A BROAD-SPECTRUM INTEGRATIVE DESIGN FOR CANCER PREVENTION AND THERAPY

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DISCLOSURES

- **Medical Director,**
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- **Editor-In-Chief,**
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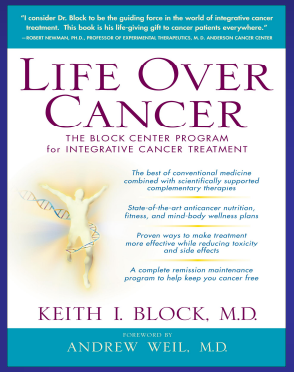
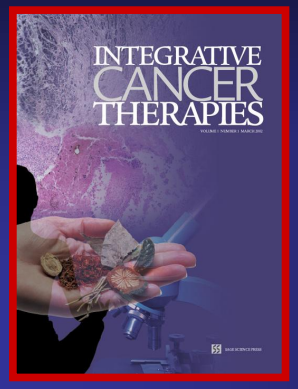
- **Author,**
  Life Over Cancer





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Block Center for Integrative Cancer Treatment
“Life Over Cancer” Training Program

A Broad-Spectrum Integrative Design for Cancer Prevention and Treatment

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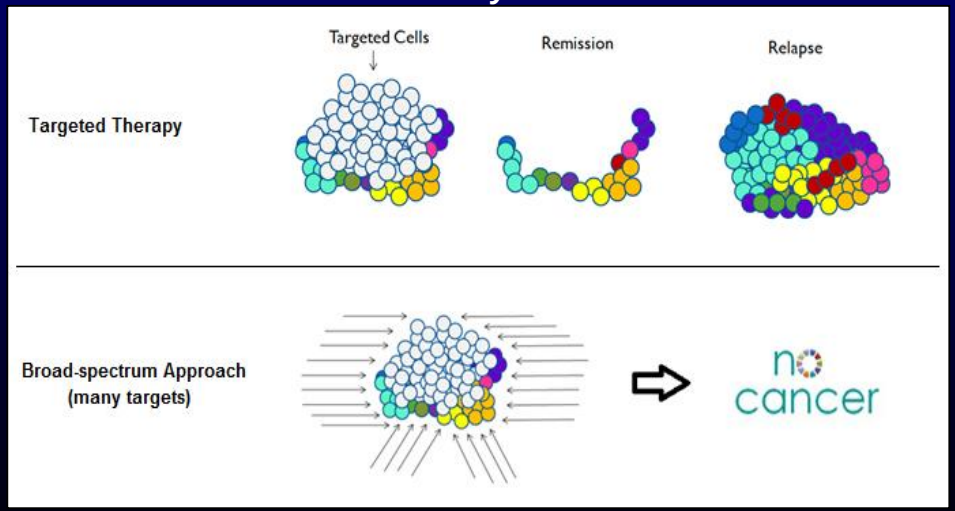
Summary

- Targeted cancer therapies eliminate cancer cells bearing specific molecular “targets,” and can produce cancer remission. However, they are expensive, can have severe side effects and can rapidly become ineffective. In most tumors, populations of cells exist that do not bear these targets so they keep growing, resulting in cancer relapse.
- Our team performed a comprehensive literature review that accounts for targets and approaches to address the hallmarks of cancer. Based on this review, we propose the development of broad-spectrum therapies that can attack many targets to destroy multiple types of therapy-resistant cells, reducing the risk of relapse. These therapeutic mixtures should consist of low-toxicity, low-cost compounds to improve outcomes and reduce costs to health systems.

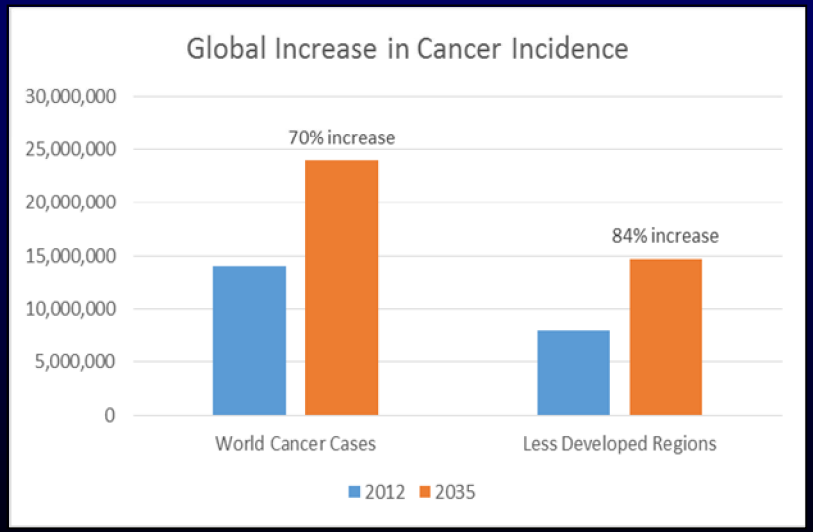


Why is this research important?

- Targeted therapies are important treatments but problematic:
  - High cost (often over $100,000 to treat one patient)
  - Short relapse-free period
  - Costs burden health systems and individual patients

- Increases in cancer incidence are projected:
  - 70% globally in next 20 years
  - 84% in developing regions

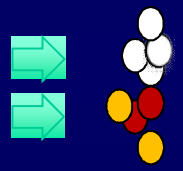
A broad-spectrum therapeutic strategy may offer a viable addition or alternative to conventional care.



Background

Due to genetic heterogeneity, most tumors contain some cells that lack targets of targeted therapy drugs (e.g., VEGF). Even with a cell kill of 90% , remaining cells can still flourish

Targeted therapy
Resistant cells



Susceptible cells with targets are killed
Resistant cells lacking targets keep growing

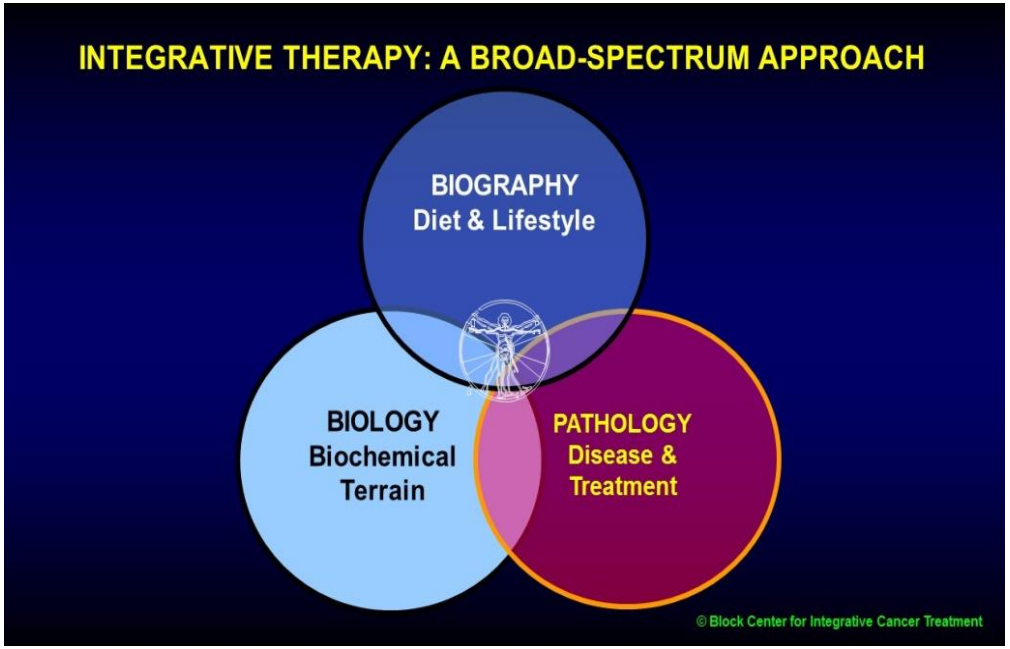
How can we systematically and effectively target multiple cancer cell growth pathways with low-cost, low-toxicity compounds?

Various models suggest and support broad-spectrum approaches

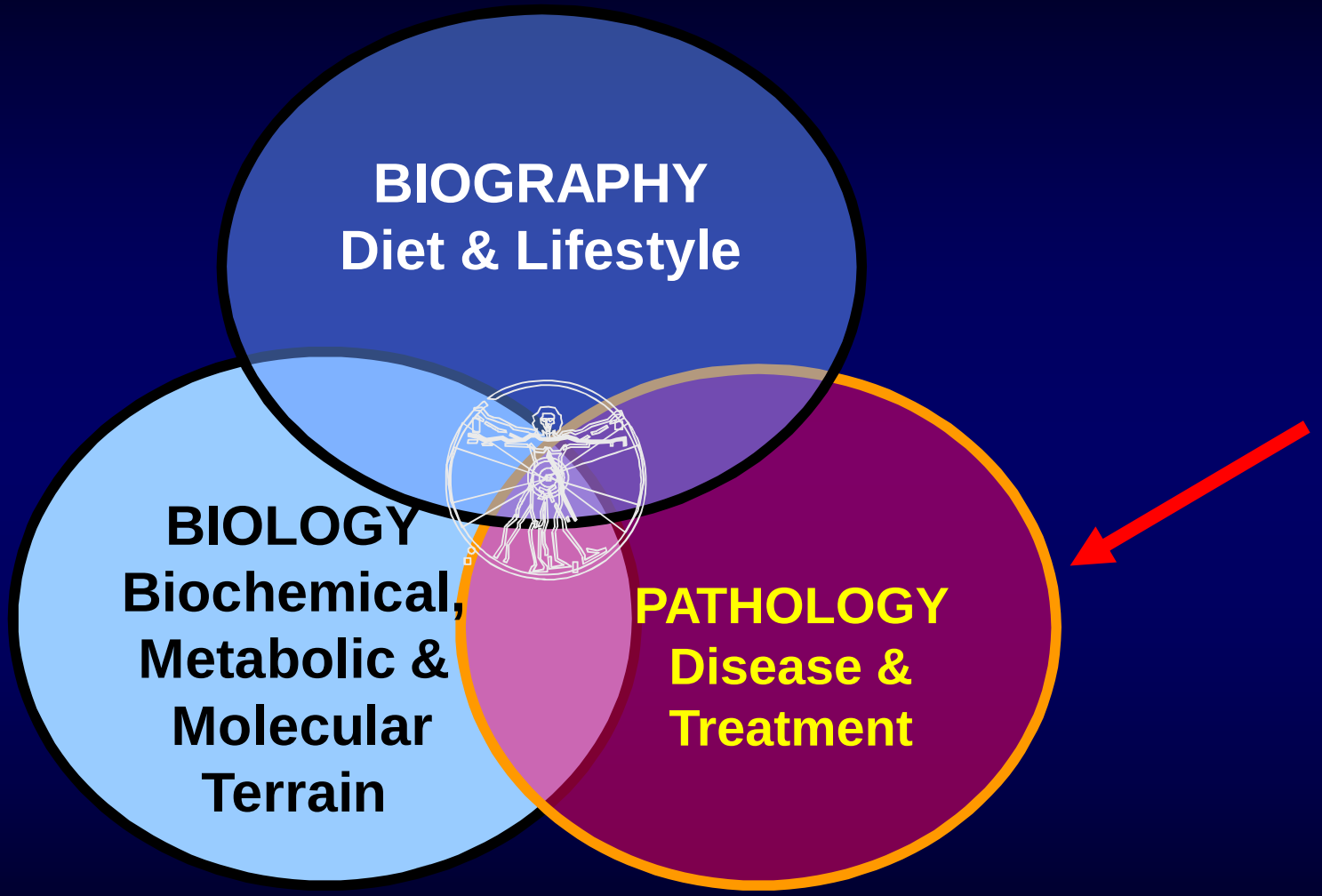
- Integrative medicine model
- Cancer genome landscape model
- Hallmarks of cancer model

Integrative design

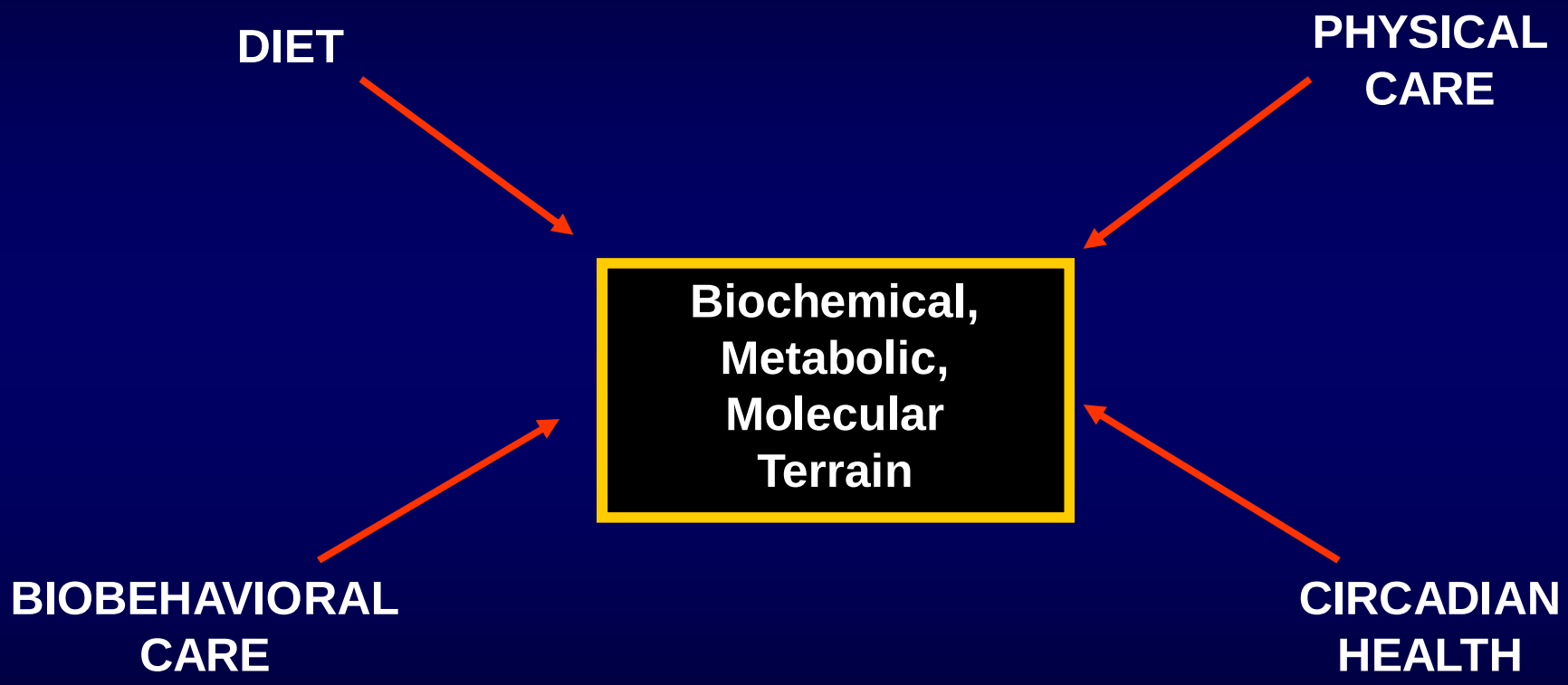
- The broad-spectrum concept is based on an integrative cancer therapy clinical model.
- Integrative cancer therapy:
  - diet
  - physical activity
  - behavioral strategies
  - circadian
  - Natural, off-label, overseas agents to modulate biochemical, metab, molec. terrain
  - Chronomodulated, immune, infusional Rx
  - innovative approaches to conventional, integrative, responsible alternative Rx …
- The Life Over Cancer approach incorporates a systematic, broad spectrum, individualized with comprehensive clinical, nutritional, physical, biobehavioral and circadian assessments resulting in individualized and innovative Rx.
- Where possible we implement 16 assessment profiles and 16 intervention modules.
- Integrative therapy deliberately addresses multiple targets through multiple therapies to improve patients' outcomes and life quality.



The *LIFE OVER CANCER* Program for INTEGRATIVE CANCER TREATMENT

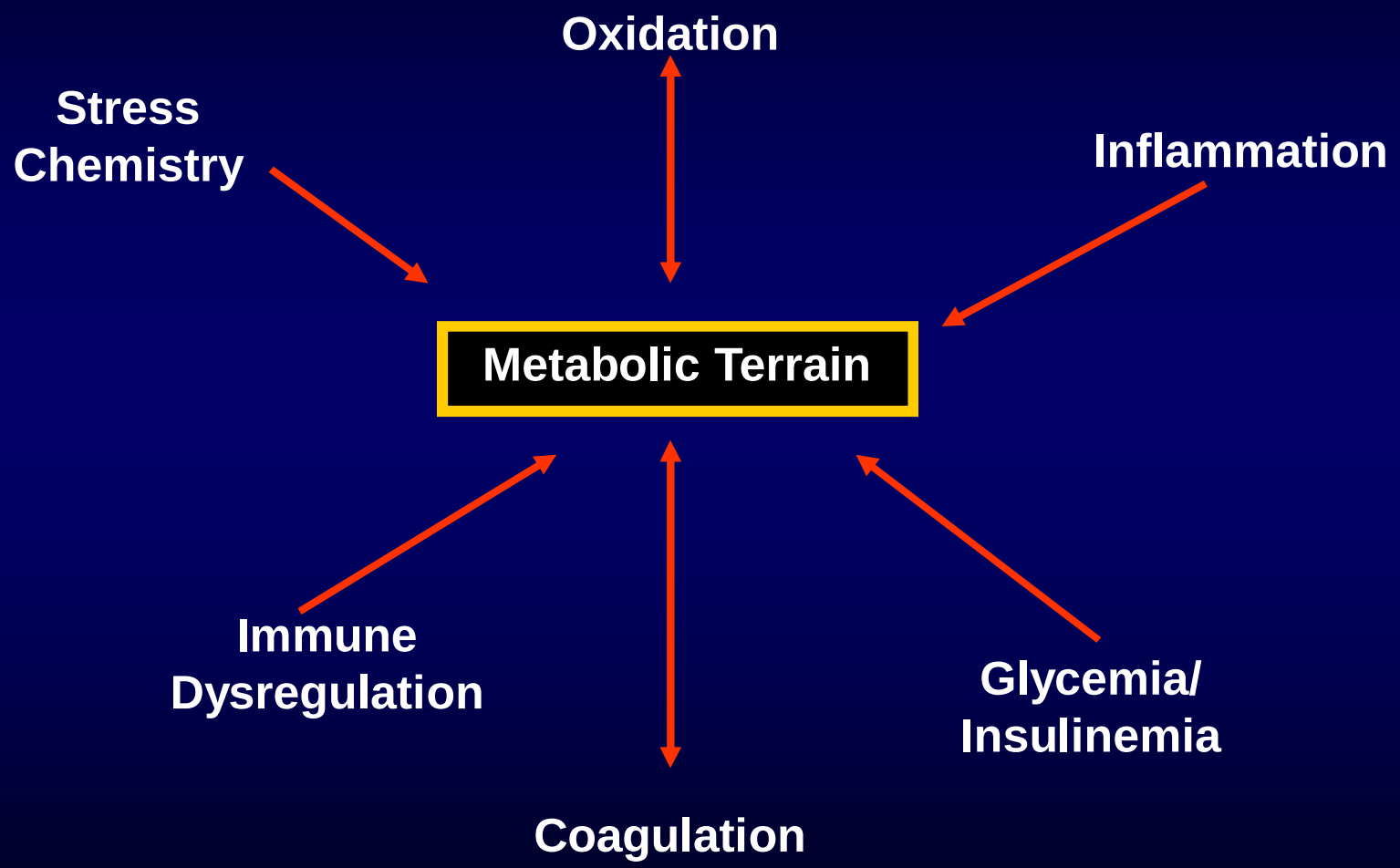


Diet & Life Style Interventions



Biochemical Terrain

Metabolic Hallmarks



Tumor Growth Progression Pathways

Molecular & Metabolic Hallmarks

Genomic Instability

Inflammation

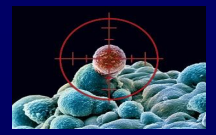
Anti-Growth signaling

Sustained Proliferation

Death Signal

Cancer Hallmarks

Immortality



MicroEnvironment
-fibroblasts
- macrophages
- endothelial cells
-platelets
-Inflammatory cells

Angiogenesis

Metabolic Dysregulation

Invasion, Dissemination Metastases

Immune Dysregulation

The Cancer Genome Landscape

138 “driver genes” propel tumorigenesis (“hills”). Whereas “passenger” mutations (“valleys”) do not confer growth advantage vs normal cells.

Most tumors contain 2-8 driver genes. More may be acquired by genetic instability. Eliminate multiple driver gene clones to control cancer.

Vogelstein, Science 2013; 339:1546-58

Cancer pathways and promoters

Driver gene pathways (Voglstein)
Notch
DNA damage
STAT
TGF-β
MAPK
RAS
PI3K
Cell cycle/apoptosis

Terrain factors and pathways of progression (Block, 1990-1998)
Inflammation
Oxidation
Glycemia
Blood coagulation
Stress chemistry
Immune evasion
Apoptosis
Treatment resistance
Proliferation
Angiogenesis
Metastasis
Impaired cellular communication
Dedifferentiation
Immortality

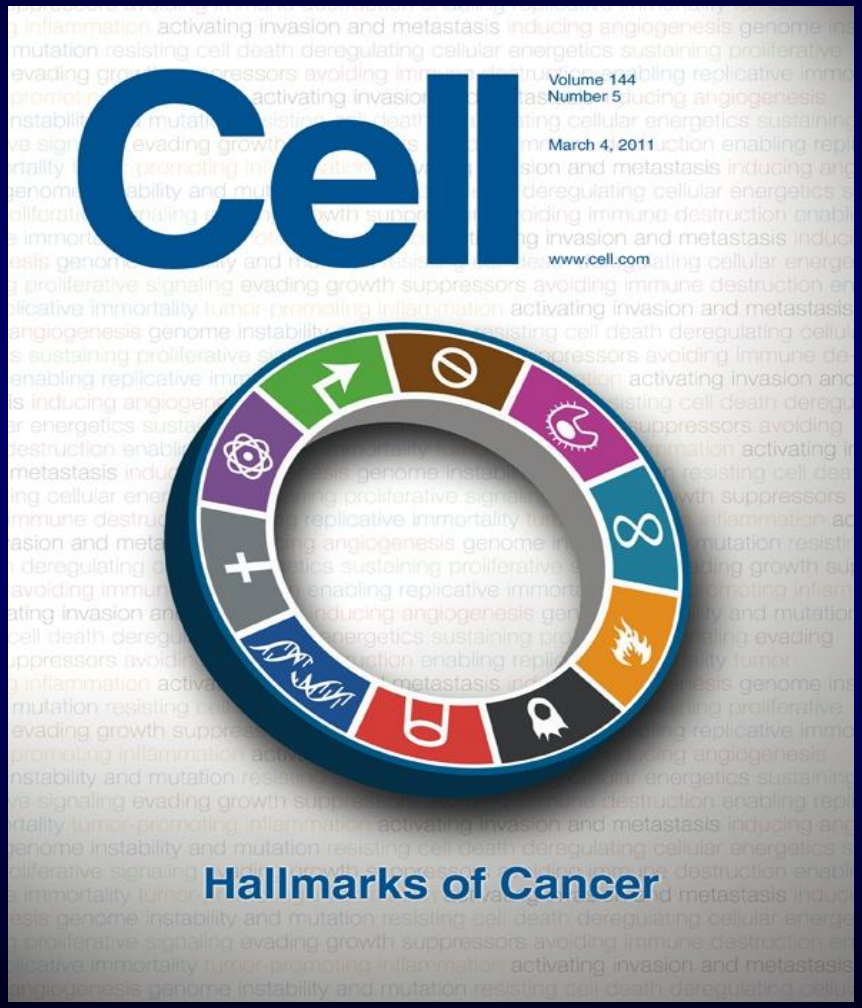
Vogelstein et al, Science 2013; 339:1546-58.
Block, Life Over Cancer, Bantam, 2009

The Hallmarks of Cancer

Article published in the journal *Cell* in January 2000

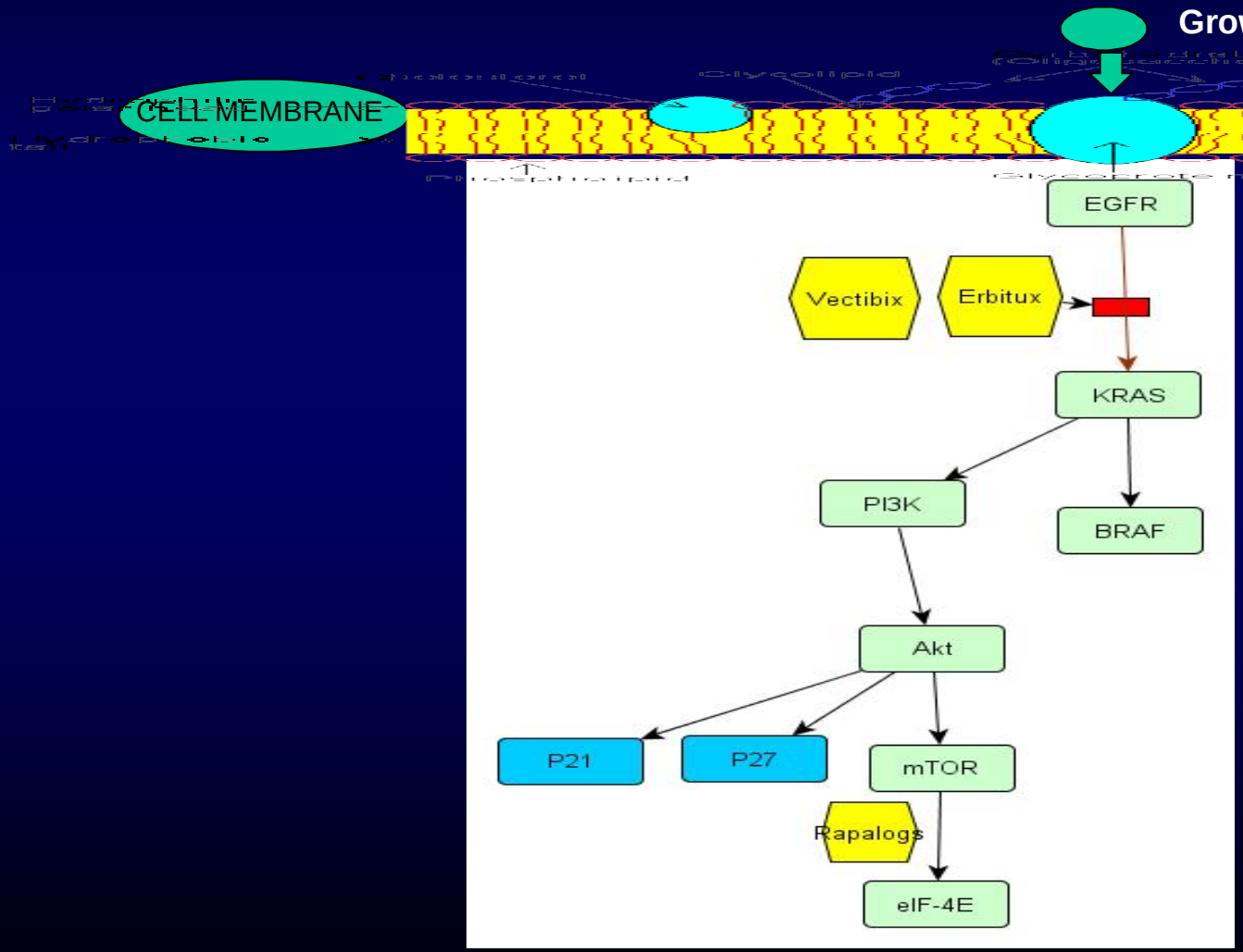
Complexity of cancer can be reduced to a small number of underlying principles.

All cancers share 6 common traits or "hallmarks" that govern the transformation of normal cells to cancer (malignant or tumor) cells.



The broad-spectrum strategy

A broad-spectrum approach combines multiple non-toxic phytochemicals and other agents to attack many targets simultaneously, suppressing growth of multiple genetically diverse cells in a tumor while reducing resistance to therapy.

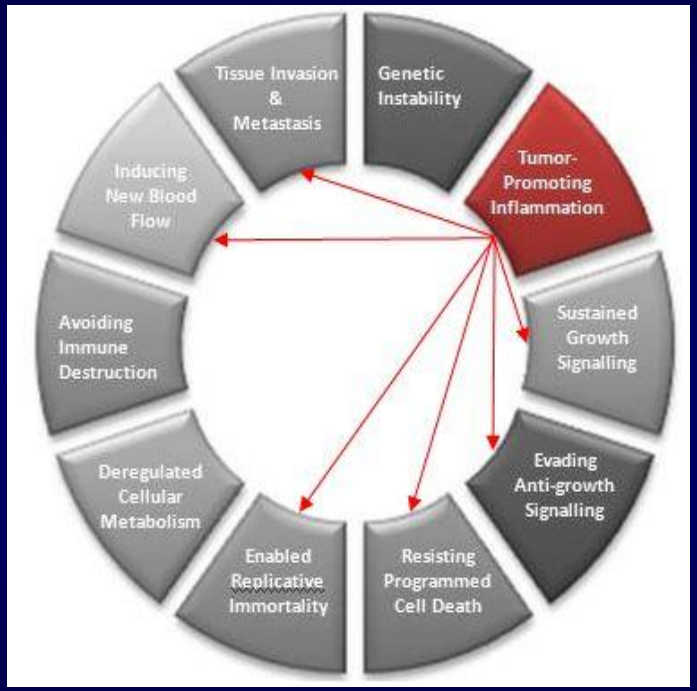


Methods: The Halifax Project

- Focus was on the 11 Cancer hallmarks: Characteristics which are critical to all cancer cells and are crucial to their growth.
- We recruited 180 researchers for an initiative called the “Halifax Project.”
- Goal: a broad-spectrum strategy that addresses all 11 hallmarks.
- 11 teams produced extensive reviews of the hallmarks, published in a special issue of *Seminars in Cancer Biology.*

  Capstone, DrBlock@BlockMedical.com
- Each team had expertise in a specific hallmark. They were directed to choose the most relevant priority targets and low cost, low risk therapeutic approaches (phytochemicals or drugs) for that specific hallmark.

Methods: the cross-validation team



- Targets and approaches (phytochemicals or drugs) were chosen to deactivate growth pathways related to each hallmark.

But since an approach or target might also activate pathways in another hallmark, it could at least theoretically stimulate cancer cells or increase growth.

A 12th team was set up to research every target and approach to locate cancer-stimulating effects on targets in all other hallmarks. We called the team the cross-validation team.

Results

- 74 high-priority cancer targets for a broad-spectrum approach were selected: VEGF, NF-κβ, PI3K/Akt, telomerase, e-cadherin, etc.
- 60 treatment approaches were selected: curcumin, EGCG from green tea, resveratrol, selenium, melatonin, some drug therapies, etc..
- Only 3.9% of targets and 1.1% of approaches had contrary cancer-stimulating effects on other hallmarks.
- Over 65% of targets and 60% of approaches complemented other hallmarks by reinforcing anticancer activities of their targets.

	Complementary (+)	Contrary (-)	None known (0)	Controversial (+/-)
Targets	66.7%	3.9%	21.7%	7.6%
Approaches	62.1%	1.1%	34.1%	2.8%

Implications

- This large international project reached agreement among diverse scientists at a wide variety of institutions on the potential utility of a broad-spectrum approach to cancer prevention and therapy.
- Extensive literature reviews resulted in lists of high-priority targets and low-toxicity, low-cost approaches agreed on by teams of researchers.
- Cross-validation of the impacts of targets and approaches on other hallmarks uncovered very few contrary interactions that would interfere with anticancer activity.
- To target multiple cancer growth pathways a single medication can only be accomplished with a combination of low-toxicity, strategically chosen phytochemicals and other well tolerated compounds.
- Research into multi-component, non-toxic, low cost, broad-spectrum therapeutic agents should be vigorously pursued.

Hallmark: Genomic Instability

In cancer cells, DNA and chromosomes are prone to mutation and aberration. Although normal cells can repair insults to DNA, cancer cells may lack this ability, allowing genetic errors to increase and multiply. The accumulation of genetic errors allows cancer cells to proliferate , invade and evolve to more aggressive forms over time.

Targets:

Prevent DNA damage
Enhance DNA repair
Target deficient DNA repair
Impair centrosome clustering
Inhibit telomerase activity

Approaches:

Carotenoids
Selenium
B-vitamins
Isothiocyanates
Vitamin D
Resveratrol
PARP inhibitors
EGCG

Hallmark: Evading antigrowth signaling

Through loss of tumor suppressor or activation of genes that override signals to stop growth, cancer cells ignore normal signals to enter apoptosis or senescense. Reactivating mutated tumor suppressors or driving normal death signals is a promising therapy.

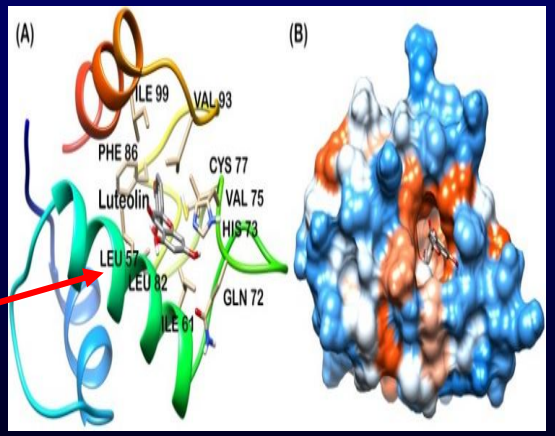
Targets:

Activate Rb
Activate p53
Activate PTEN
Enhance HIPPO
Activate GDF15*
Activate ARID1A
Inhibit Notch
Inhibit IGF1R

Approaches:

EGCG
Luteolin
Curcumin
Porfyrin
Genistein
Resveratrol
Withaferin
Diguelin

Luteolin



Hallmark: Tumor-promoting inflammation

25% of cancers are linked to chronic inflammation, which plays critical roles in various phases of tumorigenesis, including angiogenesis and metastasis. Numerous procarcinogenic products of inflammatory processes can be distinguished as targets for treatment approaches.

Targets:
Inhibit COX2
Inhibit NFκB
Inhibit MIF
Inhibit TNFα
Inhibit iNOS
Inhibit Akt
Inhibit CXC chemokines

Approaches:
Curcumin
Resveratrol
EGCG
Lycopene
Anthocyanins
Genistein