Laboratory Tests /Molecular Markers in Breast Cancer and Indicated Naturopathic Treatments

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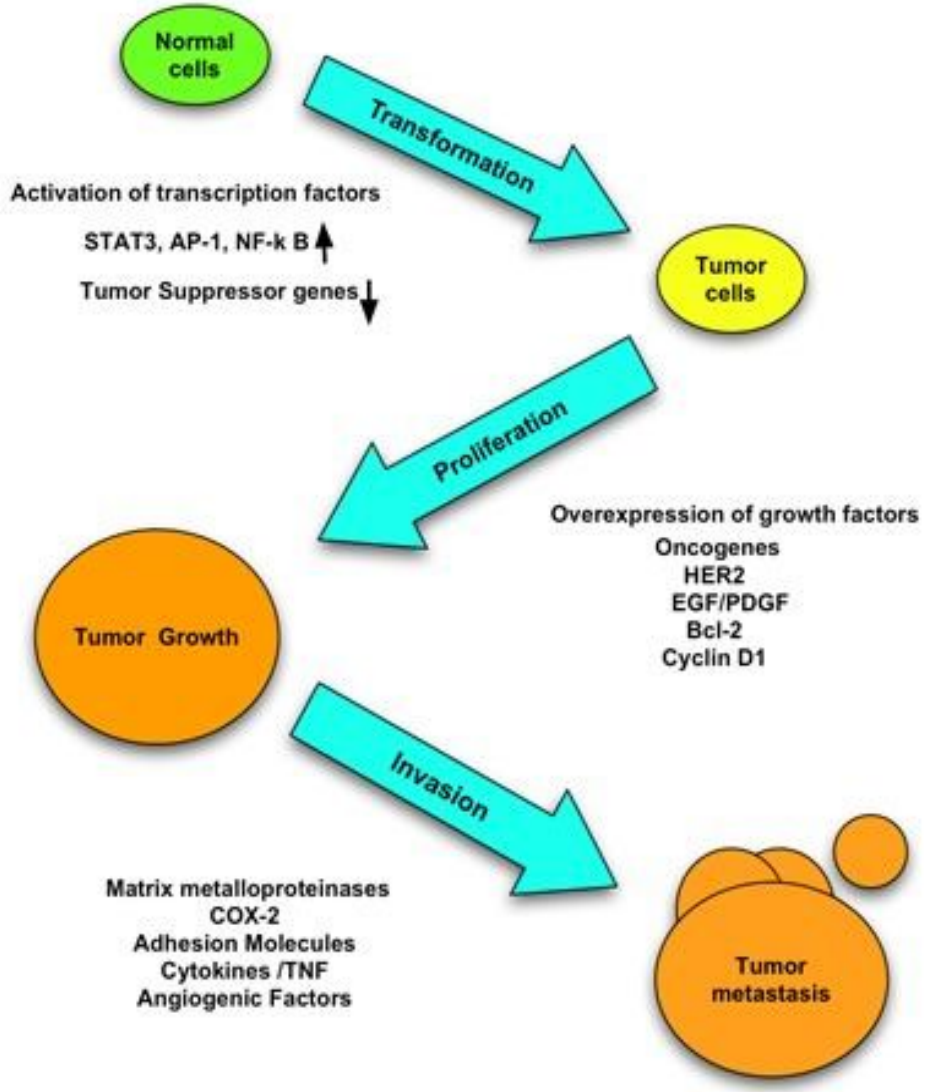
Eugene, OR

Learning Objectives

- Understand established tumor markers for breast cancer (What and When)
- Define conventional laboratory measures that may help guide ND treatments decisions
- Review independent labs parameters that can help tailor treatment.

Overview of Cancerous Growth



Party Line-- ASCO

Tissue Derived Markers

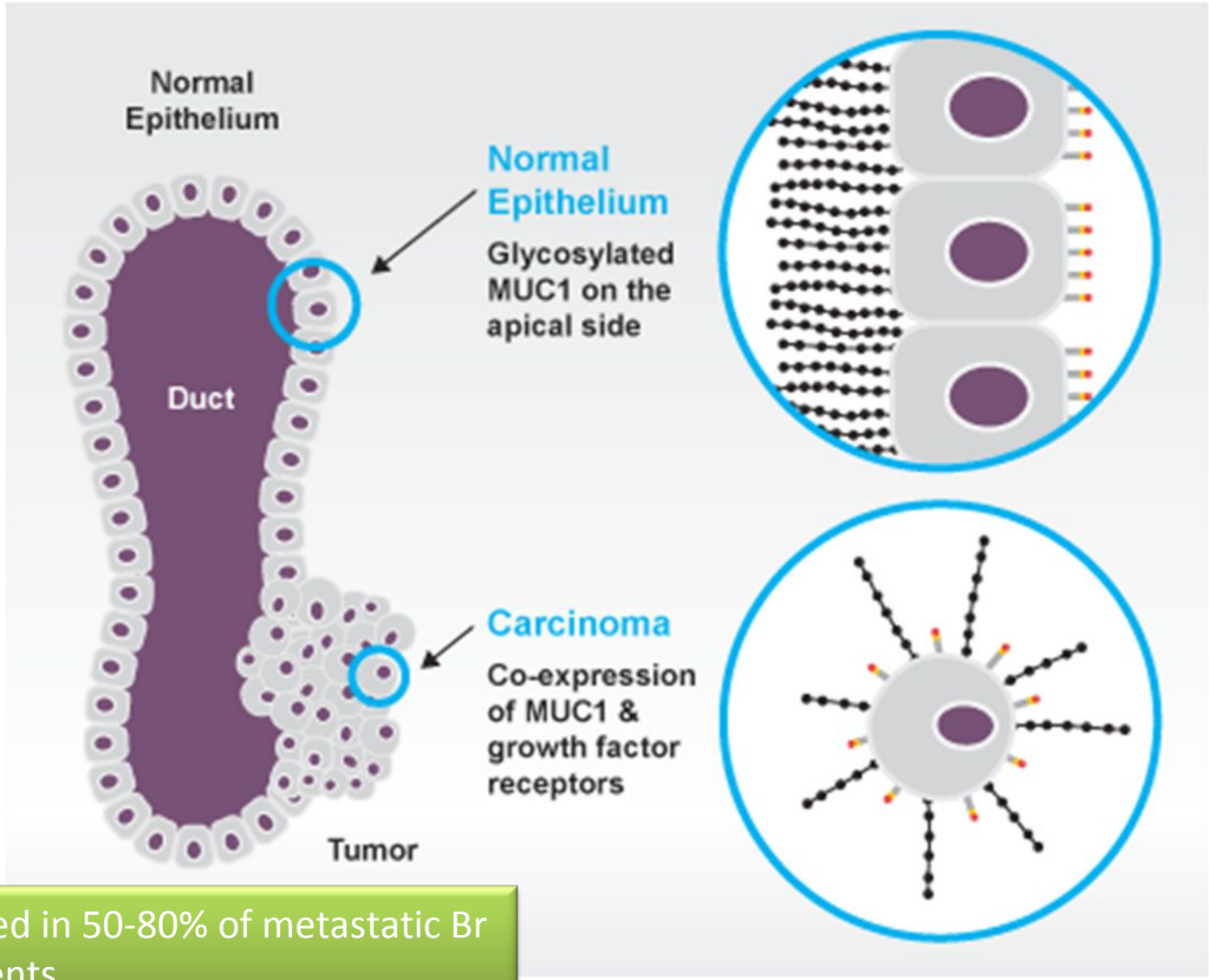
- ER/PR receptor status
- Her2/neu
- uPA/PAI-1
- Oncotype Dx

Circulating Markers

- Ca 15-3
- Ca 27-29
- CEA

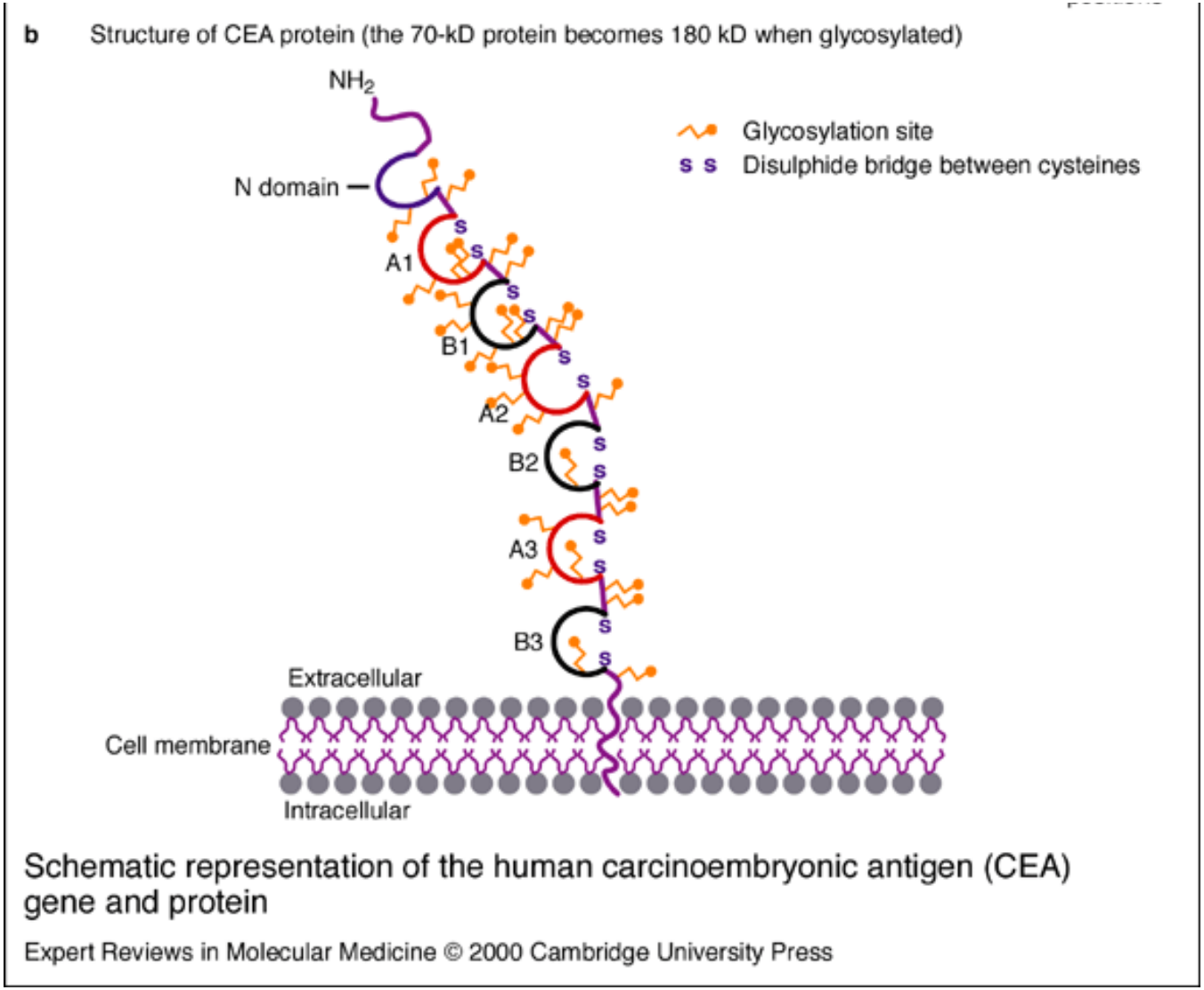
Predictive or Prognostic only;
No screening markers recommended.

MUC1 FAMILY (Ca 15-3, 27-29)



Increased in 50-80% of metastatic Br Ca patients

Carcinoembryonic Antigen (CEA)



Schematic representation of the human carcinoembryonic antigen (CEA) gene and protein

When are they recommended?

- ER/PR/ Her2/Neu: all primary tumor samples

- CEA/ Ca 15-3, 27-29: Recommended for use in patients with established metastatic disease.
  - NOT recommended for monitoring for recurrence

- Oncotype DX: Women with Stage I or II, ER positive, node negative invasive breast cancer (soon may be for node positive too)

Oncotype Dx- ER+, Node -

- 21 gene profile (measuring mRNA) to render a specific “recurrence score” (from 0-100)

- Used to assess the predictive benefit of chemotherapy in reducing distant mets in women who are taking tamoxifen for 5 years.

ASSAY DESCRIPTION

Oncotype DX™ Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score™ is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

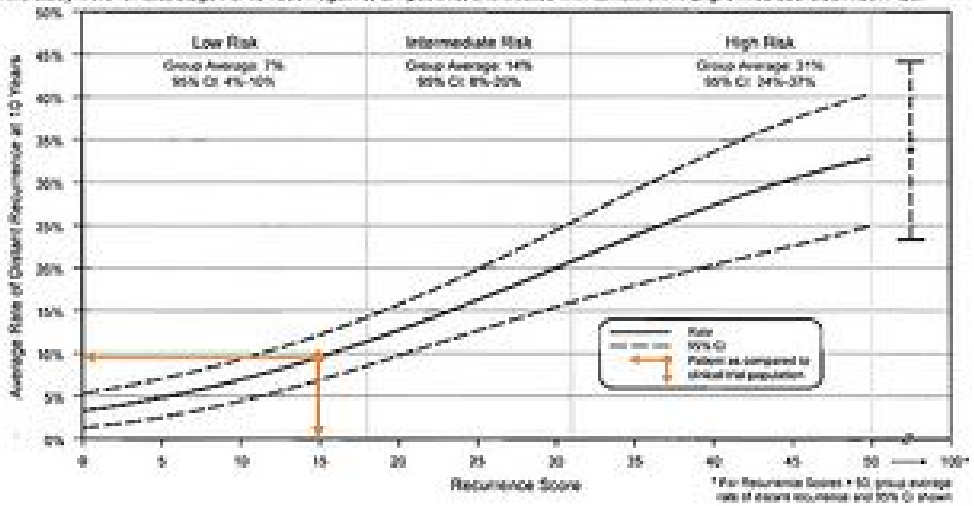
Recurrence Score = 15

Test results should be integrated using the information in the Clinical Experience section below, which applies only to patients consistent with this clinical experience.

CLINICAL EXPERIENCE

Patients with a Recurrence Score of 15 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 10% (95% CI: 7%-12%)

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018273

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

Oncotype Dx

- Score below 18: Chemo not likely beneficial
- Scores between 18-31: We don't know yet…
- Score 31-100: risk of distant recurrence is reduced by an absolute 28% with chemo (60% of women were without mets at 10 years with TAM only vs. 88% free of mets with TAM+CMF)

When all Stage I and II breast cancer patients are pooled (scores 0-100), the absolute benefit of chemo on prevention of distant mets in 10 years is 4%.

Genomic Signatures (DNA Microarray)

All look for *expressed genes* in the tumor cells

- Mammaprint®(Amsterdam 70-gene predictive profile)---Fresh
- Oncotype Dx®(21-gene recurrence score)---Fixed or Fresh
- 76-gene prognostic signature---Fresh
- Wound response---Fresh
- Two-gene ratio---Fixed

Mammaprint

- FDA Approval for lymph node negative breast cancer patients under 61 years of age with tumors of less than 5 cm.
- Stratifies patient into “low risk” or “high risk” of distant metastasis
- Unlike Oncotype, the outcome of intervention (ie, chemo) has not been assessed

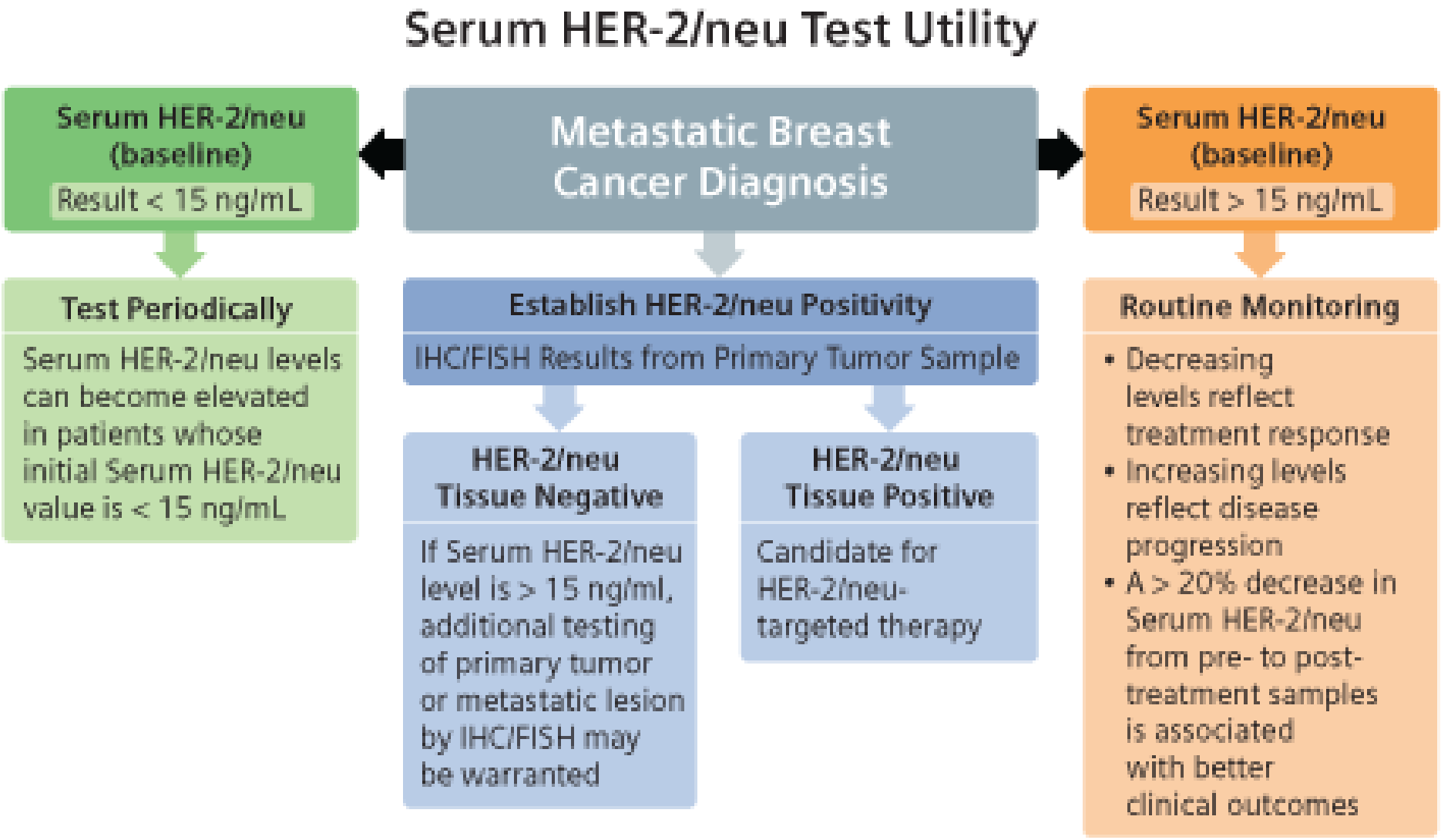
What ASCO has NOT Recommended

- Ki67, cyclin D, cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groups.
- The above tests include tissue specimens as well as serum.

Circulating Markers

- Her2/neu serum
- Capthesin D
- Cyclin E fragments
- Proteomic Analysis
- Bone marrow micrometastasis tests
- Circulating Tumor Cells (CTC's)

Serum Her-2/neu



Circulating Tumor Cells (CTC)

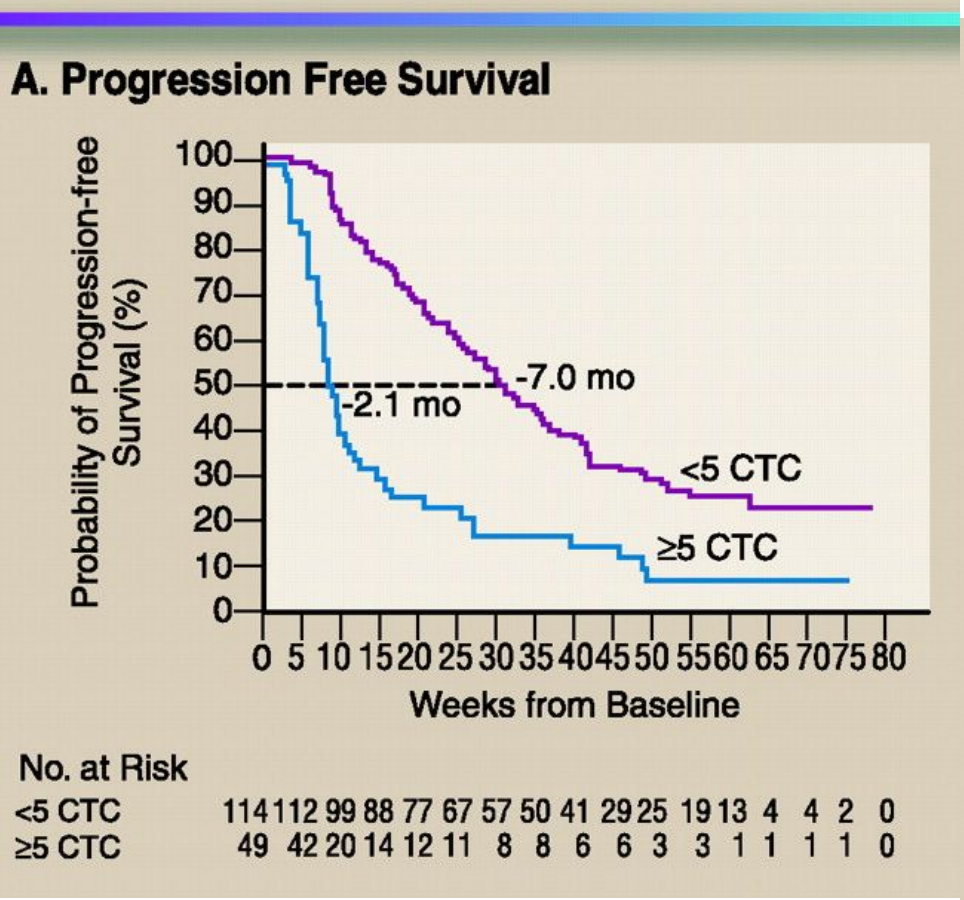
- Independent prognostic factor for distant mets free survival and Overall Survival (OS)
  - 115 pts with locally advanced operable Br Ca(f/u= 36 months)
  - 10% had >1CTC/7.5mL blood (before neoadjuvant chemo sample)

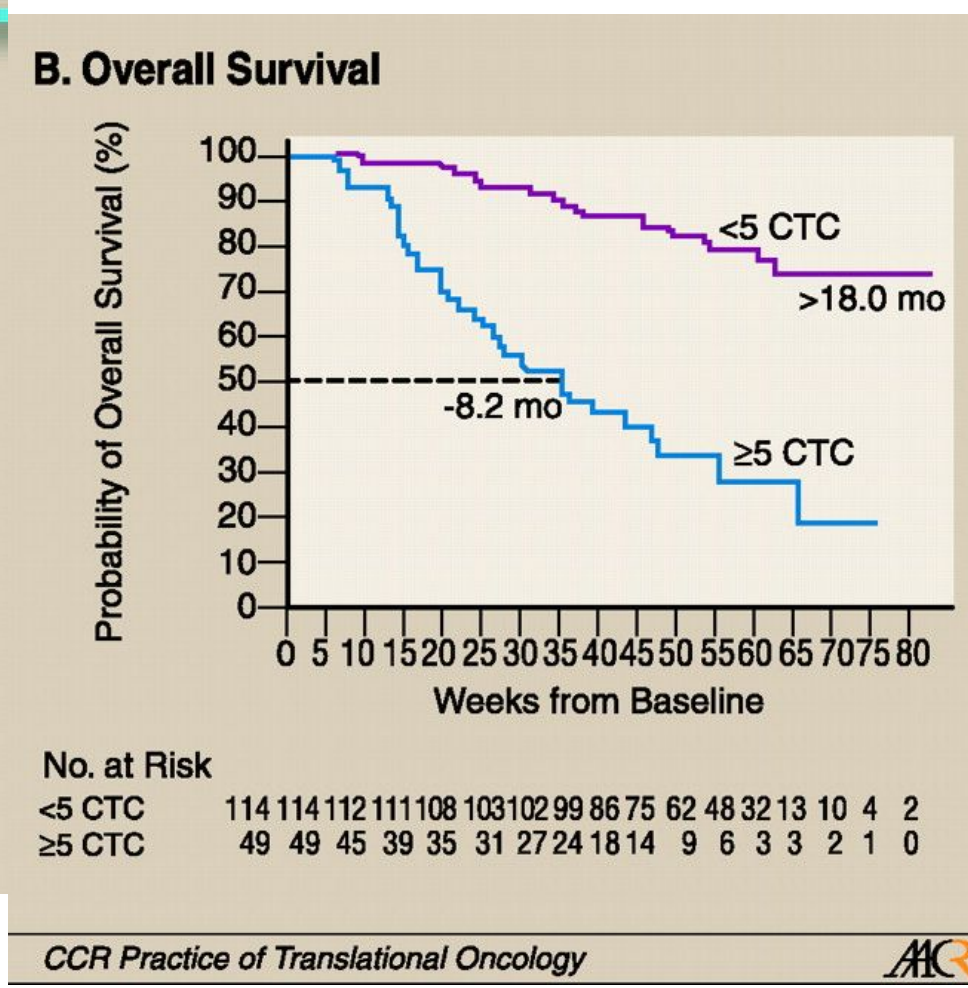
    F.-C. Bidard, Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer. *Ann Oncol October 22, 2009*
- reduced disease-free interval and overall survival, respectively, in node-negative breast cancer patients
  - 167 pts, node negative dz. Did correlate with Her2 +

    Nikos Xenidis, *Journal of Clinical Oncology*, Vol 24, No 23 (August 10), 2006: pp. 3756-3762

  Clinical Utility still being delineated…

J.-Y. Pierga, Circulating Tumor Cell Detection Predicts Early Metastatic Relapse After Neoadjuvant Chemotherapy… Clin. Cancer Res., November 1, 2008; 14(21): 7004 - 7010





Kaplan-Meier estimates of probabilities of progression-free survival and overall survival in patients with metastatic breast cancer for those with <5 CTCs per 7.5 mL of whole blood and those in the group with ≥5 CTCs in 7.5 mL of whole blood at the first follow-up visit after initiation of a new line of therapy (n=177 pts)

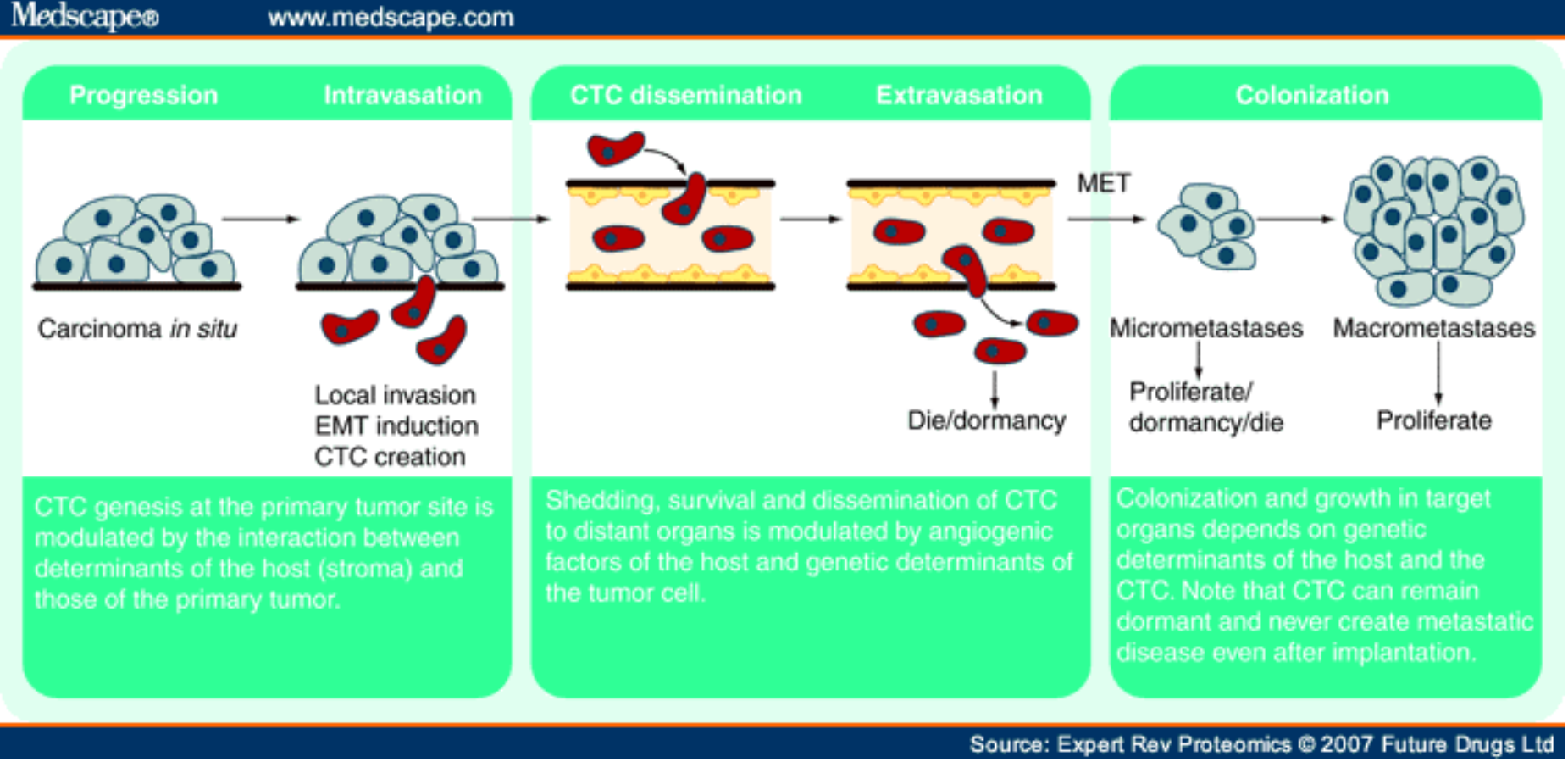
Hayes D F, Smerage J Clin Cancer Res 2008;14:3646-3650

Clinical Cancer Research

Bone Marrow Micrometastasis aka Disseminated Tumor Cells (DTC's)

Tumor type (M0)	Detection rate (%)
• Breast cancer	20-40
• Prostate cancer	20-50
• Lung cancer (NSCLC)	40-60
• Gastric cancer	35-60
• Esophageal cancer	30-40
• Pancreatic cancer	20-35
• Colorectal cancer	20-30

Review Paper: C. Alix-Panabieres, et al. Circulating Tumor Cells and Bone Marrow Micrometastasis *Clin. Cancer Res*., August 15, 2008; 14(16): 5013 - 5021.

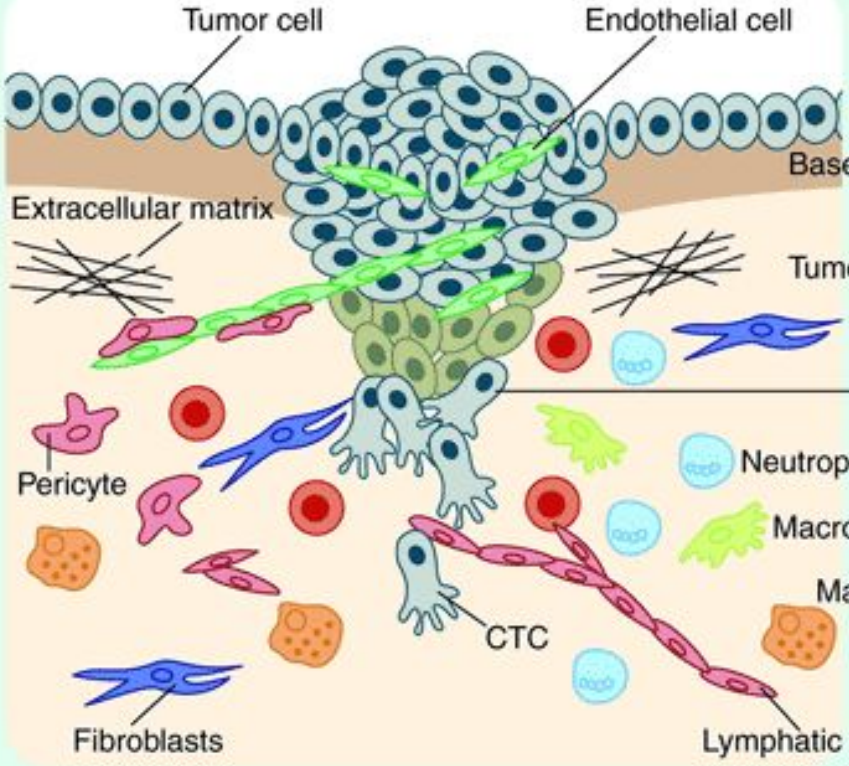


From Medscape:

Circulating Tumor Cells: Detection, Molecular Profiling & Future Prospects: The Metastatic Cascade in Carcinomas: How CTC Are Formed, When & Where They Are Shed, & How Efficient They Are in Creating Metastasis

"more than 30% of women with breast cancer have thousands of micrometastases in their bone marrow"

… less than half will have clinical metastasis.

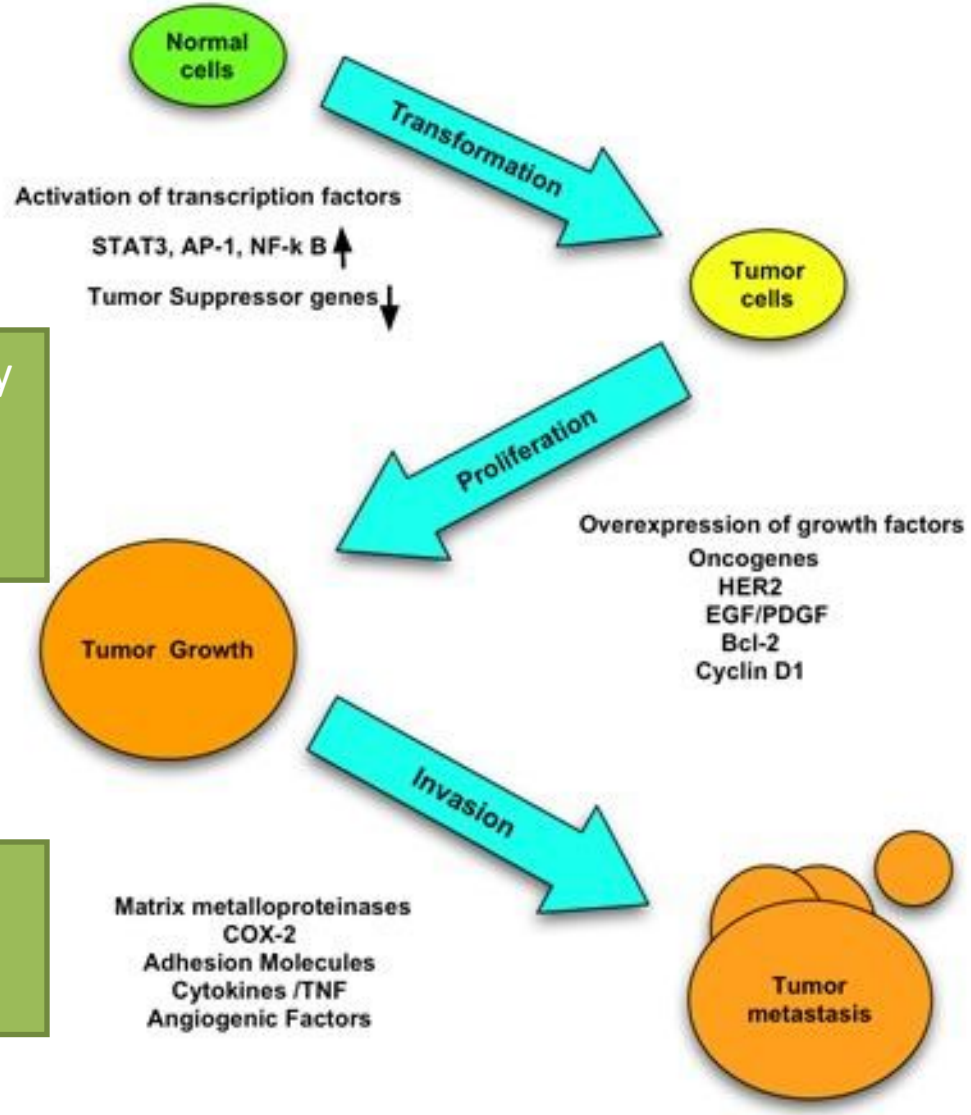


Loss of:	Gain of:
• Cytokeratin expression	• Fibroblast-like shape
• E-cadherin	• Motility
• Epithelial cell polarity	• Invasiveness
	• Mesenchymal gene expression program
	• N-cadherin and vimentin
	• Protease secretion (matrix metalloproteinase 2.9)
	• Fibronectin secretion
	• Expression of platelet-derived factor receptor and αvβ6

EMT

In order to acquire mobility and invasiveness, carcinoma cells need to shed many features of their epithelial phenotype and undergo drastic alterations, acquiring the morphology and gene expression pattern of mesenchymal cells (Figure 1). This process, termed epithelial–mesenchymal t ransition (EMT), is physiologically used for wound healing in mature organisms and, importantly, is essential during early embryogenesis .”

Overview of Cancerous Growth



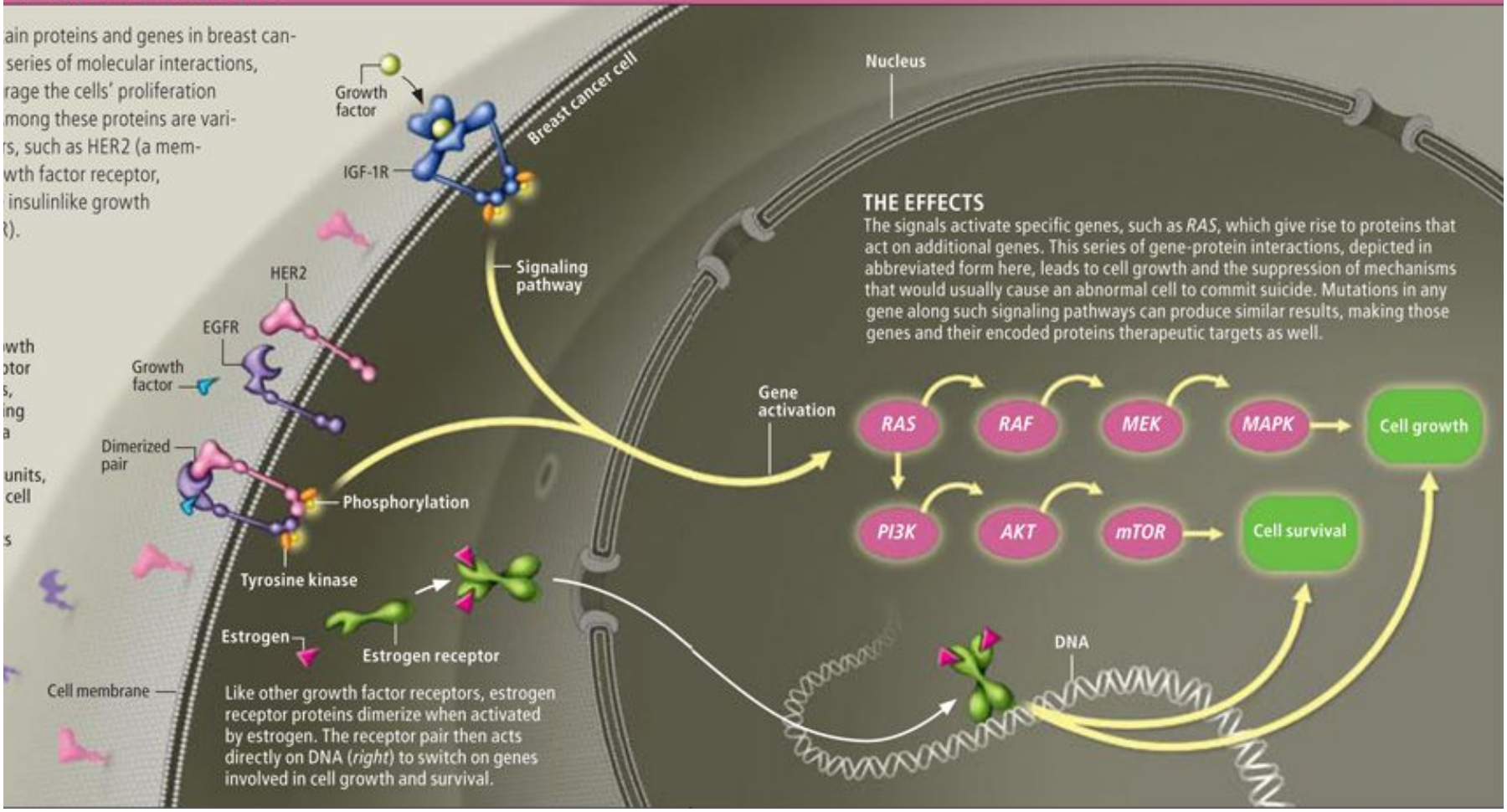
Pro-Inflammatory Molecules:
NF Kappa B
Cox-2

Growth Factors:
VEGF
IGF

Cytokines
IL-6
IL1B

PATHWAYS

ain proteins and genes in breast can-
series of molecular interactions,
rage the cells' proliferation
mong these proteins are vari-
s, such as HER2 (a mem-
wth factor receptor,
insulinlike growth
).



Growth Factors- General List

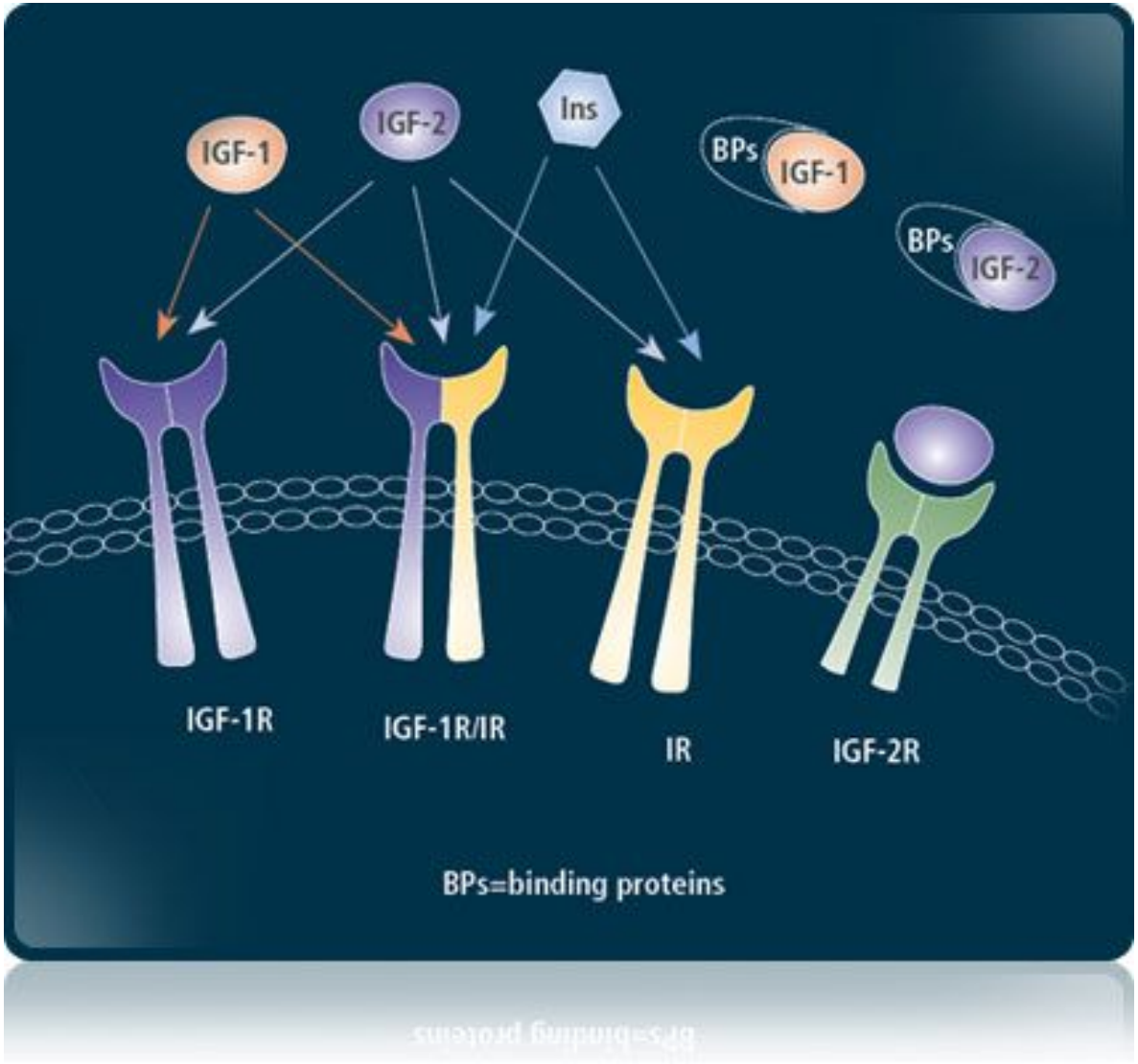
- Bone morphogenetic proteins (BMPs)
- Epidermal growth factor (EGF)
- Erythropoietin (EPO)
- Fibroblast growth factor (FGF)
- Granulocyte-colony stimulating factor (G-CSF)
- Granulocyte-macrophage colony stimulating factor (GM-CSF)
- Growth differentiation factor-9 (GDF9)
- Hepatocyte growth factor (HGF)
- Hepatoma derived growth factor (HDGF)
- Insulin-like growth factor (IGF)
- Myostatin (GDF-8)
- Nerve growth factor (NGF) and other neurotrophins
- Platelet-derived growth factor (PDGF)
- Thrombopoietin (TPO)
- Transforming growth factor alpha(TGF-α)
- Transforming growth factor beta (TGF-β)
- Vascular endothelial growth factor (VEGF)

Cancer cells use many growth factors to their advantage.

In addition to circulating GF's, many GF's are made within the tumor niche, by the cancer cells themselves or by neighboring stroma or immune cells.

Endocrine/
Autocrine/Paracrine

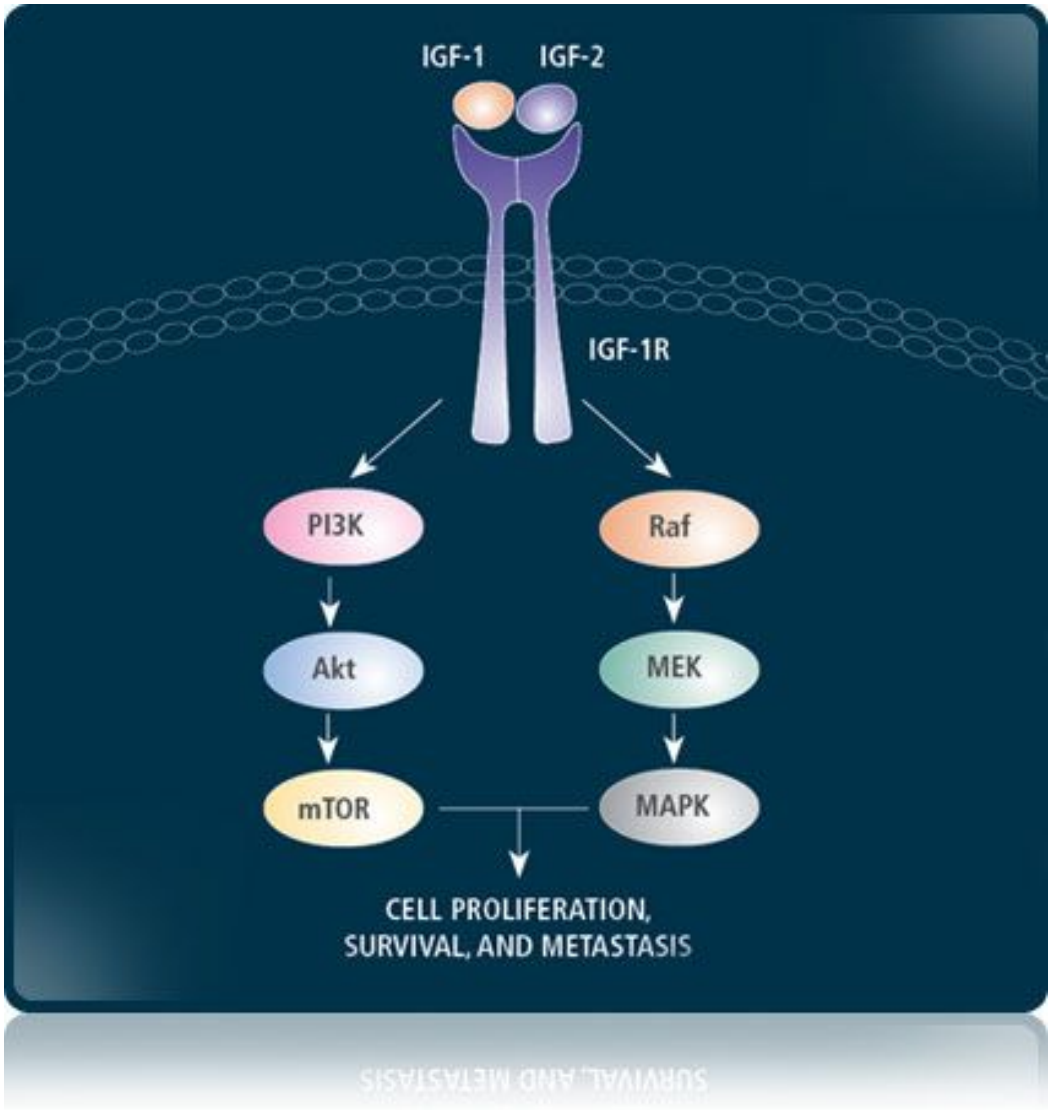
Insulin Like Growth Factor 1 and2



IGF-1, IGF-2

IGF-1 is normally produced by the liver and stimulated by Growth Hormone (GH)

Estrogen Receptor alpha (ERα) can translocate to the cell membrane and bind/ stimulate IGFR1. (Not so for ERβ)



Circulating IGF-1 levels

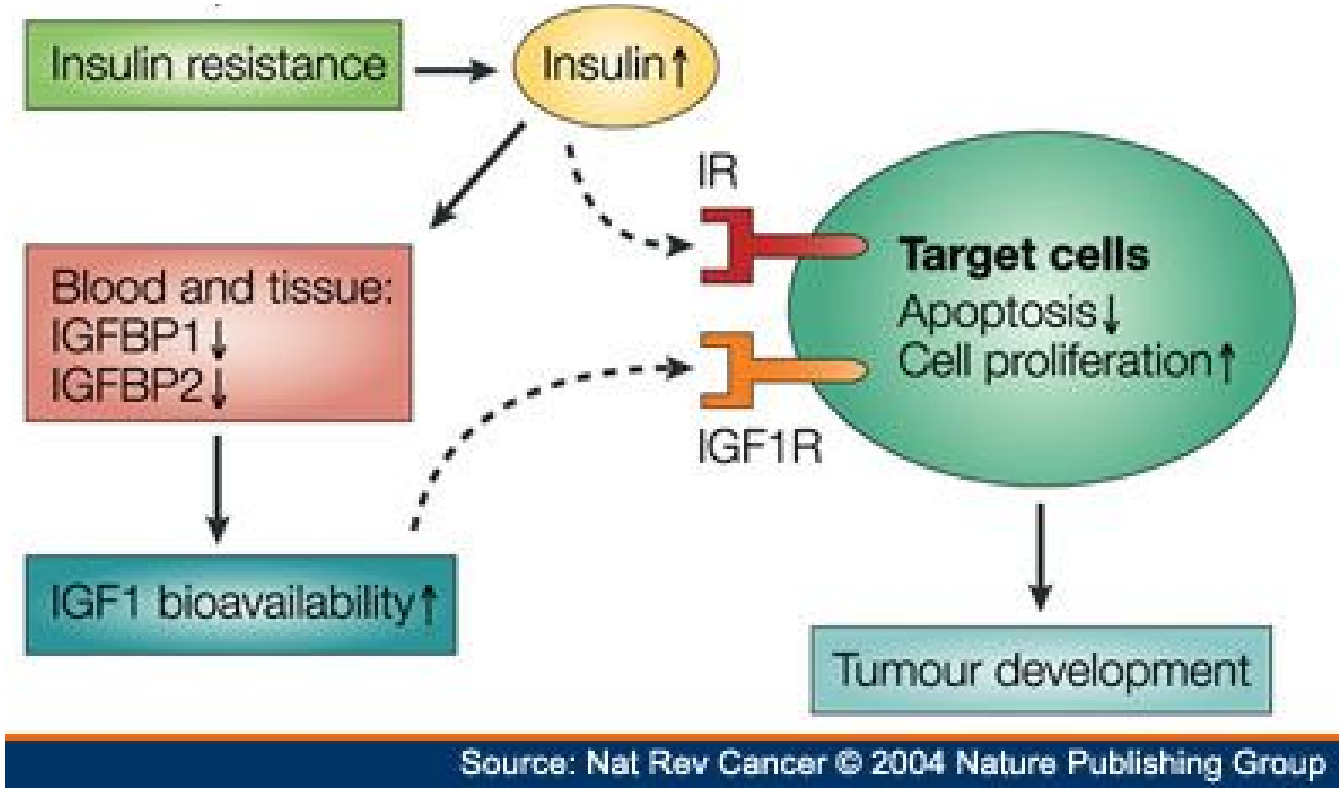
- Higher levels of IGF-1 assoc with risk in premenopausal, but not post menopasual women (A. G. Renehan, et al. Breast Cancer Online (2005), **8**:**1**:e1
- IGF-1 mRNA in the liver was positively associated with dietary casein (rats)
  - *British Journal of Nutrition* **67** (2): 257.

C-peptide/ Insulin

C-peptide is concordant with insulin levels, with less variability

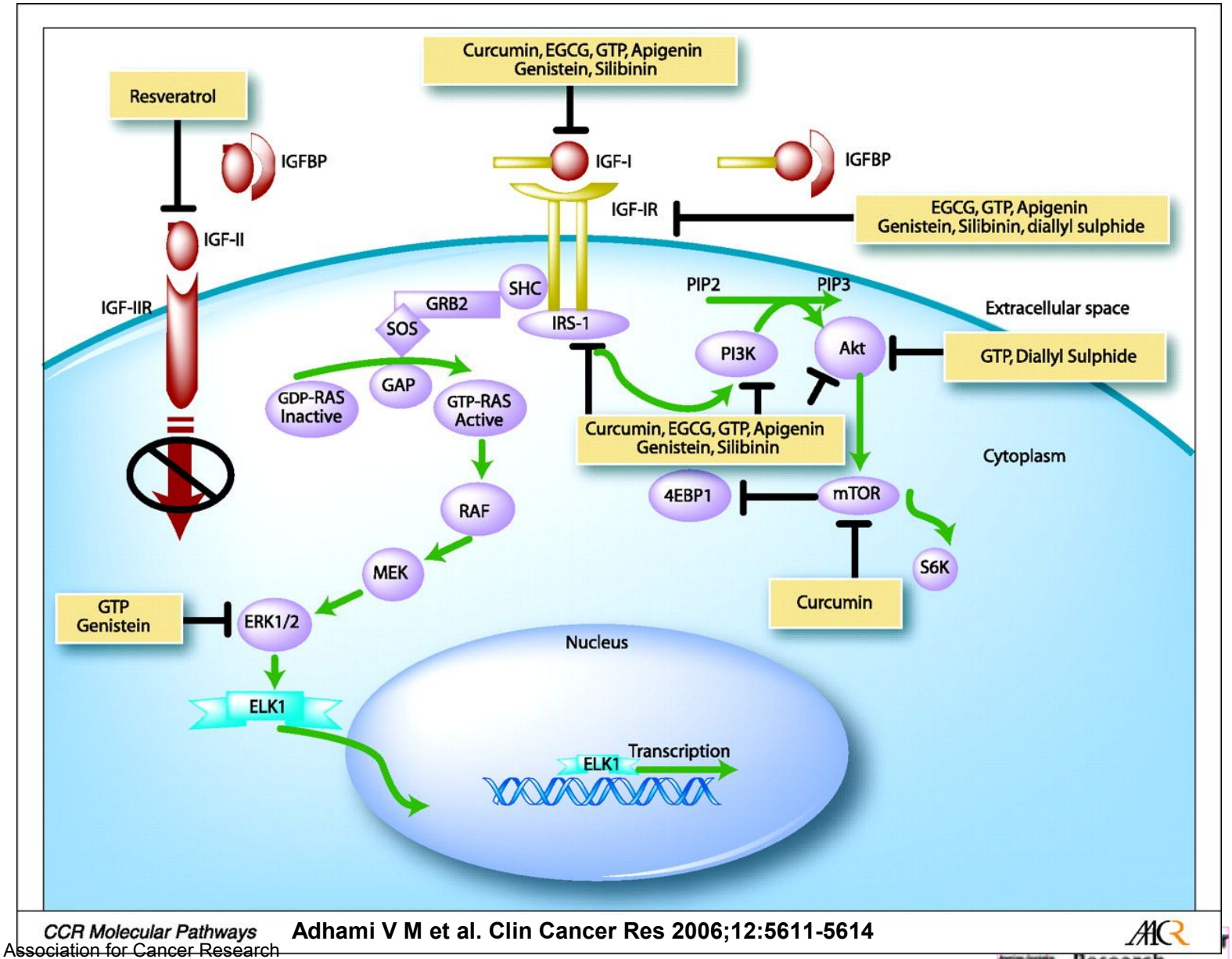
- Insulin promotes Tamoxifen resistance (via transcription factor *T-bet*)
- Insulin is known to decrease binding proteins (BP's) for IGF-1, rendering more IGF-1 available
- C-peptide is inversely assoc. with SHBG (thus increasing free estrogens)
- Higher serum levels of C-peptide assoc. with sig lower EFS(1)

(1)Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Vol 24, No 18S (June 20 Supplement), 2006: 524



- Diet
- Exercise
- Avoidance of exogenous IGF-1 or GH
- Caution with some “anti-aging” protocols that raise GH

IGF-I and Natural Agents that block downstream signals of growth, survival and metastasis



CCR Molecular Pathways Adhami V M et al. Clin Cancer Res 2006;12:5611-5614

Natural agents that block/ lower IGF-1

- green tea polyphenol (GTP in pathway)
- lycopene
- curcumin
- silibinin
- apigenin
- resveratrol
- genistein
- Retinoic acid increases BP-3 (the predominant BP)
- $1,25(OH)_2D_3$ increases BP-3
- Melatonin

Estrogens and their metabolites

- Goal: Inc. 2 and decrease 16 metabolites
- Avoid exogenous Est's
- Fish oil
- Flax seeds
- I3C/ DIM
- Isoflavones (?)
- Weight loss
- Exercise
- Rosemary
- Turmeric

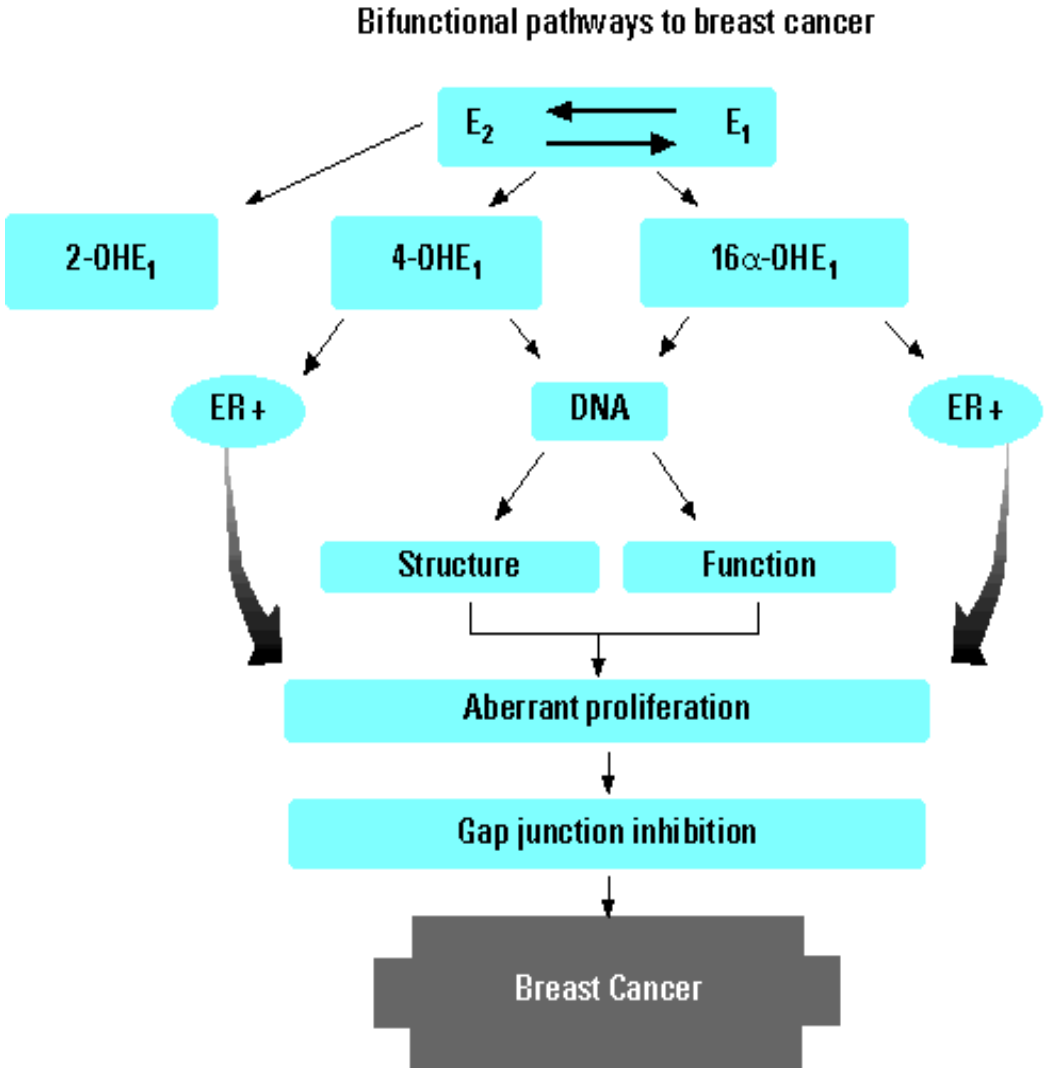


Table 1
Pharmacological effects of indole-3-carbinol metabolites in cancer cells

Metabolite	Cellular responses	Signaling targets		Ref.
DIM	1. Apoptosis induction and cell cycle arrest 2. Inhibition of angiogenesis 3. Androgen receptor (AR) down- regulation 4. Activation of aryl hydrocarbon receptor (AhR) and consequent activation gene expression of Phase I and II enzymes 5. Inhibition of ERα-dependent gene expression	↓ ↑	Akt phosphorylation NF-κB signaling Survivin expression Bcl-2 expression Cdc25A expression CDK 6 expression AR expression ERα signaling $p21^{WAF1}$ expression $p27^{kip1}$ expression DR5 expression AhR signaling	[14,38–46,50,51]
ICZ	Activation of AhR and consequent activation of gene expression of Phase I and II enzymes	↑	AhR signaling	[47,48]
LTr_1	1. An antagonist of estrogen receptor (ER)α 2. A weak agonist of AhR	↓ ↑	ER signaling AhR signaling	[52]
CTr	A potent agonist of (ER)α	↑	ER signaling	[53]
CTet	Cell cycle arrest	↓ ↑	CDK 6 expression $p27^{kip1}$ expression	[49]

↓, down-regulation; ↑, up-regulation.

Estrogenomics-

- Tests for the presence of SNP's in metabolic pathways of estrogen metabolism
- Inflammatory markers
- Vitamin D receptor
- Coagulation

Estrogenomics

Estrogen Metabolism

- CYP1A1 • CYP1B1
- GST (M1 and P1)
- COMT (catechol-O-methyl transferase)

HyperCoagulation

- GP3a (Glycoprotein 3)
- PAI-1 (Plasminogen activator inhibitor-1)
- Factor 2 (Prothrombin)
- Factor 5 (Leiden)

Cardiovascular

- Apo E (Apoliprotein E)
- MTHFR
- TNF-α • IL-6

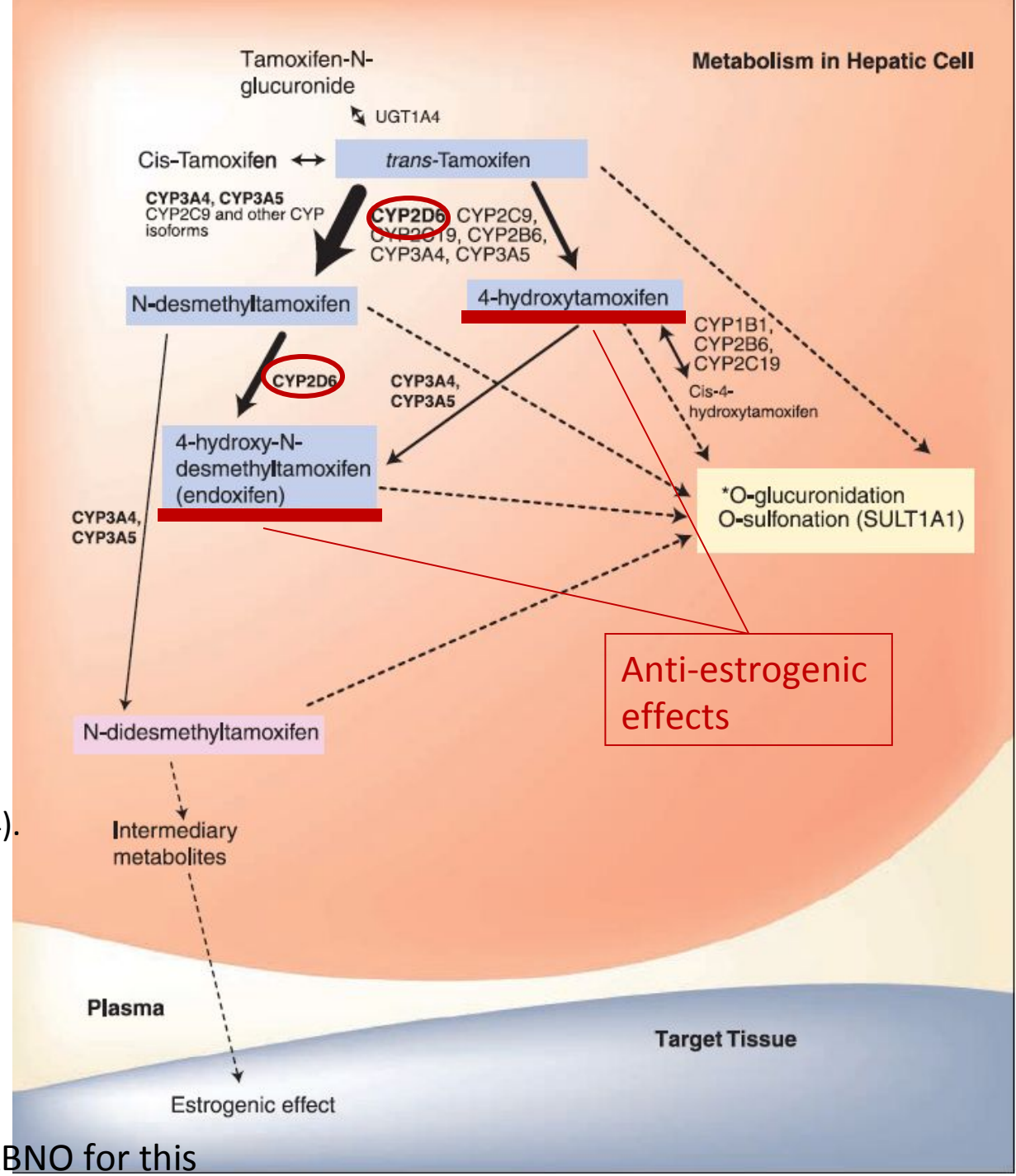
Osteoporosis

- VDR • COL1A1
- TNF-α • IL-6

SNPs and Tamoxifen metabolism

Women with SNP in CYP2D6 who are poor metabolizers do not benefit from Tamoxifen and have a 3.8x increased risk of recurrence

Tan, et al. Clin Cancer Res, 2008; 14(24).

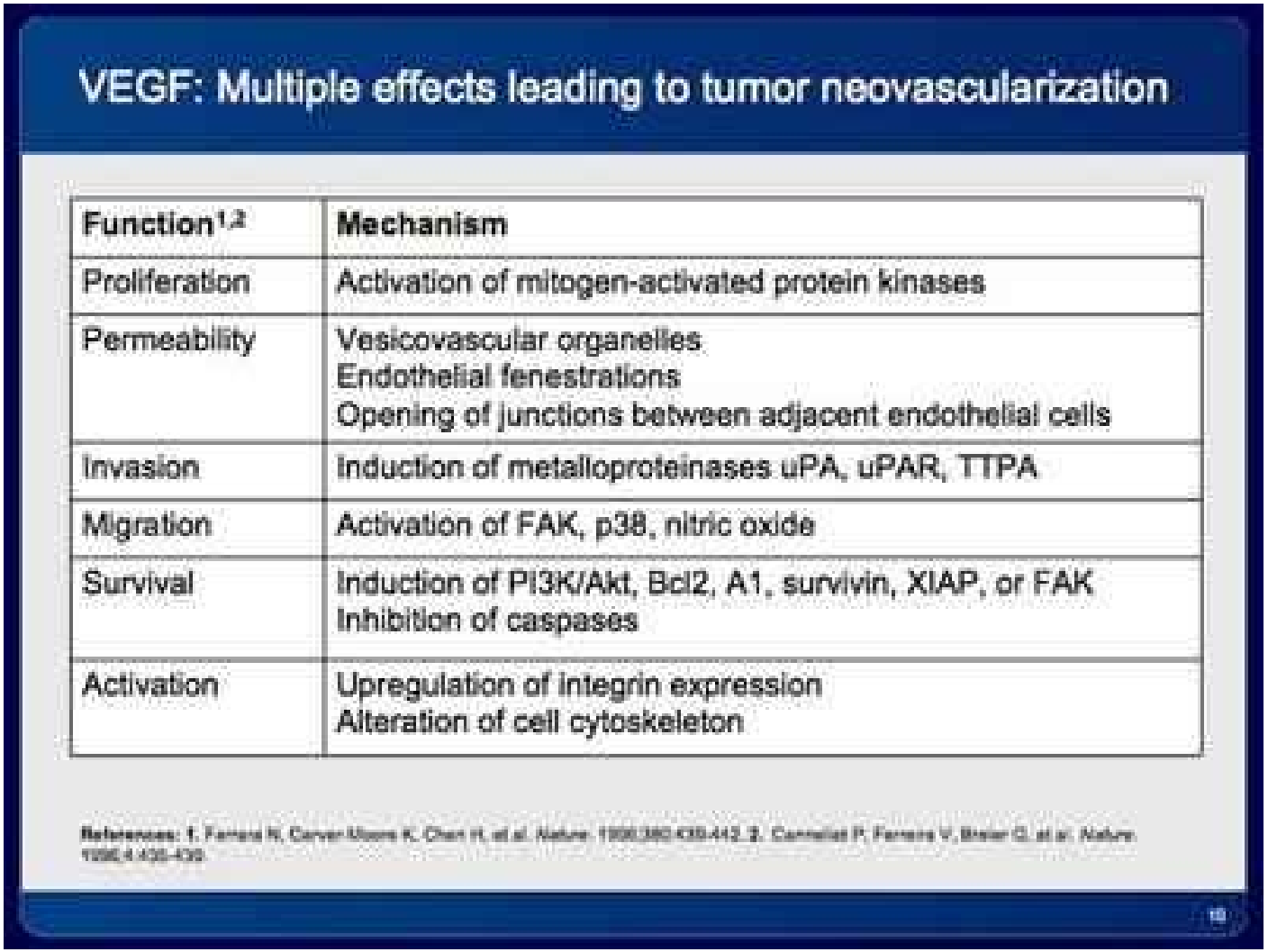


Gratitude to Lise Alschuler, ND, FABNO for this

Should we test estrogens? Metabolites? SNP's?

- Serum Estradiol, SHBG, testosterone
  - Salivary testing?
- 2/16 metabolite testing
  - Yes: in patients not taking aromatase inhibitors
  - Measure baseline when patient is living a lifestyle they can permanently maintain
- Estrogenomics

Vascular Endothelial Growth Factor



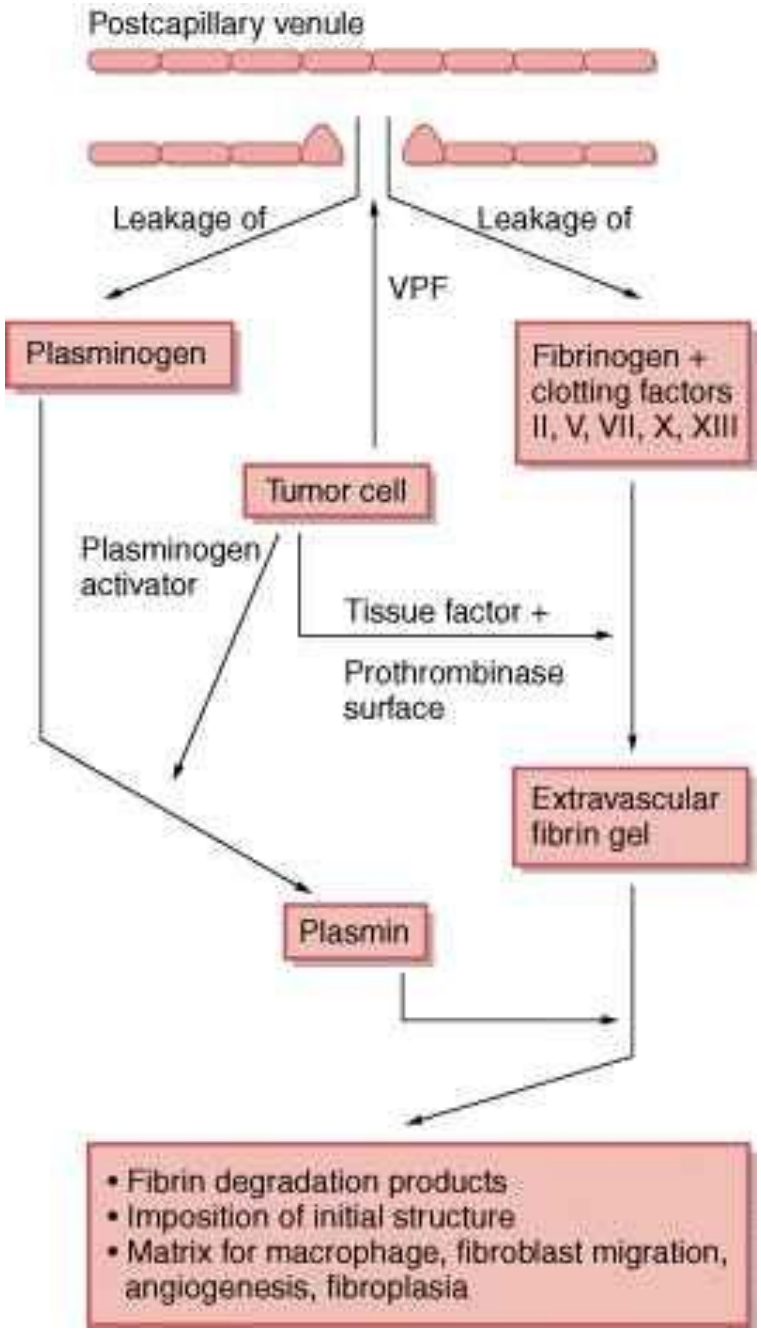
VEGF: Multiple effects leading to tumor neovascularization

Function[1,2]	Mechanism
Proliferation	Activation of mitogen-activated protein kinases
Permeability	Vesicovascular organelles Endothelial fenestrations Opening of junctions between adjacent endothelial cells
Invasion	Induction of metalloproteinases uPA, uPAR, TTPA
Migration	Activation of FAK, p38, nitric oxide
Survival	Induction of PI3K/Akt, Bcl2, A1, survivin, XIAP, or FAK Inhibition of caspases
Activation	Upregulation of integrin expression Alteration of cell cytoskeleton

References: 1. Ferrara N, Carver-Moore K, Chen H, et al. Nature. 1996;380:439-442. 2. Connolly P, Ferrara V, Breier G, et al. Nature. 1996;4:439-439.

Vascular Endothelial Growth Factor

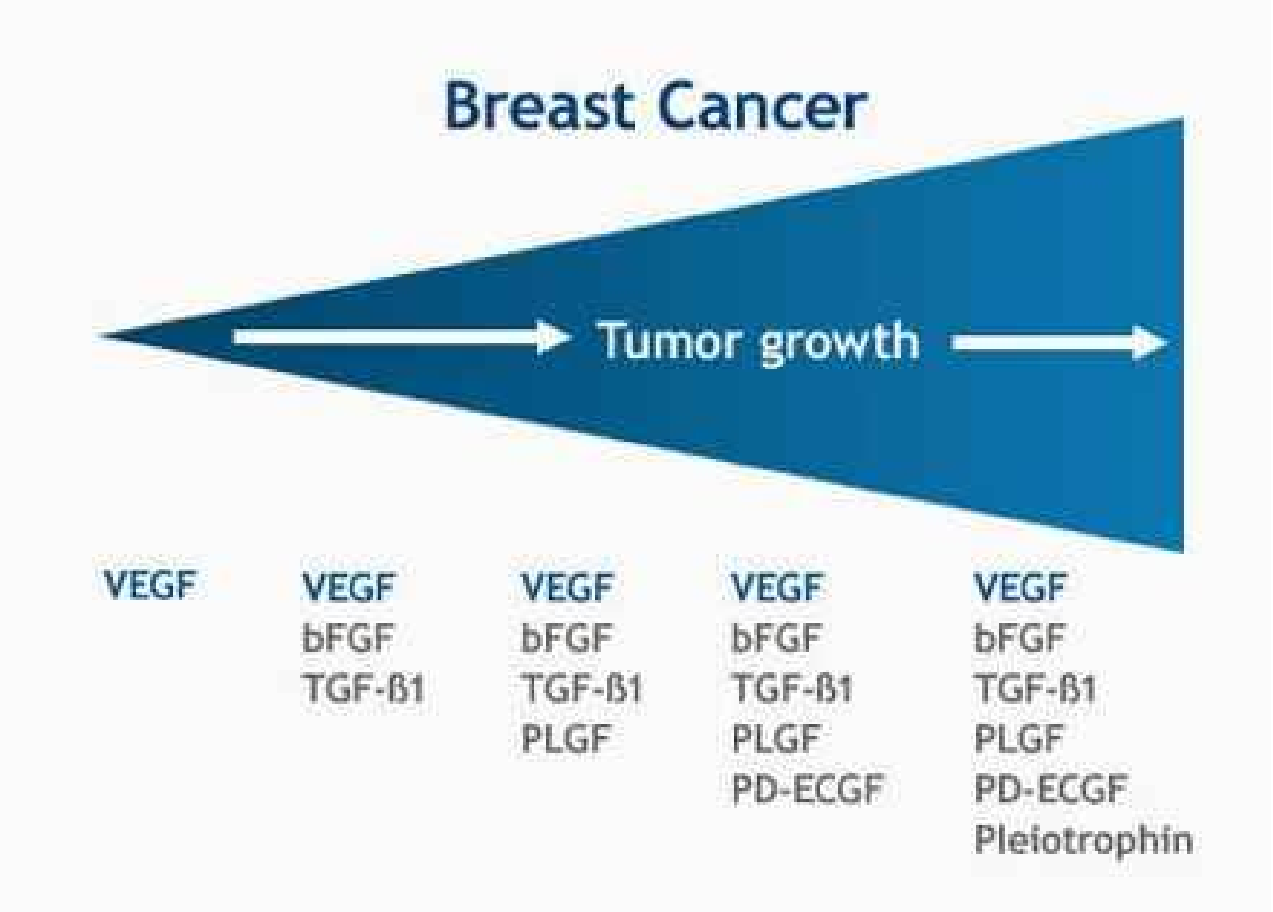
- VEGF is expressed in the majority of invasive ductal carcinoma's, regardless of stage/ grade/ histology
- VEGF expression in tumor tissue is strongly associated with high microvascular density (poorer prognosis)
- Over-expression of VEGF in cancer cells correlates with poor prognosis in breast cancer
- 50,000 x more powerful than histamine at increasing capillary permeability

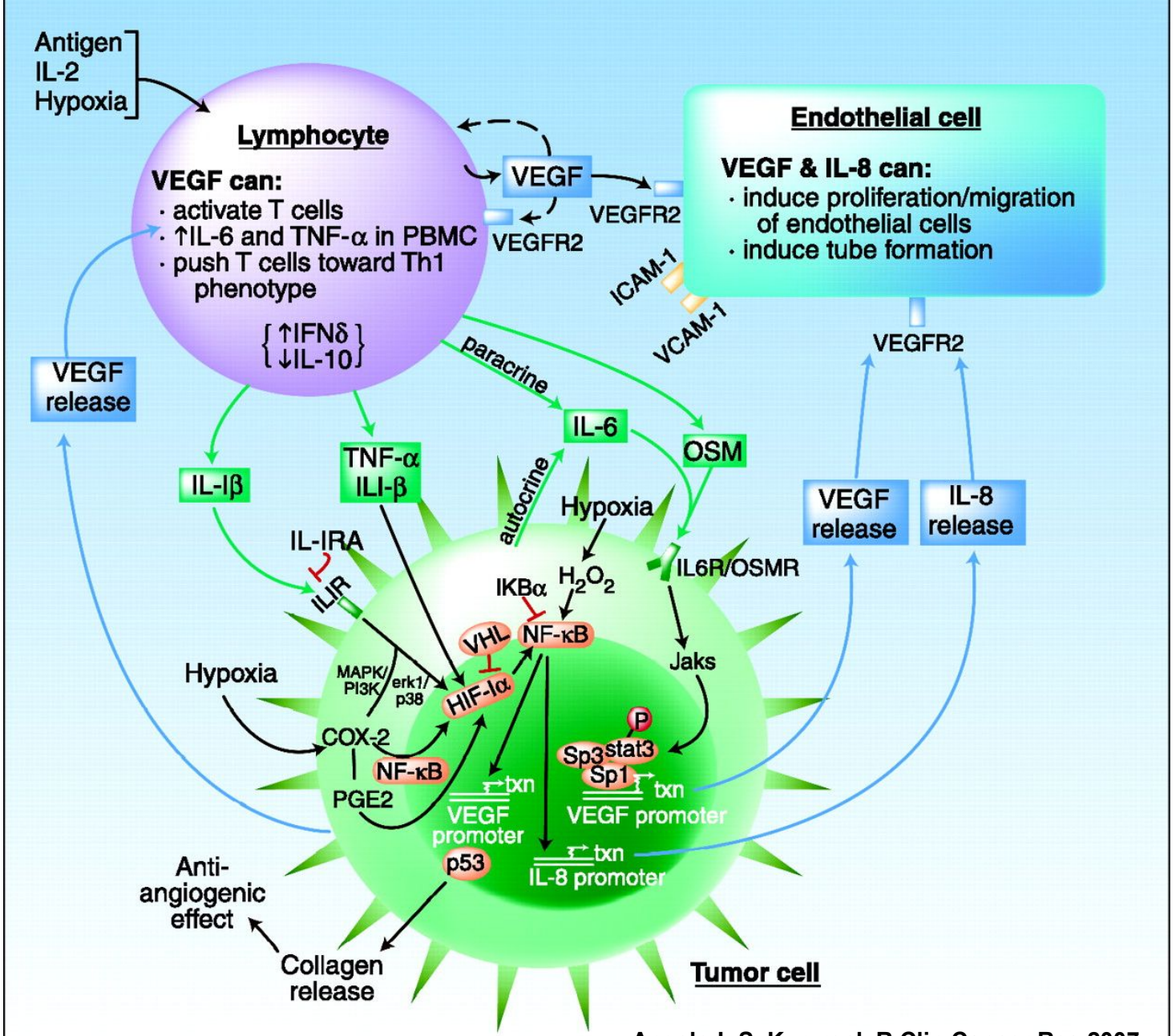


Fibrinogen/ fibrin and angiogenesis

- D-dimers and Fibrinogen correlated with extent of breast cancer, progression rate and survival (*British Journal of Cancer* (2002) **86**, 389–395.
- Ultimately, lowering VEGF is goal
- Lower Fibrinogen with:
  - Curcumin
  - Garlic

VEGF- expressed throughout growth





Angelo L S, Kurzrock R Clin Cancer Res 2007; 13:2825-2830

Circulating VEGF and IL-6

- No significant difference in levels of serum VEGF or platelet derived VEGF, in normal(n=26) vs. local(n=31) vs. metastatic (n=73)breast cancers.

- Serum levels of IL-6 were 10 times higher in women with distant metastasis compared to locoregional disease.
  - (Clin Breast Cancer. 2002 Jan;2(4):311-5. Serum interleukin 6, EGF, serum VEGF, and VEGF platelet load in breast cancer patients)

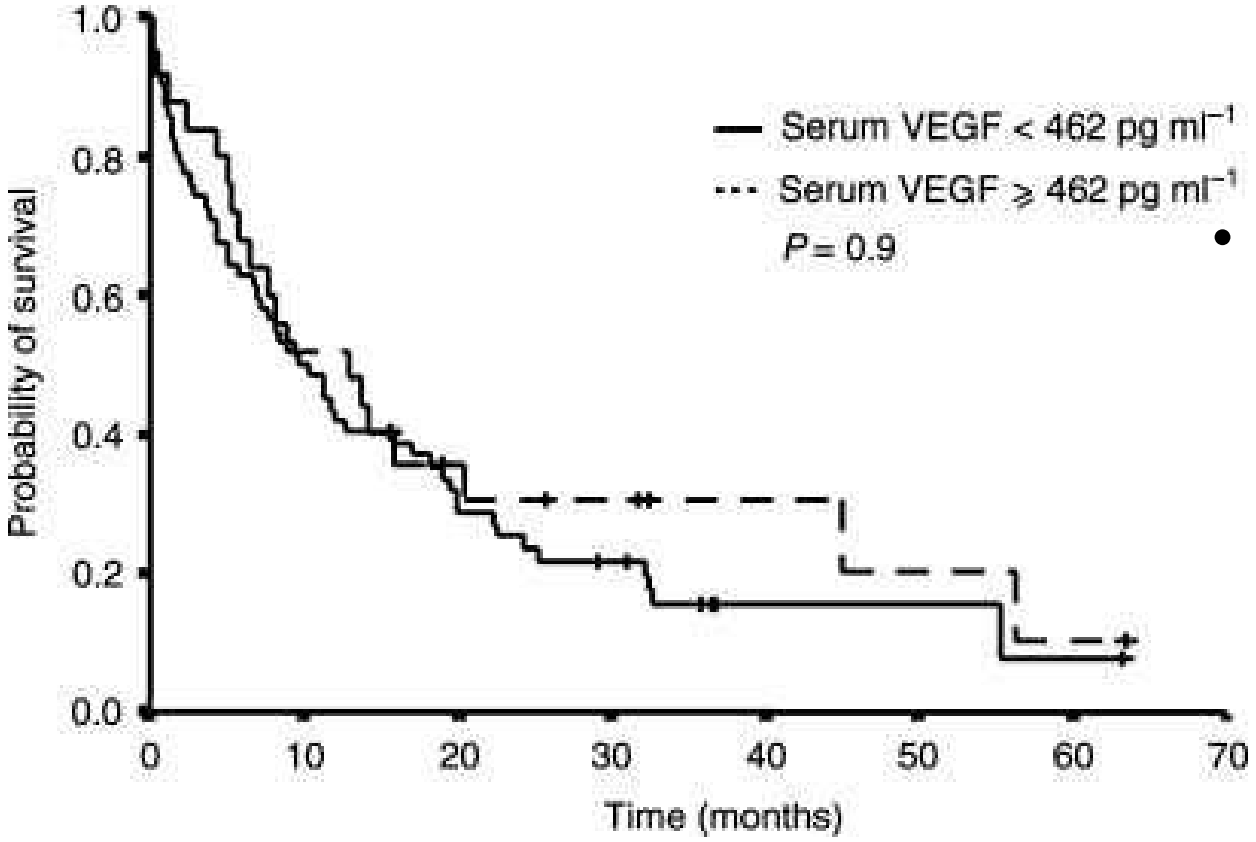
Interleukin-6

- Serum and plasma concentrations of VEGF and serum concentration of IL-6 were measured in 87 patients with a fully documented history of hormone-refractory metastatic breast cancer…

- The presence of high levels of serum IL-6, but not VEGF, was significantly correlated with shorter survival.

Bachelot et al. Br J Cancer, 2003

VEGF levels not correlated to survival



- plasma or serum VEGF not correlated with survival in metastatic breast cancer patients

However, where there's VEGF, there's IL-6…

Interleukin-6

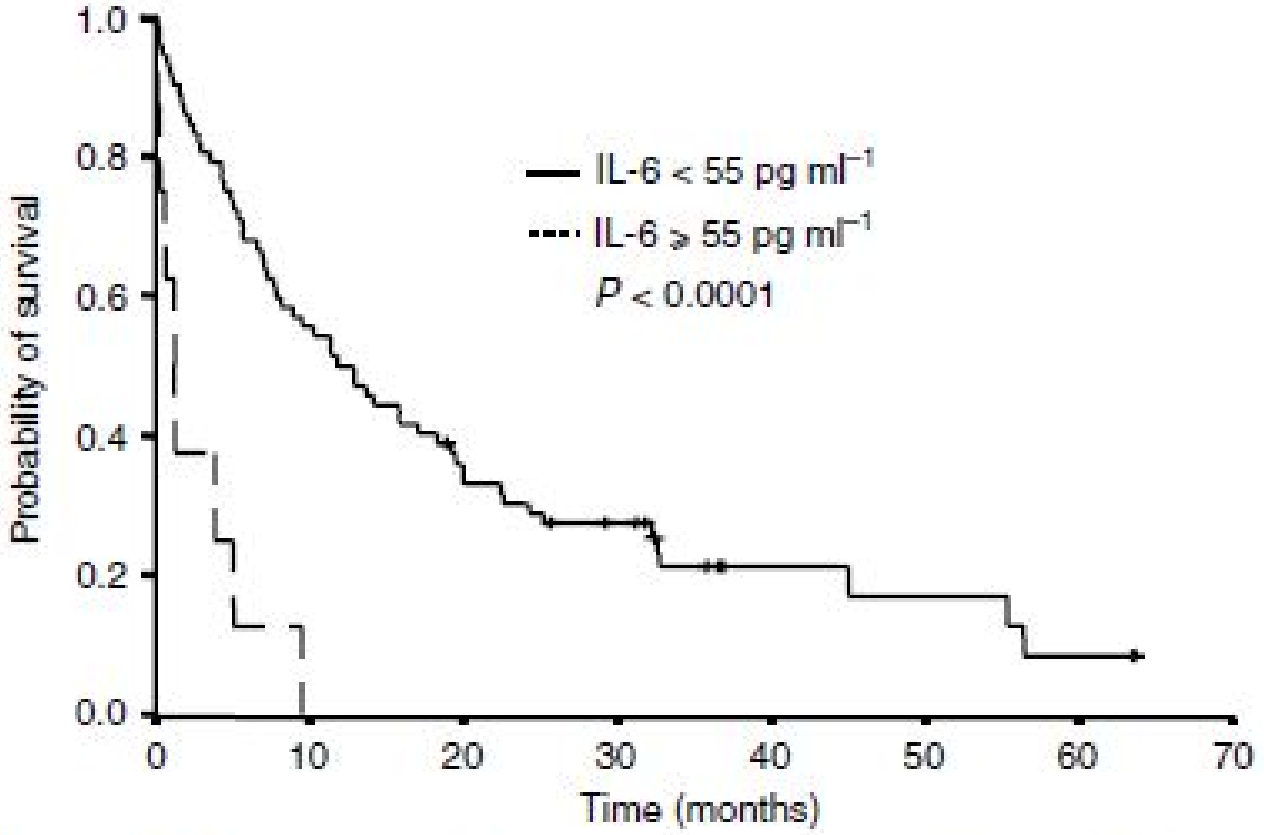


Figure 2 Survival of patients as a function of serum IL-6 levels. Patients with high levels of serum IL-6 constituted a subgroup of very poor prognosis. The cutoff value (55 pg ml^{-1}) represents the highest quartile for serum IL-6 levels when detectable.

Bachelot et al. Br J Cancer, 2003

IL-6

- Il-6 expression of tumors of women with early stage carcinomas correlated with low grade, ER+ status and better prognosis
- IL-6 upregulates aromatase in malignant tissue
- Inhibits apoptosis
- Promotes osteoclast formation and inhibits dendritic cell differentiation

Should we test IL-6?

- As with all testing that renders prognostic information, the clinical benefit is weighed against the possible psychological risk.

Natural Agents that inhibit VEGF

- Alliin
- Caffeic acid
- Capsaicin
- Curcumin
- Diallyl disulfide, diallyl sulfide
- Gingerol, perillyl alcohol (D-limonene)
- Phytic acid
- rosmarinic acid
- sulforaphane

Herbs that decrease VEGF

Artemisia annua (Chinese wormwood)
Viscum album (European mistletoe)
Curcuma longa (turmeric)
Camellia sinensis (green tea)
Vitis vinifera (grape seed extract)
Angelica sinensis (dong quai)
Taxus brevifolia (Pacific yew)
Scutellaria baicalensis (Chinese skullcap)
Polygonum cuspidatum (Japanese knotweed)
Silybum marianum (milk thistle)
Magnolia seed cones
Other Chinese herbs (see Table VI)

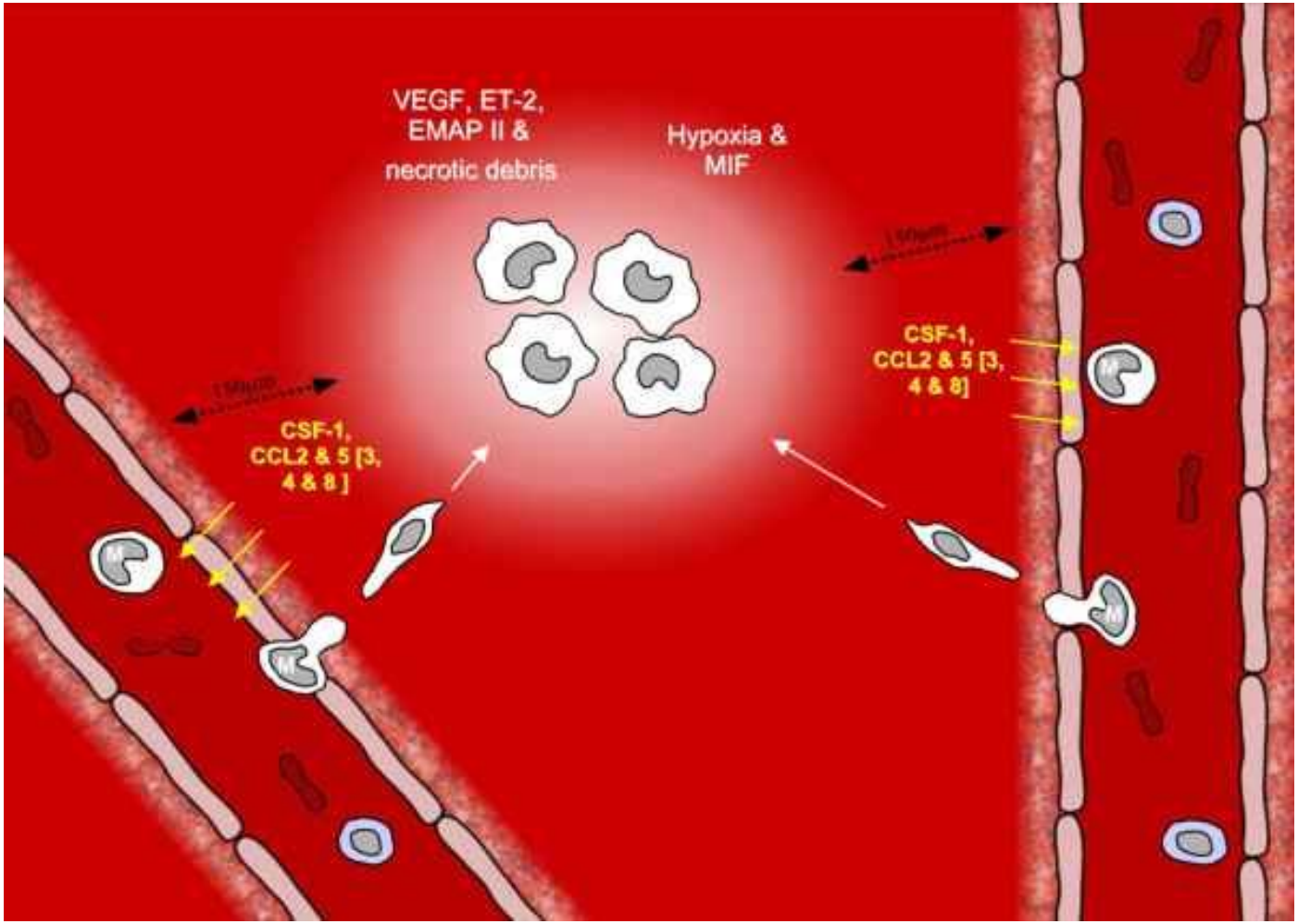
Sagar et al. Curr Oncology, 2006;13(1)

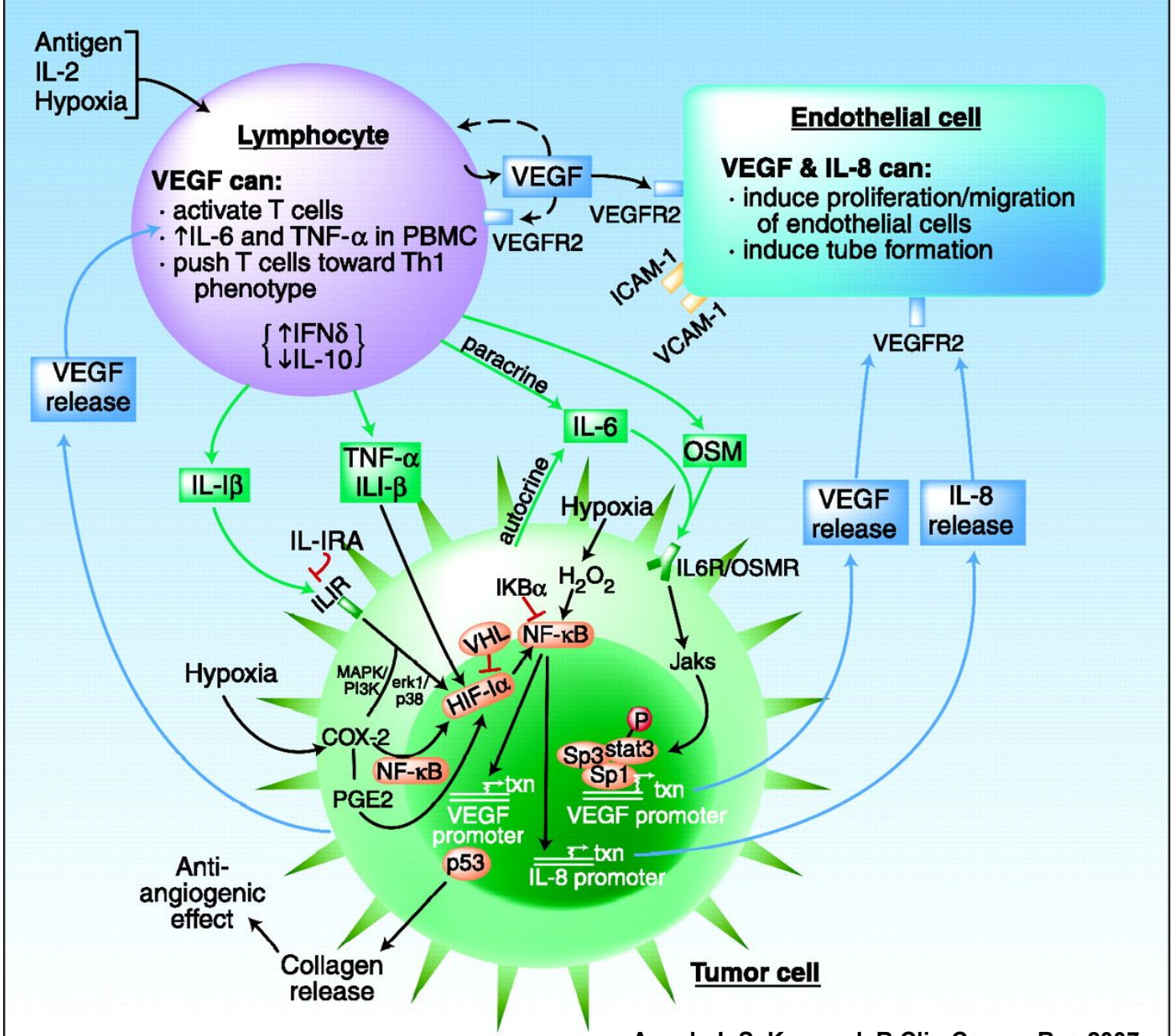
Natural Agents that inhibit IL-6

- Resveratrol– 300-500 mg transresveratrol qd
- Green Tea--
- Luteolin—celery, parsley, tomatoes,
- Apigenin- food derived
- Curcumin--

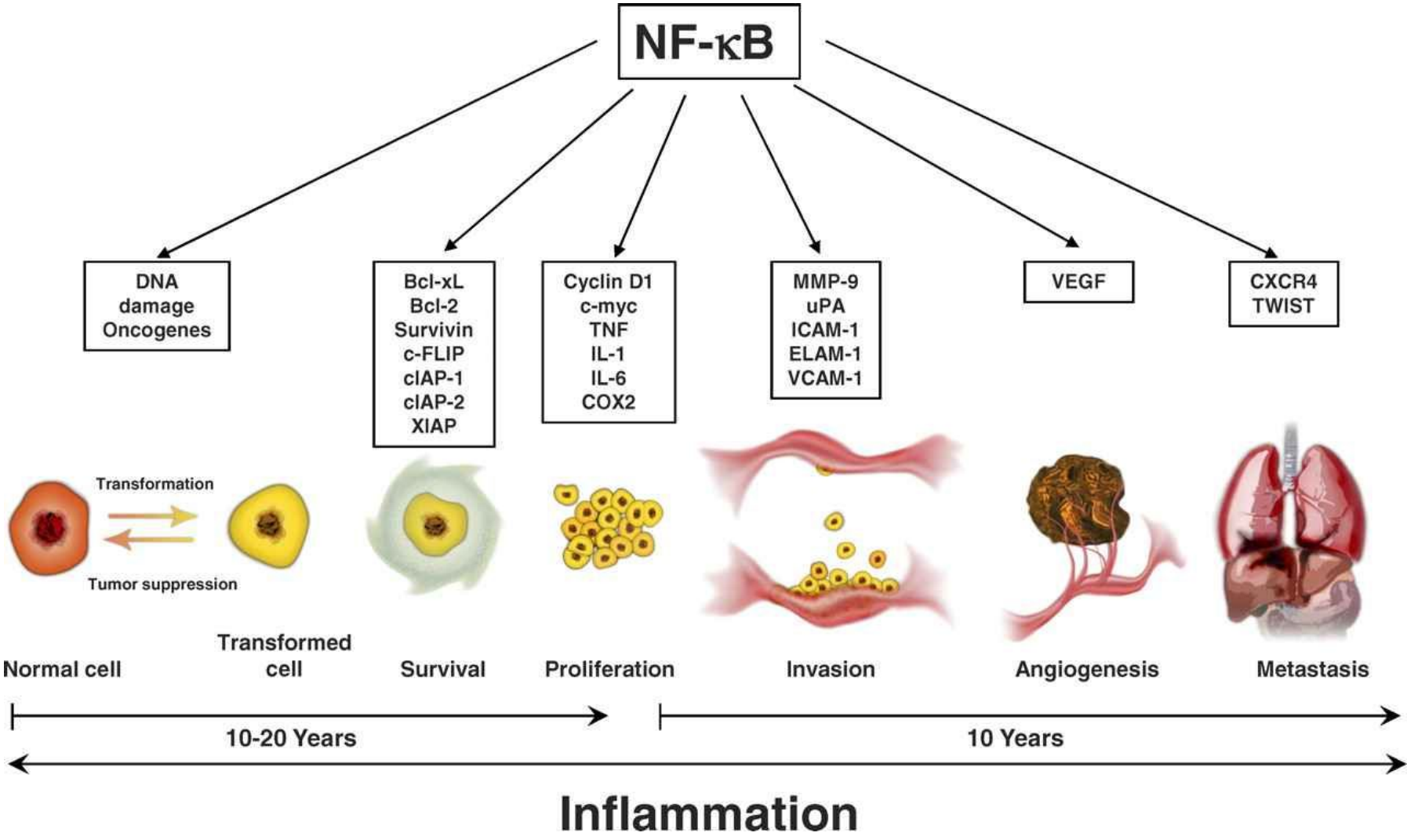
- Shifting to immune balance from Th2 to Th1
  - Trametes
  - Ganoderma
  - Agaricus

Monocytes/ Macrophages





Angelo L S, Kurzrock R Clin Cancer Res 2007; 13:2825-2830

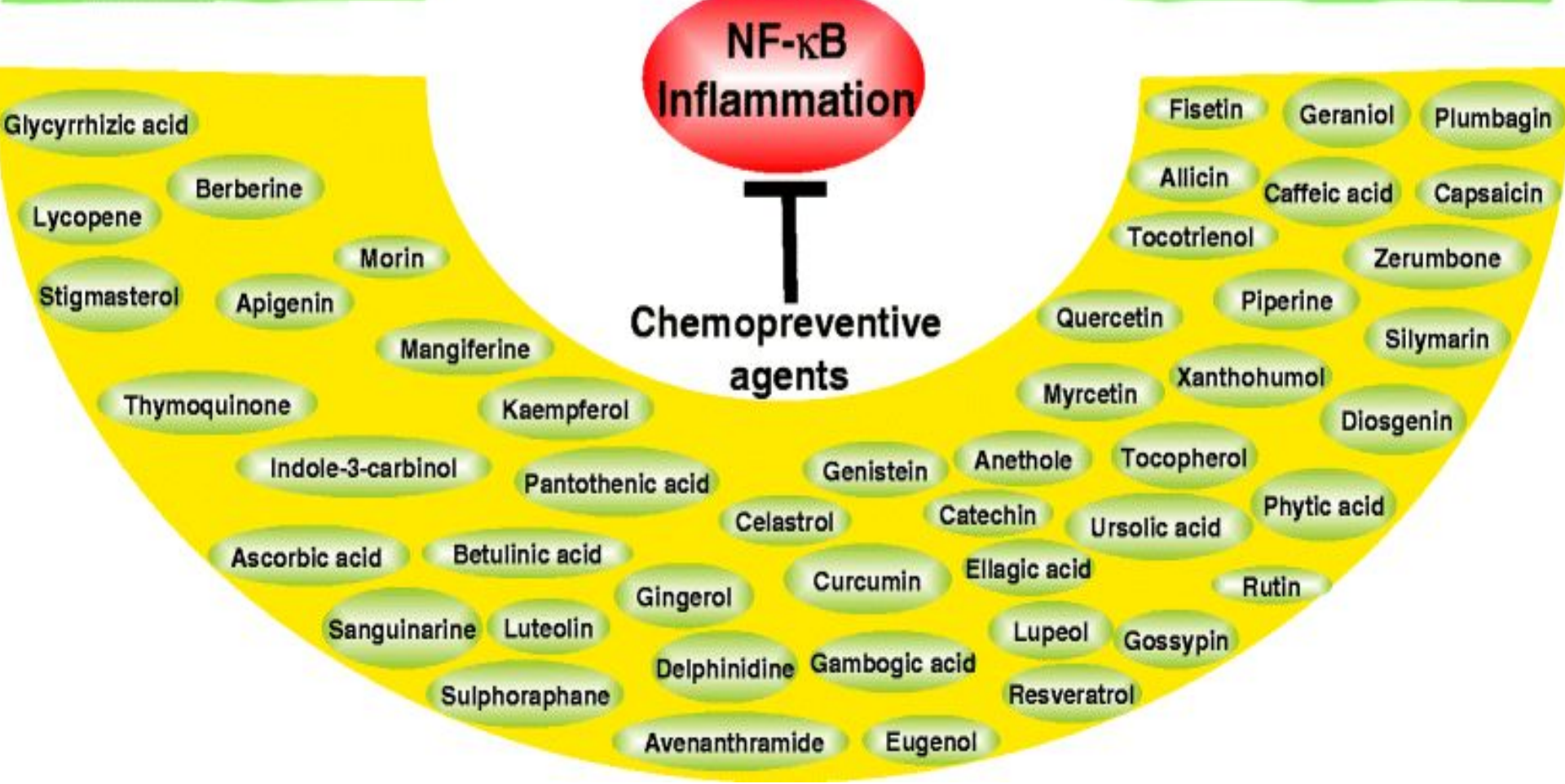


Think NF KappaB and Cox-2 inhibitors to dampen many of the proliferative, angiogenic, metastatic and cachexic pathways all at once.

C Reactive Protein

- "CRP may be important prognostic markers for long-term survival in breast cancer patients, independent of race, tumor stage, and body mass index."
  - Higher CRP correlated with reduced DFS
    - (Pierce BL, Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol. 2009 Jul 20;27(21):3437-44. Epub 2009 May 26.)

- CRP measured in Br Ca patients (NED) at 31 months
  - Positively correlated with BMI, smoking, waist circumference, age, less physical activity
  - Negatively correlated with Vitamin E and Tamoxifen use
    - Pierce BL. Cancer Res Treat. 2009 Mar;114(1):155-67. Epub 2008 Apr 10.



Above image from: Cancer is a Preventable Disease that Requires Major Lifestyle Changes. *Pharmaceutical Research* [Volume 25, Number 9 / September, 2008]

ORIGINAL INVESTIGATION

Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation

Michael R. Irwin, MD; Minge Wang, MSN; Capella O. Campomayor, MS; Alicia Collado-Hidalgo, PhD; Steve Cole, PhD

Background: Inflammation is associated with increased risk of cardiovascular disorders, arthritis, diabetes mellitus, and mortality. The effects of sleep loss on the cellular and genomic mechanisms that contribute to inflammatory cytokine activity are not known.

Methods: In 30 healthy adults, monocyte intracellular proinflammatory cytokine production was repeatedly assessed during the day across 3 baseline periods and after partial sleep deprivation (awake from 11 PM to 3 AM). We analyzed the impact of sleep loss on transcription of proinflammatory cytokine genes and used DNA microarray analyses to characterize candidate transcription-control pathways that might mediate the effects of sleep loss on leukocyte gene expression.

Results: In the morning after a night of sleep loss, monocyte production of interleukin 6 and tumor necrosis factor α was significantly greater compared with morning levels following uninterrupted sleep. In addition, sleep loss induced a more than 3-fold increase in transcription of interleukin 6 messenger RNA and a 2-fold increase in tumor necrosis factor α messenger RNA. Bioinformatics analyses suggested that the inflammatory response was mediated by the nuclear factor κB inflammatory signaling system as well as through classic hormone and growth factor response pathways.

Conclusions: Sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response. A modest amount of sleep loss also alters molecular processes that drive cellular immune activation and induce inflammatory cytokines; mapping the dynamics of sleep loss on molecular signaling pathways has implications for understanding the role of sleep in altering immune cell physiologic characteristics. Interventions that target sleep might constitute new strategies to constrain inflammation with effects on inflammatory disease risk.

Arch Intern Med. 2006;166:1756-1762

Arch Intern Med 2006;166:1756-1762

Extended treatment with physiologic concentrations of dietary phytochemicals results in altered gene expression, reduced growth, and apoptosis of cancer cells

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Abstract

Dietary phytochemicals exhibit chemopreventive potential *in vivo* through persistent low-dose exposures, whereas mechanistic *in vitro* studies with these agents generally use a high-dose single treatment. Because the latter approach is not representative of an *in vivo* steady state, we investigated antitumor activity of curcumin, 3,3′-diindolylmethane (DIM), epigallocatechin gallate (EGCG), genistein, or indole-3-carbinol (I3C) in breast cancer MDAMB-231 cells, exposed in long-term culture to low concentrations, achievable *in vivo*. Curcumin and EGCG increased cell doubling time. Curcumin, EGCG, and I3C inhibited clonogenic growth by 55% to 60% and induced 1.5- to 2-fold higher levels of the basal caspase-3/7 activity. No changes in expression of cell cycle–related proteins or survivin were found; however, I3C reduced epidermal growth factor receptor expression, contributing to apoptosis. Because some phytochemicals are shown to inhibit DNA and histone modification, modulation of expression by the agents in a set of genes (*cadherin-11*, *p21Cip1*, *urokinase-type plasminogen activator*, and *interleukin-6*) was compared with changes induced by inhibitors of DNA methylation or histone deacetylation. The phytochemicals modified protein and/or RNA expression of these genes, with EGCG eliciting the least and DIM the most changes in gene expression. DIM and curcumin decreased cadherin-11 and increased urokinase-type plasminogen activator levels correlated with increased cell motility. Curcumin, DIM, EGCG, and genistein reduced cell sensitivity to radiation-induced DNA damage without affecting DNA repair. This model has revealed that apoptosis and not arrest is likely to be responsible for growth inhibition. It also implicated new molecular targets and activities of the agents under conditions relevant to human exposure. [Mol Cancer Ther 2007;6(11):3071–9]

Introduction

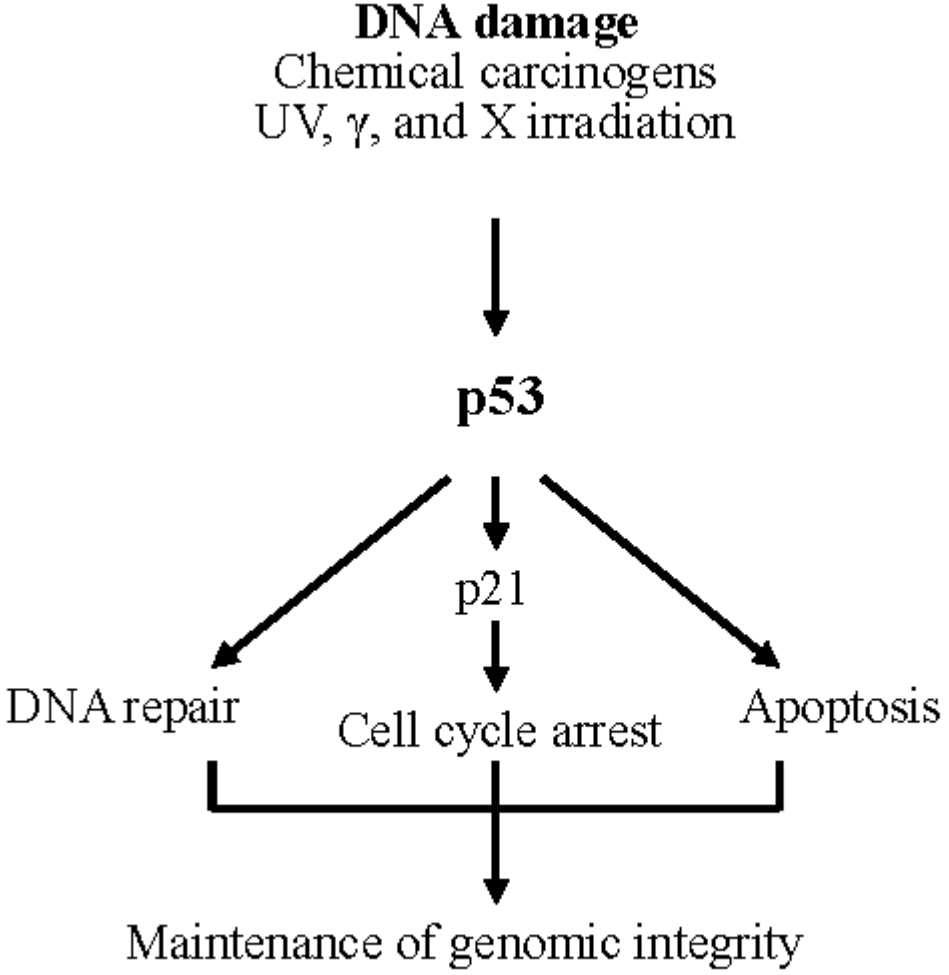
Epidemiologic studies indicate that consumption of vegetables, containing dietary phytochemicals, reduces cancer risk (1). Many dietary phytochemicals not only block development of tumors but also inhibit metastatic growth in animal models (Supplementary Table S1).[3] Potential use of dietary agents in combination therapies has been considered among novel treatment approaches because combining phytochemicals with radiotherapy and chemotherapy improves outcome in animal models (Supplementary Table S1).[3]

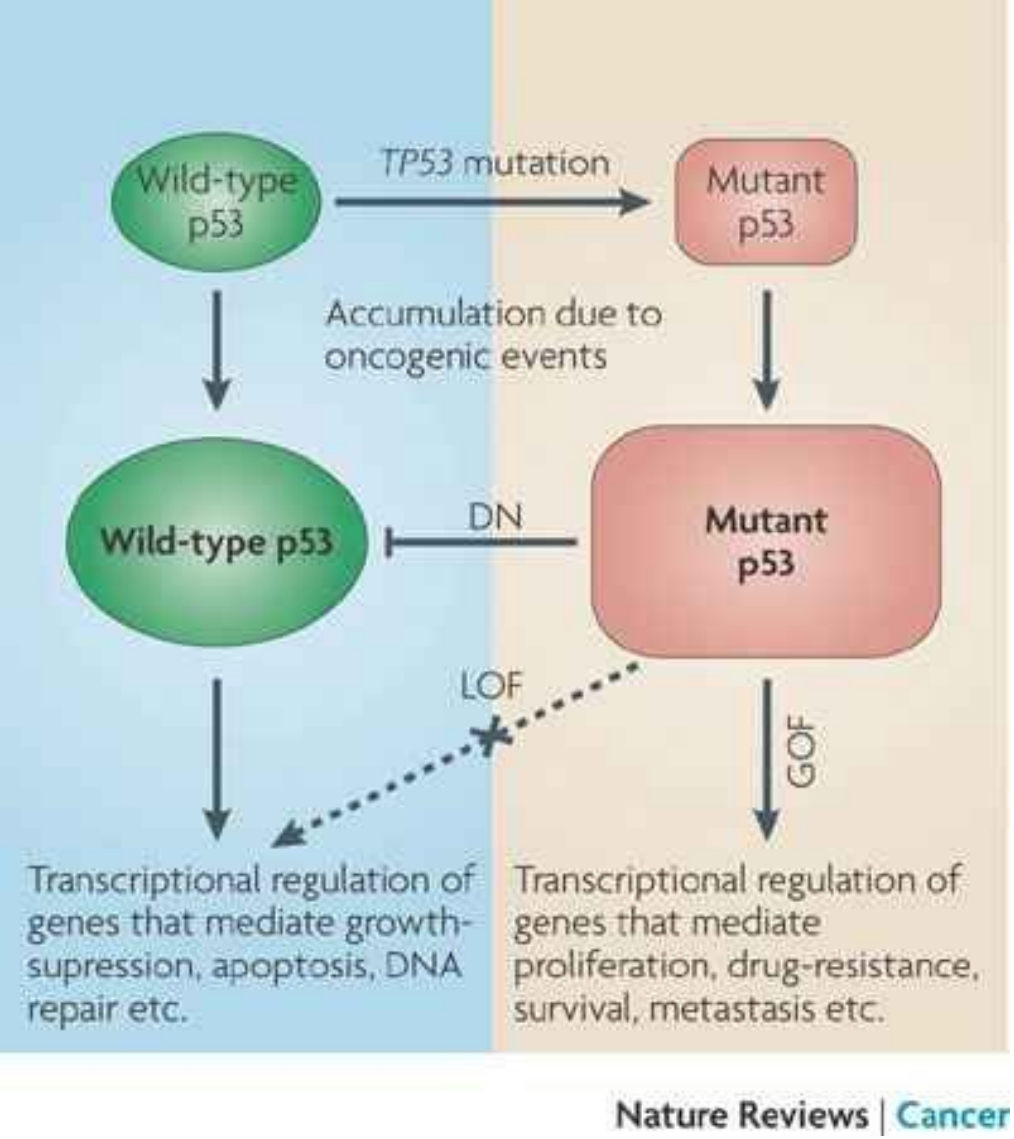
The majority of studies on these agents in cell culture use short exposure times to high concentrations, often orders of magnitude greater than those achievable *in vivo*. Moreover, treatment with a single dose provides data on an acute induction response, whereas *in vivo* anticancer activity arises from a steady-state response to the continued presence of dietary agents. Therefore, many reported effects obtained in cell culture studies may be irrelevant for *in vivo* activity. All the chemopreventive phytochemicals induce cell cy… albeit … investi… (e.g., growth, apoptosis, and expression of selected biomarkers) could be detected following extended treatments

EGCG
Curcumin
I3C
Genestein

Mol Cancer Ther Nov 2007;6(11)

P53 tumor suppressor





Serum anti-p53 antibodies are correlated with decreased survival in cancer patients.
Muller. Int J Oncology 2006

Could p53 be used to help determine therapy?:
206 node neg patients.
31 pts had mutant p53 (tumor tissue) Radiation tx sig increased EFS in pts with mutant p53 but not wild type
J Clin Oncol. 1995 Nov;13(11):2745-51.

GOF= Gain of Function
LOF= Loss of Function

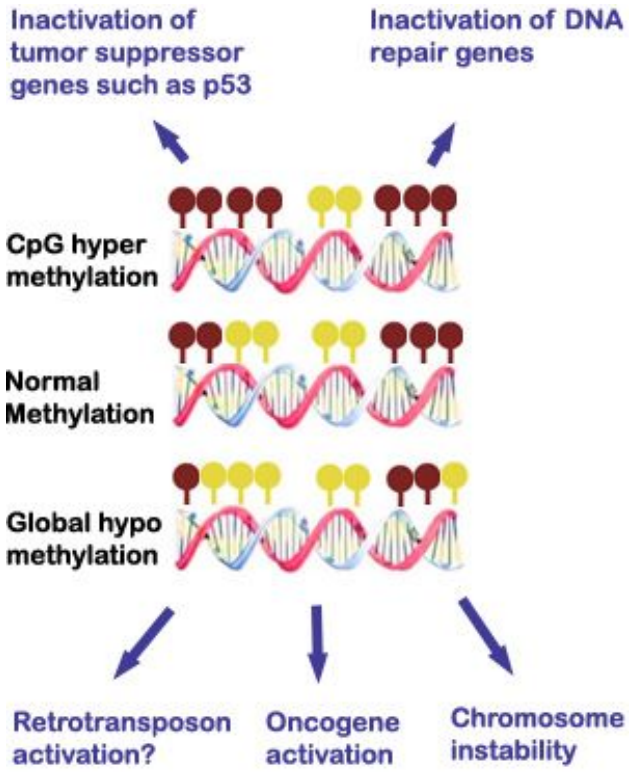
Inducers of Apoptosis indepent of p53:
Vitamin D (1,25) Vitamin E, Genestein

Apoptotic agents

- Flavonoids: luteolin, genistein, naringenin, apigenin and diazein
- Garlic
- Resveratrol
- Curcumin

Homocysteine

Silencing of CpG Regions



Hypo/ hypermethylation

- Some SNP's in in MTHFR gene confer greater risk for several cancers:
  - Including breast
- Hypomethylation by a group of demethylases
- Hypermethylation through DNA methlytransferase
  - Green tea inhibits this enzyme

The CoRN Reports…

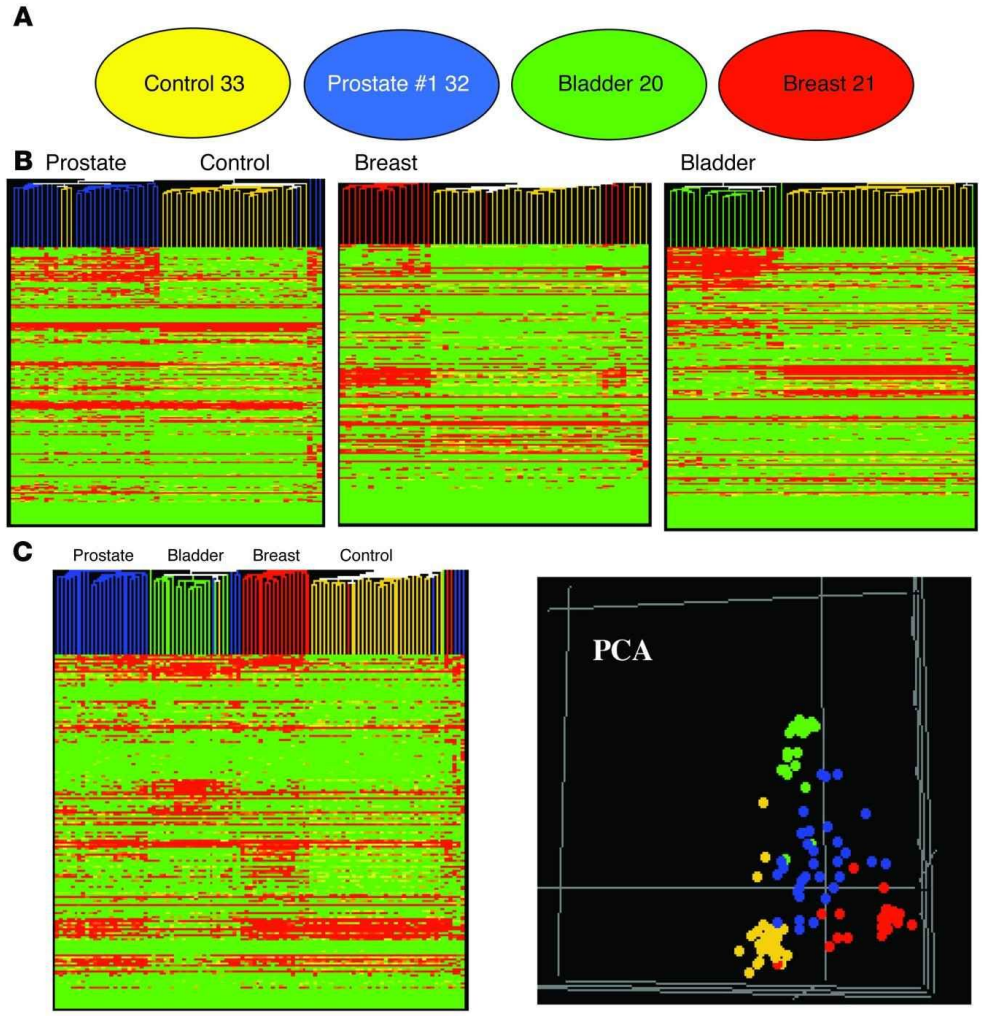
- CoRN= CoQ10 (100mg), Riboflavin (10mg), Niacin (50mg)
  - Reduced CEA and 15-3
  - Decrease in serum IL-1beta, IL-6, IL-8, TNF-alpha and VEGF
  - Counteracts TAM induced hyperlipidemia
  - Increased antioxidant status while decreasing lipid peroxide levels

Tests to do with your patients

- Vitamin D (25-dihydroxycholecalciferol)
- C- Reactive Protein
- Hemoglobin A1C, C-peptide, insulin
- 2/16 hydroxyestrone metabolites
- Homocysteine
- Estrogenomics (?)
- IgG food allergies (will affect inflammation…)
- IL-6(?) or VEGF?– more well established for patients with stage III or IV

The future?

- Proteomics looks at protein patterns in the blood. Patterns unique to certain diseases emerge and may predict the presence of disease long before imaging.



On the fringe…

- Worthy of noting for their potential, but clinical utility not yet known:
- All tests mentioned, but not yet recommended by ASCO (earlier slide)
- Mammoglobin= unique protein + in 72% of br ca pts
- Autoantibodies to c-myc, p53, MUC1 (1/8/2010; http://etheses.nottingham.ac.uk/876/

Websites for more info

- VEGF: Researchvegf.com
- Oncotypedx.com– click on “clinical summary”
- Oncologystat.com
- Medscape
- Cellsignalling.com-- pathways