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

If we only had enough time

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"

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

Effective Therapies – may require better diagnosis

- Most diagnosis depends on microscopic/ histopathological analysis (remember the staging?)
- This method does NOT account for the heterologous population of cells nor the various mutations of driver/passenger genes, specific oncogenes or tumor suppressors.
- Some markers are being used but not widely and the number of oncologists that understand these markers and use them is questionable except in most advanced cases

"Targeted" Cancer Treatment

How does it work?

Attack targets which are specific for the cancer cell and are critical for its survival or for its malignant behavior

Why is it better than chemotherapy?

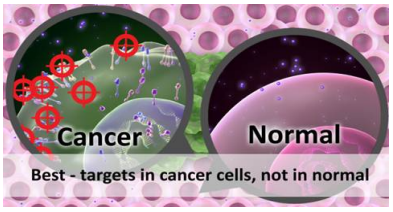
More specific for cancer cells –

chemotherapy hits rapidly growing cells

not all cancer cells grow that rapidly some normal cells grow rapidly

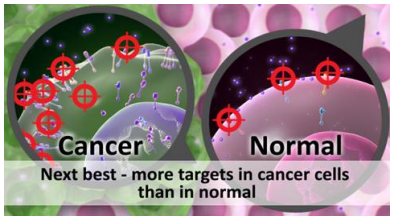
Possibly more effective

Cancer Targets



From National Cancer Institute, US National Institutes of Health.

Cancer Targets



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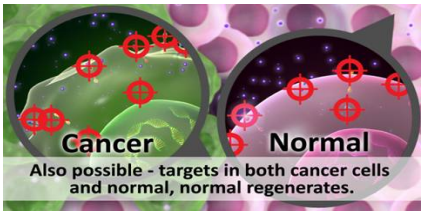
Cancer Targets

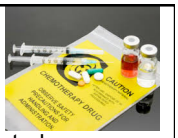


From National Cancer Institute, US National Institutes of Health.

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.

Should we treat all cancer?

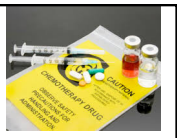


- Weinberg postulates that…

Not all cancers should or can be treated

- Case 1 – Indolent (of disease condition causing no little or no pain): low invasive or metastatic potential likely to stay in this state for lifetime of patient
  - Surgery may provoke growth
  - Example – pancreatic islet "incedentalomas" tumors. 3% of carcinomas and typically found while looking for some other medical issue. 86% five year survival rate. Yet, removal is high risk of morbidity. ~0.07% of annual US deaths are due to this disease.
- Question point – worth treating or not?

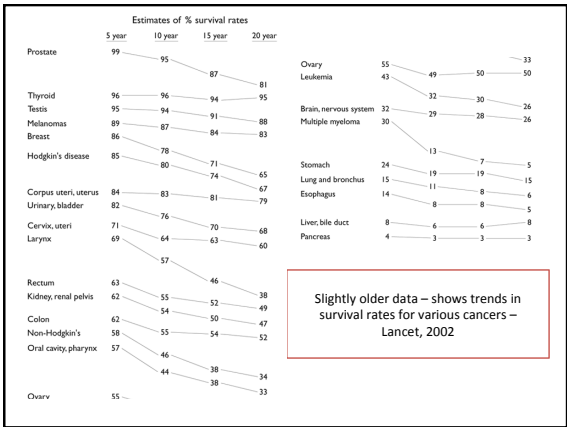
Should we treat all cancer?



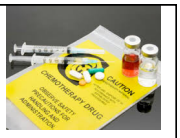
- Weinberg postulates that…

Not all cancers should or can be treated

- Case 2 – Highly aggressive tumors with propensity to metastasize, high grade at time of diagnosis
  - Author states that few truly effective treatments (look at survival rates) and should not be treated
  - Opposing viewpoint that treatment of such tumors may ameliorate symptoms for extended periods giving a longer but not cured life).
- Question point – worth treating or not?



Should we treat all cancer?



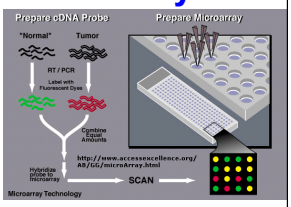
- Weinberg postulates that…

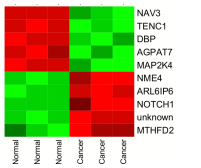
Not all cancers should or can be treated

- Case 3 – Tumors of intermediate grade with potential to metastasize and invade but can be treated
  - In between tumors can achieve long term curative responses
  - Most effective point options for long term survival. Where targeted treatment is most effective, but are we? Personal stories…
- Question point – worth treating or not?

Gene Expression Arrays

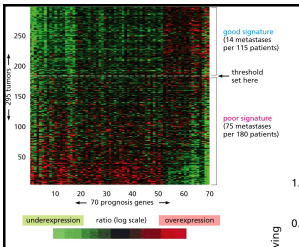
- Powerful detection of what proteins (mRNA) is expressed. Like doing thousands of western blots. Can analyze entire genome!
- If a gene is not expressed in either tissue, the spot will appear black. Genes expressed only in tumor tissue will be red, while control only green. Those in both will be a combination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





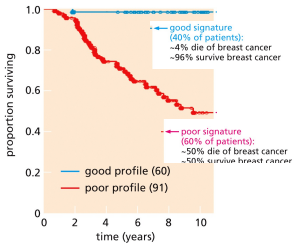
Histology – not cutting it

- Using functional genomics and microarrays to analyze for tumors responsive to therapies. Use this to target which tumors should be treated…
  - Stratifying breast cancers which look the same under a microscope
  - 295 1º BC in women less than 53 years old
  - With and without lymph node progression
  - 70 marker/prognosis genes were analyzed and grouped into two groups after following patients for 7 years
  - Patients were set into two groups based on outcome and gene expression signature



Will it be done?

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

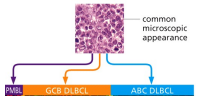


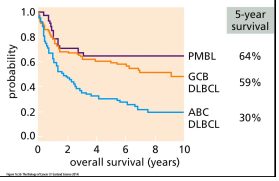
B Cell lymphoma

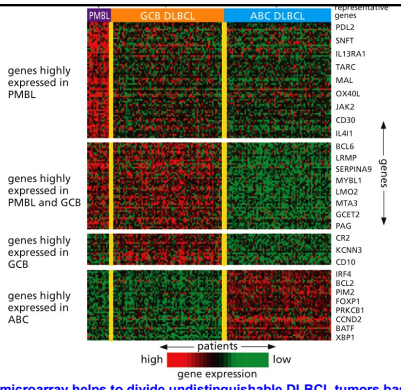
Common histopathology, yet – some patients die within weeks of diagnosis while others achieve 10-year remission without clinical symptoms.

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)





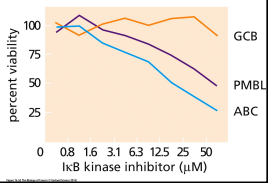


- **Use of microarray helps to divide undistinguishable DLBCL tumors based on expression of oncogenes, tumor suppressor, apoptosis, proteases and EMT genes**

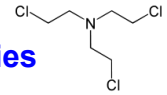
NF Kappa B Kinase Inhibitor

- Classification of expression show trends for several markers and possible treatments

GCB DLBCL	ABC DLBCL	PMBL	
16%	0	25%	c-rel amplification
45%	0	18%	BCL-2 translocation
0	24%	5%	gain chr. 3q
0	6%	43%	gain/amp chr. 9p24
–	+	+	constitutive NF-κB activation



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

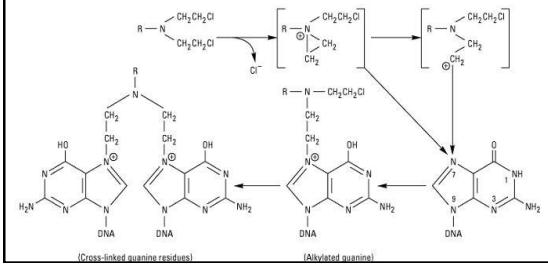
Classification of Chemotherapy Drugs

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

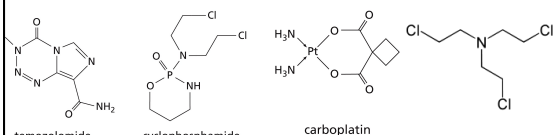
Alkylating Agents

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



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

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.

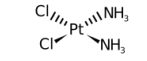
- Risk after alkylating agents is highest about 5 to 10 years after treatment
- Considered a "second cancer" not a recurrence – Risk is dose dependent (13,175, 3-year survivors were treated and 55 developed secondary bone cancer) Less than a 0.9% risk of developing secondary cancer within 20 years J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

Three Classes of Alkylating agents

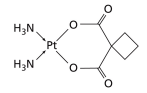
- **Classical Agents** – Nitrogen mustards (mechlorethamine, chlorambucil, cyclophosphamide-cytoxan), Nitrosoureas (streptozocin, carmustine, lomustine), Solfonates (busulfan)…
- **Alkylating Like** – Platinum drugs (cisplatin, carboplatin, oxalaplatin) more likely to cause secondary cancer – leukemia (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…

Cisplatin – The Penicillin of Cancer

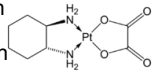
- Widely used – thus the nickname, simple molecule, used for many cancers. Discovered at Mich State as a product of platinum electrodes used for electroysis – NOT patented
- Chloride ions (cisplatin) are displaced by water called aquation which allows platinum to bind to N7 of guanine (purines) as well 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

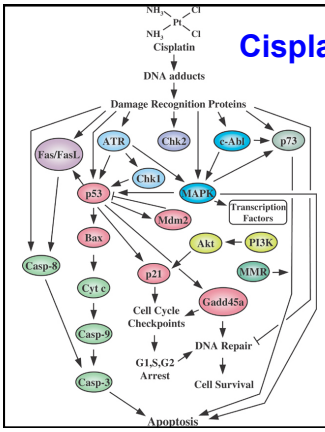


Carboplatin



Oxaliplatin

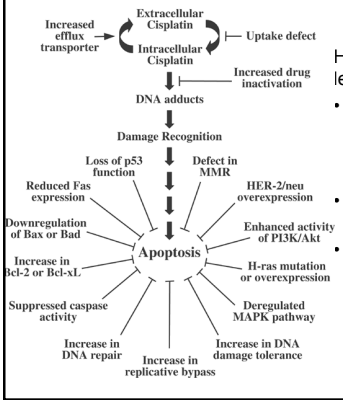
Cisplatin Signaling



- 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.

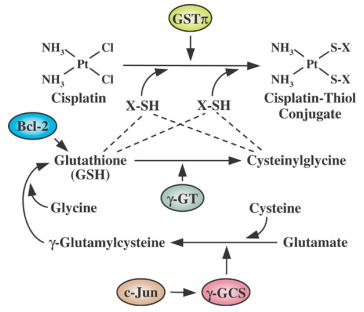
Cisplatin Resistance



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

Inactivation of Pt drugs

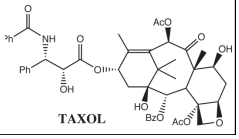


- Inactivation of cisplatin by glutathione

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)

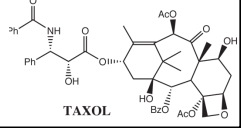


TAXOL

Taxol – natural drug

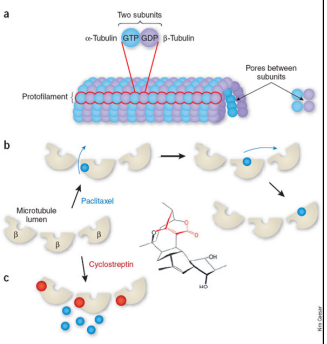
From Pacific yew tree – one of the sources of the "rainforest can cure cancer" lore…

- 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)*



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



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

Metabolism, Metabolomics and Cancer

Taken with permission from
David Wishart
University of Alberta, Edmonton, AB, Canada
ASBMB – Metabolism: Warburg at 90, Boston, MA, March 31, 2015

Otto Warburg

- Observed in 1924 that cancer cells use aerobic glycolysis to fuel growth instead of oxidative phosphorylation
- Won the Nobel Prize in 1931
- Advocated that: "replacement of oxygen-respiration by fermentation is the prime cause of cancer"
- The metabolic view of cancer predominated thinking from 1920's up to the 1960's and most cancer therapies were called "anti-metabolites"

Anti-Metabolite Cancer Drugs

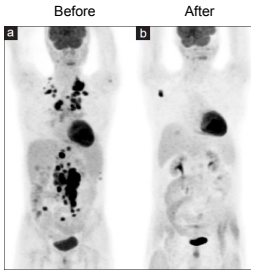
Anti-metabolite	Metabolite equivalent
5-Fluorouracil (5-FU) - 1957	Uracil
Gemcitabine (Ara-C) - 1981	Cytosine
6-Mercaptopurine - 1951	Adenine/Guanine
Fludarapine (Ara-A) - 1968	Adenine
Methotrexate - 1956	Folate
Aminopterin - 1947	Folate
Megestrol acetate - 1956	Progesterone
Hydroxyurea - 1967	Cytosine

40 Years of Oncogenes & Warburg's Revenge

Oncogene or Tumor Suppressor	Metabolic Effect
Akt	Enhances glucose uptake, activates hexokinase II
c-Myc	Enhances glycolysis, activates LDH-A
h-Ras, k-Ras	Enhances glycolysis, activates complex II
Src	Phosphorylates PKM2, upregulates c-Myc
Brc-abl	Enhances glucose uptake, activates G6PD & HK II
Her2/neu	Enhances glycolysis, activates LDH and HSF1
Succinate dehydrogenase	Sustains TCA cycle, loss leads to HIF activation
Fumarate hydratase	Sustains TCA cycle, loss leads to HIF activation
Isocitrate dehydrogenase	Sustains TCA cycle, loss leads to DNA methylation
p53	Promotes OXPHOS, loss leads to glycolysis

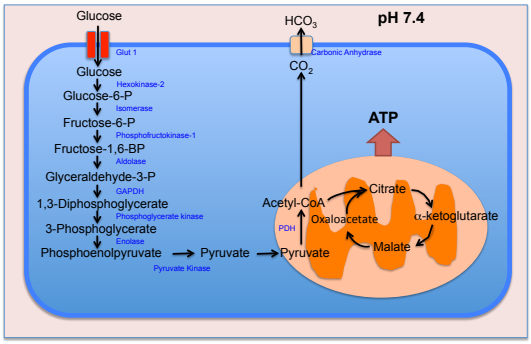
Cancer is a Metabolic Disease

- Cancer cells consume 100-200X more glucose that other cells in the body
- This unique metabolism is the basis to PET (positron emission tomography) scans for cancer using fluorinated deoxyglucose
- This metabolic shift is called the Warburg effect or cytosolic aerobic glycolysis

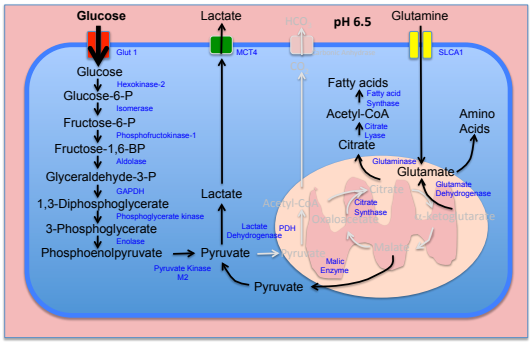


Tumors are marked in black in this PET image (lots of glucose)

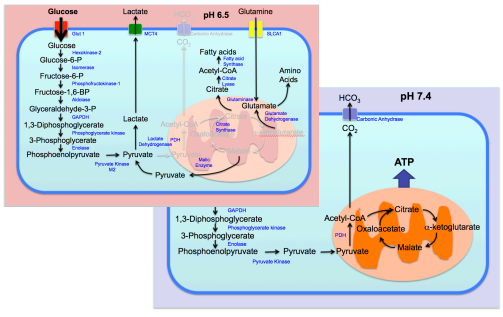
Normal Cell Metabolism



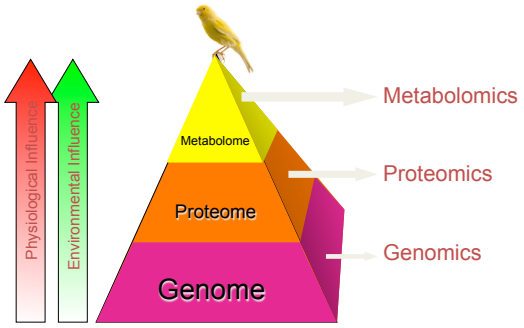
Cancer Cell Metabolism



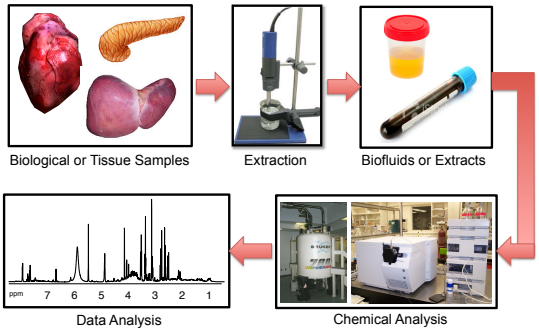
How To Measure All These Metabolic Changes?



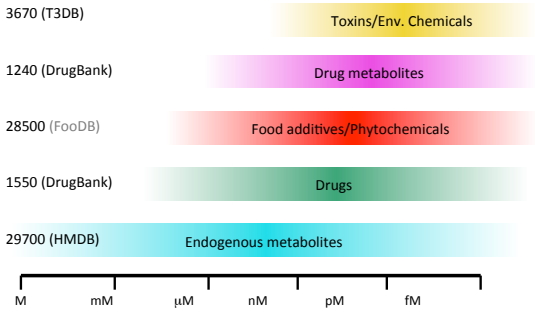
Answer: Metabolomics



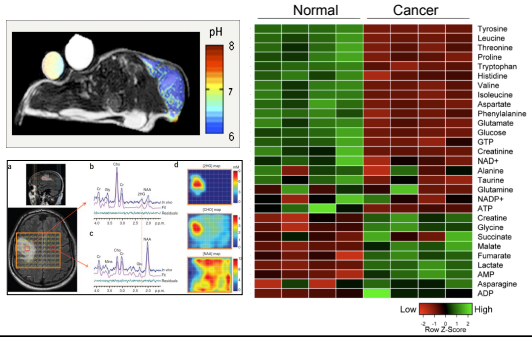
Measuring Metabolism with Metabolomics



Human Metabolomes (2015)



Metabolomics & Cancer



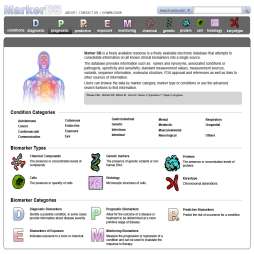
Metabolomics is Discovering Oncometabolites

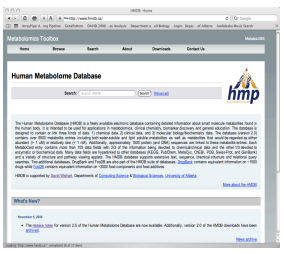
Oncometabolite	Effect or Mechanism
Lactate	Promotes tumor metastasis
2-Hydroxyglutarate	Alters histone/DNA methylation
Fumarate	HIF activation/alters DNA methylation/binds GSH
Succinate	HIF activation/alters DNA methylation
Glucose	Fuels Warburg effect
Sarcosine	Promotes tumor metastasis
Kynurenine	Activates aryl hydrocarbon receptor, tumorigenesis
Glutamine	Fuels glutaminolysis, promotes tumor growth
3-Hydroxybutyrate	Promotes tumor growth, reverse Warburg effect

Metabolomics is Discovering Cancer Biomarkers

- Vanillylmandelic acid (neuroblastoma + pheochromocytomoa)
- 3-Hydroxymandelic acid (neuroblastoma)
- 3,4-Dihydroxymandelic acid (neuroblastoma)
- Homovanillic acid (neuroblastoma)
- Sarcosine (metastatic prostate cancer)
- 2-hydroxyglutarate (glioma + acute myeloid leukemia)
- Ribothymidine (breast cancer)
- 1-methylguanosine (breast cancer)
- 1-methyladenosine (cholangioma + cervical cancer)
- Cadaverine (pancreatic cancer)
- 5-hydroxyindoleacetic acid (carcinoid tumors)
- 3-methoxytyramine (carcinoid tumors)
- Testosterone glucuronide (adrenocortical tumors)
- 3a,16a-dihydroxyandrostenone (adrenal carcinoma)
- 5-methoxyindoleacetate (lung + stomach + colon cancer)
- 21-deoxycortisol (testicular cancer)
- 3,5-diiodothyronine (brain tumors)
- Androstendione (thyroid cancer)
- Thromboxane A2 (Hepatocellular carcinoma)
- Deoxypyridinoline (Multiple myeloma)

Cancer & Metabolite Biomarkers





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Building Better Biomarkers

Abstract ▾ Send to: ▾

Metabolomics. 2013 Apr;9(2):280-299. Epub 2012 Dec 4.

Translational biomarker discovery in clinical metabolomics: an introductory tutorial.

Xia J[1], Broadhurst DI, Wilson M, Wishart DS.

Author information

Abstract

Metabolomics is increasingly being applied towards the identification of biomarkers for disease diagnosis, prognosis and risk prediction. Unfortunately among the many published metabolomic studies focusing on biomarker discovery, there is very little consistency and relatively little rigor in how researchers select, assess or report their candidate biomarkers. In particular, few studies report any measure of sensitivity, specificity, or provide receiver operator characteristic (ROC) curves with associated confidence intervals. Even fewer studies explicitly describe or release the biomarker model used to generate their ROC curves. This is surprising given that for biomarker studies in most other biomedical fields, ROC curve analysis is generally considered the standard method for performance assessment. Because the ultimate goal of biomarker discovery is the translation of those biomarkers to clinical practice, it is clear that the metabolomics community needs to start "speaking the same language" in terms of biomarker analysis and reporting-especially if it wants to see metabolite markers being routinely used in the clinic. In this tutorial, we will first introduce the concept of ROC curves and describe their use in single biomarker analysis for clinical chemistry. This includes the construction of ROC curves, understanding the meaning of area under ROC curves (AUC) and partial AUC, as well as the calculation of confidence intervals. The second part of the tutorial focuses on biomarker analyses within the context of metabolomics. This section describes different statistical and machine learning strategies that can be used to create *multi-metabolite* biomarker models and explains how these models can be assessed using ROC curves. In the third part of the tutorial we discuss common issues and potential pitfalls associated with different analysis methods and provide readers with a list of nine recommendations for biomarker analysis and reporting. To help readers test, visualize and explore the concepts presented in this tutorial, we also introduce a web-based tool called ROCCET (ROC Curve Explorer & Tester, http://www.roccet.ca). ROCCET was originally developed as a teaching aid but it can also serve as a training and testing resource to assist metabolomics researchers build biomarker models and conduct a range of common ROC curve analyses for biomarker studies.

KEYWORDS: AUC; Biomarker analysis; Biomarker validation and reporting; Bootstrapping; Confidence intervals; Cross validation; Optimal threshold; ROC curve; Sample size

PMID: 23543913 [PubMed] PMCID: PMC3608878 **Free PMC Article**

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

Conclusions

- Cancer is a metabolic disease
  - Cancer cells exhibit a 200x increase in glucose consumption
  - Most known oncogenes and tumor suppressors fundamentally alter glucose metabolism
  - Oncometabolites promote cancer
  - Antimetabolites stop cancer
  - High abundance metabolites play key cancer signaling roles
  - Metabolic disorders such as diabetes and obesity increase cancer risk substantially
  - Cachexia (a metabolic disorder) is a manifestation of cancer
  - Some of the best cancer biomarkers are metabolites

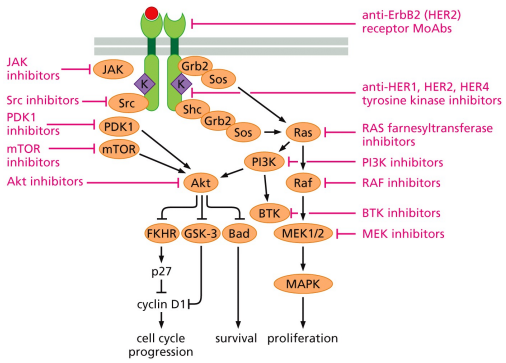
Conclusions

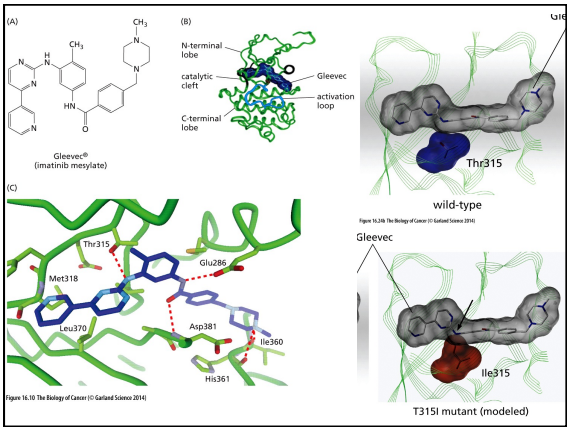
- If cancer is a metabolic disease…
  - New kinds of drug targets
  - New methods for cancer prevention (diets?)
  - New approaches for early diagnosis
  - New methods for risk prediction
  - New techniques to look at cancer
  - New ways of integrating genomics with metabolomics
  - New kinds of drugs…

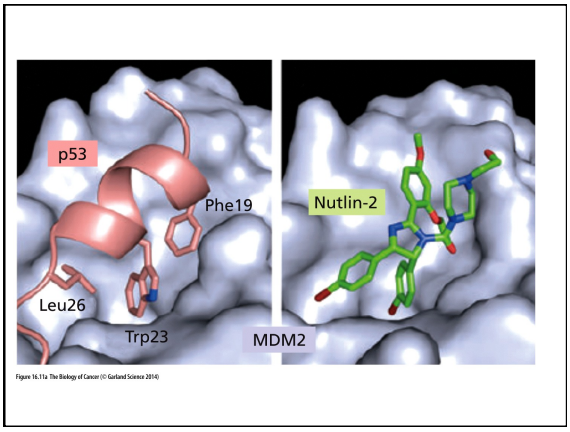
Cancer Drugs That Reverse The Warburg Effect

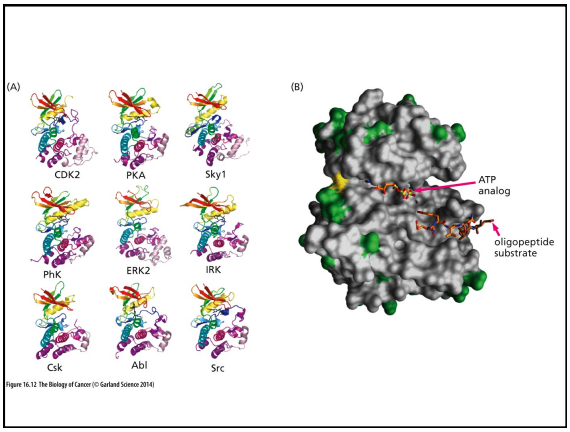
Drug	Mechanism
Gleevec	Inhibits Bcr-Abl, downregulates HK & G6PDH
Dicholoracetate (DCA)	Targets and inhibits pyruvate kinase
Orlistat	Targets and inhibits fatty acid synthase
Metformin	Downregulates mTOR, Activates AMPK
Rapamycin	Inhibits mTOR
Trastuzumab	Inhibits glycolysis via LDH and HSF1 downregulation

Targeted Therapies









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

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

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

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

Monoclonal Antibodies

FDA-Approved "Naked" (Non-Conjugated) MoAbs

Generic Name	Brand Name	Target	Cancer(s)
Alemtuzumab	Campath	CD52	CLL
Bevacizumab	Avastin	VEGF	Multiple
Cetuximab	Erbitux	EGFR1	Colon, H&N
Panitumumab	Vectibix	EGFR1	Colon
Rituximab	Rituxan	CD20	Lymphomas
Trastuzumab	Herceptin	HER-2	Breast

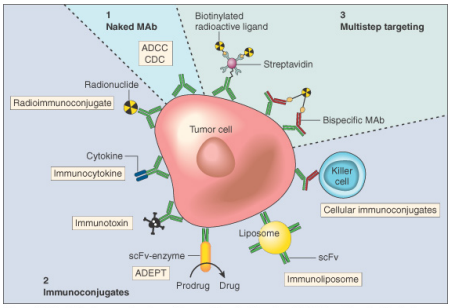


Figure 34-1 • Effector mechanisms of monoclonal antibodies. ADEPT, antibody-directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain variable fragment.

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

Monoclonal Antibodies

- Conjugated antibodies currently approved
  - Radio-conjugated antibodies
    - Tositumomab (Bexxar)
    - Ibritumomab (Zevalin)
    - Both used against refractory lymphomas
  - Toxin-conjugated antibody
    - Gemtuzumab ozogamicin (Mylotarg)
    - Used against AML

Monoclonal Antibodies In Development

- Epratuzumab
- Matuzumab
- Nimotuzumab
- Zalutumumab
- Pertuzumab
- Mapatumumab
- Lexatumumab
- Volociximab
- Pemtumomab
- Labetuzumab
- ch806
- CP-751,871
- IMC-A12
- VEGF-Trap
- IMC-18F1
- IMC-1121B
- IMC-3G3
- Vitaxin
- CNTO 95

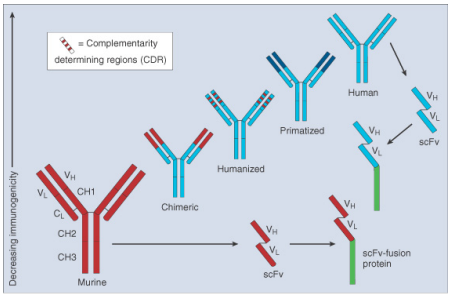


Figure 34-2 • Immunogenicity of MAb. CH1, CH2, and CH3, constant region domains of an IgG heavy chain; scFv, single chain variable fragment; V_H, variable region of the heavy chain; V_L, variable region of the light chain. *Red,* mouse; *blue,* human; *green,* recombinant protein to which scFv is genetically fused.

Types of MoAbs

Structure	***% Human***	***Example***	***Comments***
Mouse	0	Tositumomab, Ibritumomab	Radio-conjugates
Chimeric	65	Cetuximab, Rituximab	
Humanized	95	Trastuzumab	
Human	100	Panitumumab	Transgenic mice

Nomenclature of MoAbs

- Last syllable is always *–mab*
- Next to last syllable
  - *-u-* human (100%) : Panitum<u>u</u>mab
  - *-zu-* humanized (95%) : Trastu<u>zu</u>mab
  - *-xi-* chimeric (65%) : Ritux<u>i</u>mab
  - *-o-* mouse, *-a-* rat, *-e-* hamster, *-i-* primate : Tositum<u>o</u>mab
- Previous syllable
  - *-tu(m)-* for tumor in general [*-ma(r)-* breast, *-pr(o)-* prostate, *-co(l)-* colon, etc.]
  - *-ci(r)-* for circulatory : Beva<u>ci</u>zumab

New Directions

- Combination of different targeted therapies (multiple TKIs, TKI with MoAb; occasionally multiple MoAbs)
- Combination with standard chemotherapy or with radiotherapy
- Targeted agents to “clean up” after surgery
- Use with other novel agents