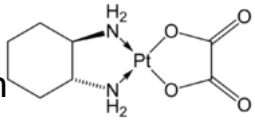
- Widely used – thus the nickname, simple molecule, used for many cancers. Discovered at Mich State as a product of platinum electrodes used for electroysis – NOT patented
- Chloride ions (cisplatin) are displaced by water called aquation which allows platinum to bind to N7 of guanine (purines) as well as intra/interstrand crosslinking
- Nucleophilic substitution, square flat nature of molecule create exchange with other ligands
- Some isomers form mono-adducts which do not crosslink
- Inactivated by glutathione



Cisplatin



Carboplatin



Oxaliplatin

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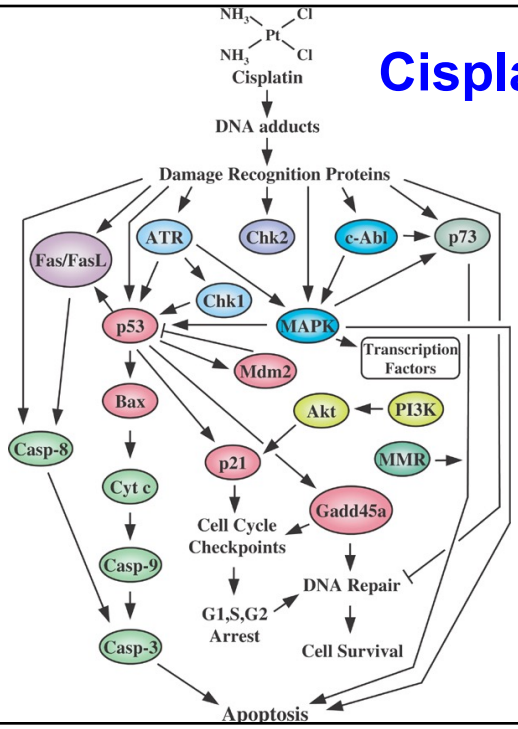
Cisplatin Signaling



- An overview of pathways involved in mediating cisplatin-induced cellular effects. Cell death or cell survival will depend on the relative intensity of the signals generated and the crosstalk between the pathways involved

Oncogene: (2003) 22, 7265-7279 Cisplatin: mode of cytotoxic action and molecular basis of resistance.

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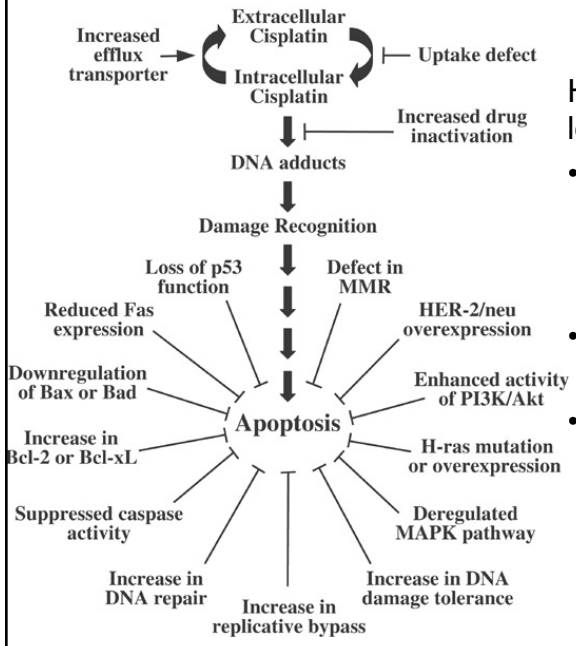
Cisplatin Resistance



Higher doses of Pt drugs leads to resistance:

- Decreased accumulation due to MDR pumps or other inward transporter issues
- Sulfur containing reactions nullify actions
- Some cells gain an enhanced repair mechanism – repair proteins (xeroderma pigmentosum group E binding factor) increases in cisplatin resistance

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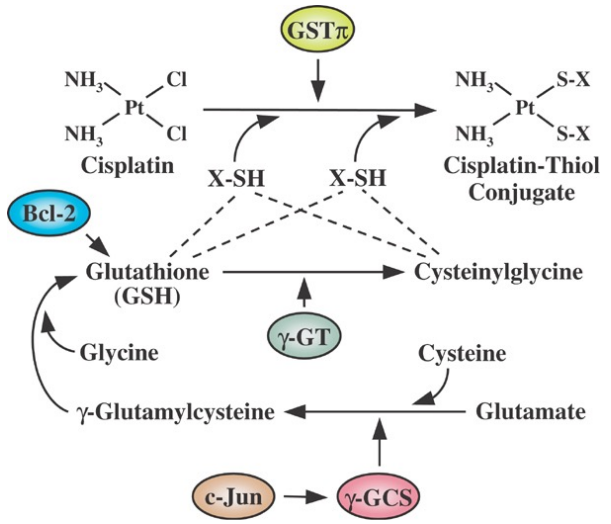
Inactivation of Pt drugs



- Inactivation of cisplatin by glutathione

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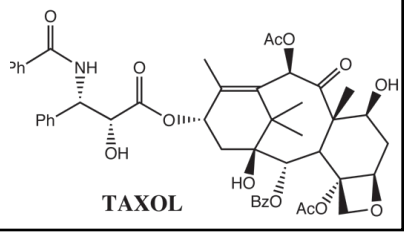
Mitotic Chemotherapy Inhibitors

Often derived from plant alkaloids and block M phase of mitosis (with other damage) blocks the separation and distribution of chromosoms between daughter & mother cell

- Treat range of cancers: breast, myelomas, lymphomas, leukemia, lung
- Examples include: Taxols (paclitaxel), Epothilones (Ixempra), Vinca alkaloids (Velban & oncovin) and Estramustine (Emcyt)



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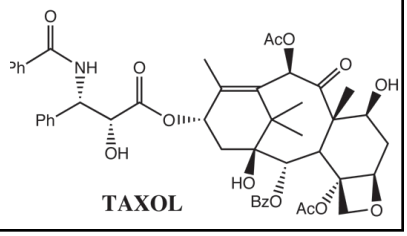
Taxol – natural drug

From Pacific yew tree – one of the sources of the "rainforest can cure cancer" lore…

- USDA researchers paid by the NCI sought natural products to fight cancer (1962)
- Extracts from the bark showed anticancer activity (now
- Difficult to harvest or to synthesize slowed use
- Precursor from a more common plant *Taxus baccata (yew tree) can be converted (semi-synthesis by Brustol-Myers Squibb).*
- *Total synthesis – reported by a number of groups. Complicated and expensive ($6,000 for four cycles of treatment)*



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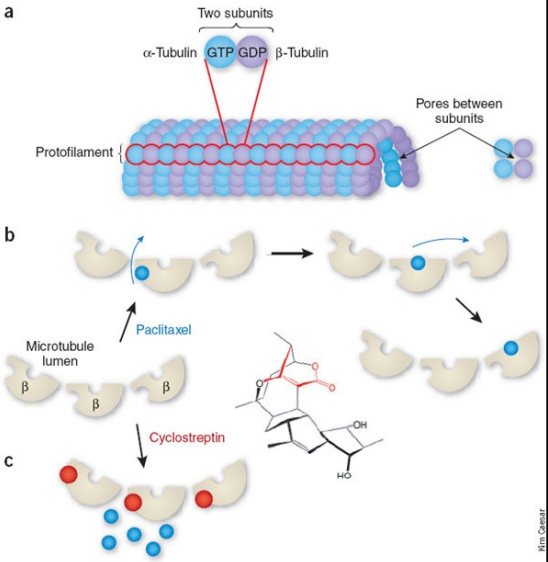
Binding up your cytoskeleton

- Enhances the polymerization of tubulin by interactin directly with the microtubules stabilizing them against depolymerization.
- Blocks G2/M phase transition
- Other mitotic drugs block tubulin assembly



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Antimetabolites–back to the Warburg

- Can interfere with DNA/RNA production or directly with metabolism
- First set of anticancer therapy drugs
- Small molecules – mimic natural metabolite (competitive) and other MM vs regulatory control of metabolism
- Commonly used for many types of cancer
- Typical forms mimic purine/pyrimadine
- Metabolomics is bringing this type of treatment back to the fore

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Cancer & Biomarkers

- Historically most biomarkers were single molecules – these uni-molecule markers lack specificity & sensitivity
- Omics methods offer the ability to measure multiple biomarkers, this improves sensitivity & specificity
- Many metabolite-based cancer biomarkers outperform existing gene or protein biomarkers
- Utility of metabolites is not unexpected

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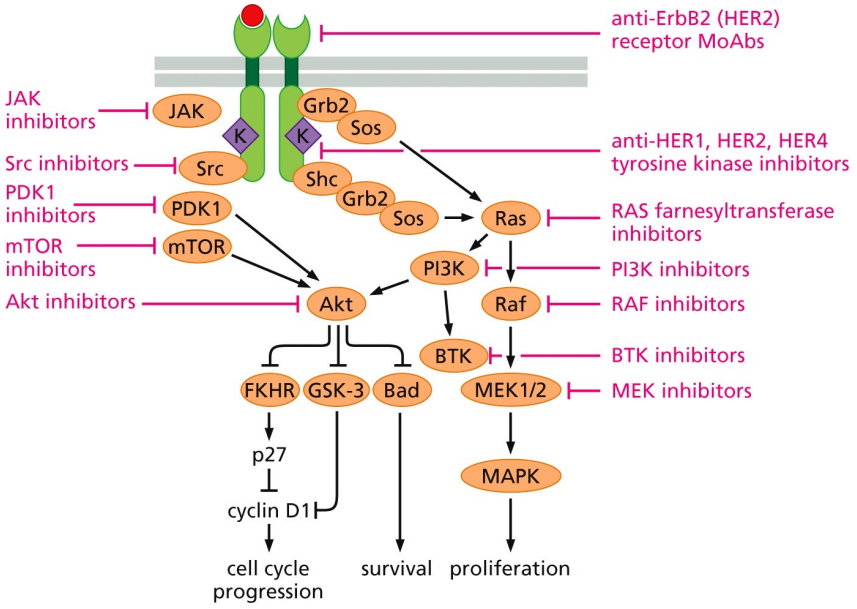
Targeted Therapies



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Kinase inhibitors still dominate

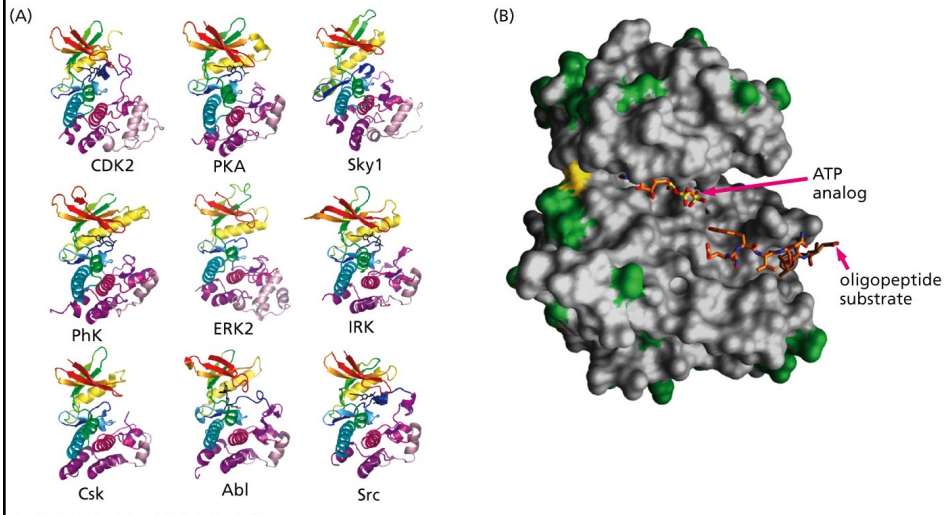

Figure 16.12 The Biology of Cancer (© Garland Science 2014)

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Monoclonal Antibodies

- Another type of targeted therapy – they are large molecules produced through genetic engineering
- They usually have to be given IV
- Side effects can include reactions to non-human proteins
- They can cause cell damage in several ways, most often by attacking cell-surface receptors

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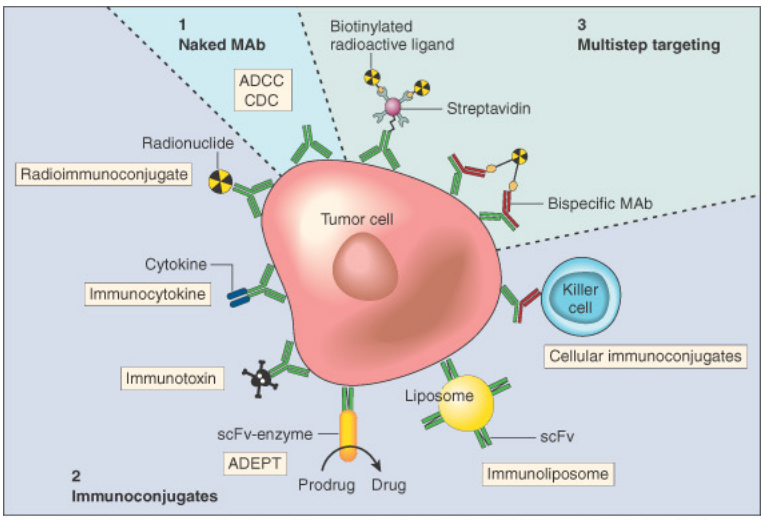

Figure 34-1 • Effector mechanisms of monoclonal antibodies. ADEPT, antibody-directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain variable fragment.

(Modified from Carter P, Improving the efficacy of antibody-based cancer therapies. Nat Rev Cancer 2001;1:118–129.)

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Trastuzumab

- Monoclonal antibody against epidermal growth factor receptor 2 (EGFR2, HER-2)
- Very effective against breast cancers in which HER-2 is "over-expressed" (more than usual amount per cell) (about 20% of all breast cancers)
- Often used in combination with chemotherapy

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Cetuximab

- Monoclonal antibody against epidermal growth factor receptor 1 (EGFR1)
- Effective in colon cancer and head and neck cancer; possibly useful in lung cancer
- Used with chemotherapy and with radiation therapy

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Bevacizumab

- Monoclonal antibody against vascular endothelial growth factor (VEGF), which stimulates angiogenesis (growth of new blood vessels into tumor)
- Deprives tumors of the blood supply they need for growth and invasion
- Effective against cancers of colon, lung, breast, kidney, and brain

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