

Anticancer Potential of Curcumin:

An Old Spice With New Targets

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International Symposium



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on *Molecular Aspects of Apoptosis and Cancer : Bench to Bedside*

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www.apoptosis2005.org

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Golden Triangle

Modern technology



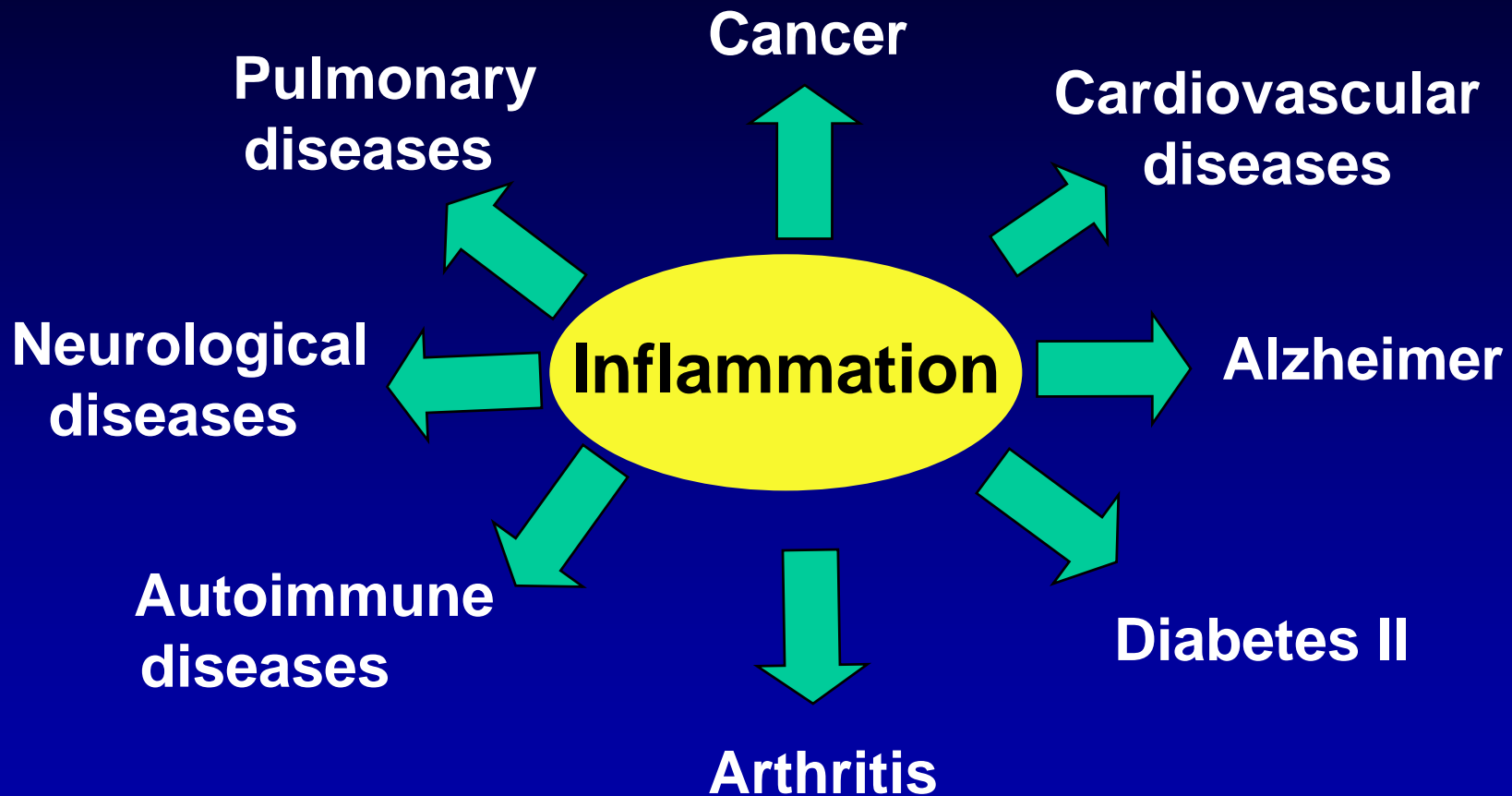
Traditional Knowledge

(Ayurvedic medicine
Egyptian medicine
Kampo, TCM)

Modern Knowledge

(Allopathic medicine)

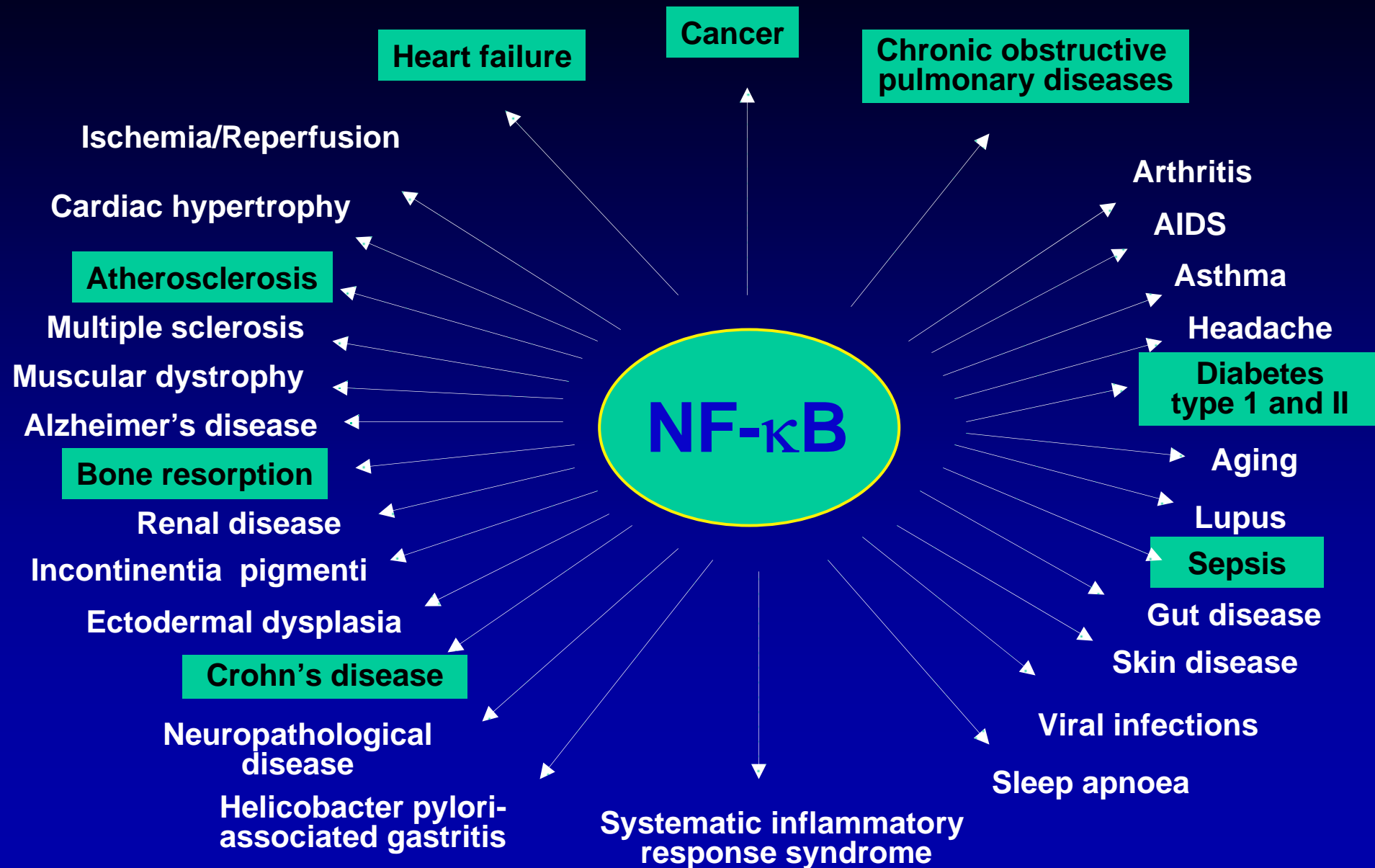
Inflammation plays a major in development of most diseases



Hypothesis!

NF- κ B activation is a major mediator of inflammation in most diseases & inhibition of NF- κ B activation can suppresses inflammation

NF- κ B has been linked to several diseases



Hypothesis!

- **Most carcinogens activate NF- κ B**
- **NF- κ B activation mediates carcinogenesis/tumorigenesis**
- **Inhibition of NF- κ B activation suppresses tumorigenesis**

Inflammation and cancer: back to Virchow?

Balkwill F, Mantovani A.

Lancet. 2001;357:539-45.

NF-kappa B: arresting a major culprit in cancer

Haefner B

Drug Discov Today. 2002;7:653-63

NF-kappaB in cancer: from innocent bystander to major culprit

Karin M, Cao Y, Greten FR, Li ZW.

Nat Rev Cancer. 2002;2:301-10.

Nuclear transcription factor-kappaB as a target for cancer drug development.

Garg A, Aggarwal BB.

Leukemia. 2002;16:1053-68.

NF-kappaB: Holy Grail for rheumatoid arthritis?

Firestein GS

Arthritis Rheum. 2004 Aug;50(8):2381-6.

NF- κ B and Stress

Transcription factor NF- κ B as a potential biomarker for oxidative stress.

van den Berg R, Haenen GR, van den Berg H, Bast A. Br J Nutr. 2001 Aug;86 Suppl 1:S121-7. Review.

NF- κ B activation is higher in peripheral blood mononuclear cells of male smokers.

van den Berg R, Haenen GR, van den Berg H, Bast A. Environ. Toxicol. Pharmacol.. 2001;9(4):147-151.

NF- κ B activation in sarcoidosis.

Drent M, van den Berg R, Haenen GR, van den Berg H, Wouters EF, Bast A. Sarcoidosis Vasc Diffuse Lung Dis. 2001 Mar;18(1):50-6.

Aging activates NF- κ B

Growing old with nuclear factor- κ B.

Giardina C, Hubbard AK. ,Cell Stress Chaperones. 2002 Apr;7(2):207-12. Review.

Characterization of aging-associated up-regulation of constitutive NF- κ B binding activity.

Helenius M, Kyrylenko S, Vehvilainen P, Salminen A. Antioxid Redox Signal. 2001 Feb;3(1):147-56.

Age-dependent increase of heme oxygenase-1 gene expression in the liver mediated by NF- κ B.

Lavrovsky Y, Song CS, Chatterjee B, Roy AK. Mech Ageing Dev. 2000 Feb 22;114(1):49-60.

Age-dependent increase of NF- κ B translocation and PDGF-B expression in aortic endothelial cells of hypercholesterolemic rats.

Zhou L, Dong J, Yu M, Yin H, She M. , Exp Gerontol. 2003 Oct;38(10):1161-8.

Aging activates NF- κ B

Free radical-dependent changes in constitutive NF- κ B in the aged hippocampus.

Kaufmann JA, Bickford PC, Taglialatela G. , Neuroreport. 2002 Oct 28;13(15):1917-20.

Augmented expression of inducible NO synthase in vascular smooth muscle cells during aging is associated with enhanced NF- κ B activation.

Yan ZQ, et al. ,Arterioscler Thromb Vasc Biol. 1999 Dec;19(12):2854-62.

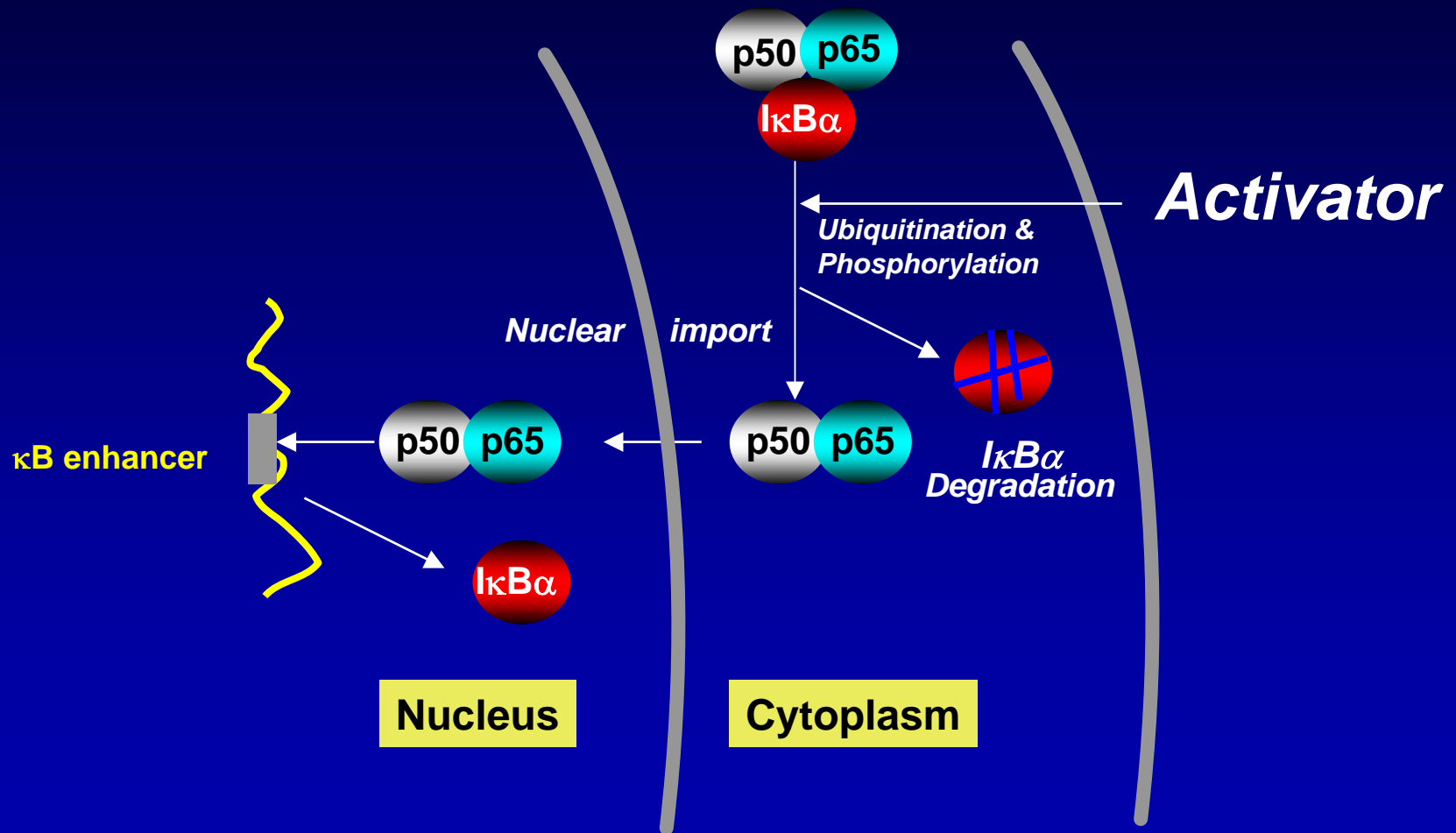
Constitutive activation of NF- κ B in an animal model of aging.

Spencer NF, Poynter ME, Im SY, Daynes RA.Int Immunol. 1997 Oct;9(10):1581-8.

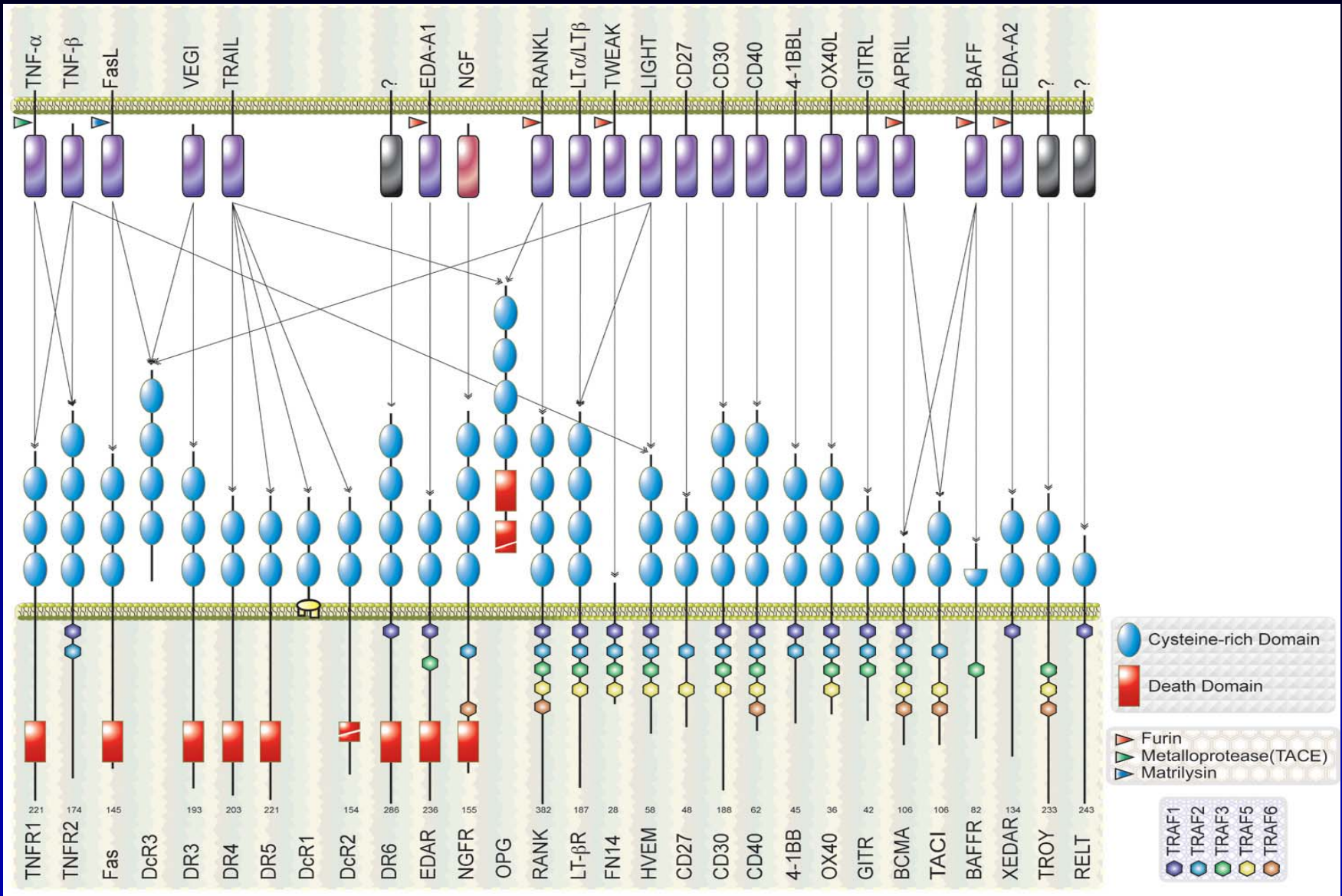
Age-related changes in the regulation of transcription factor NF- κ B in rat brain.

Korhonen P, Helenius M, Salminen A. Neurosci Lett. 1997 Mar 28;225(1):61-4.

What is $\text{NF-}\kappa\text{B}$?

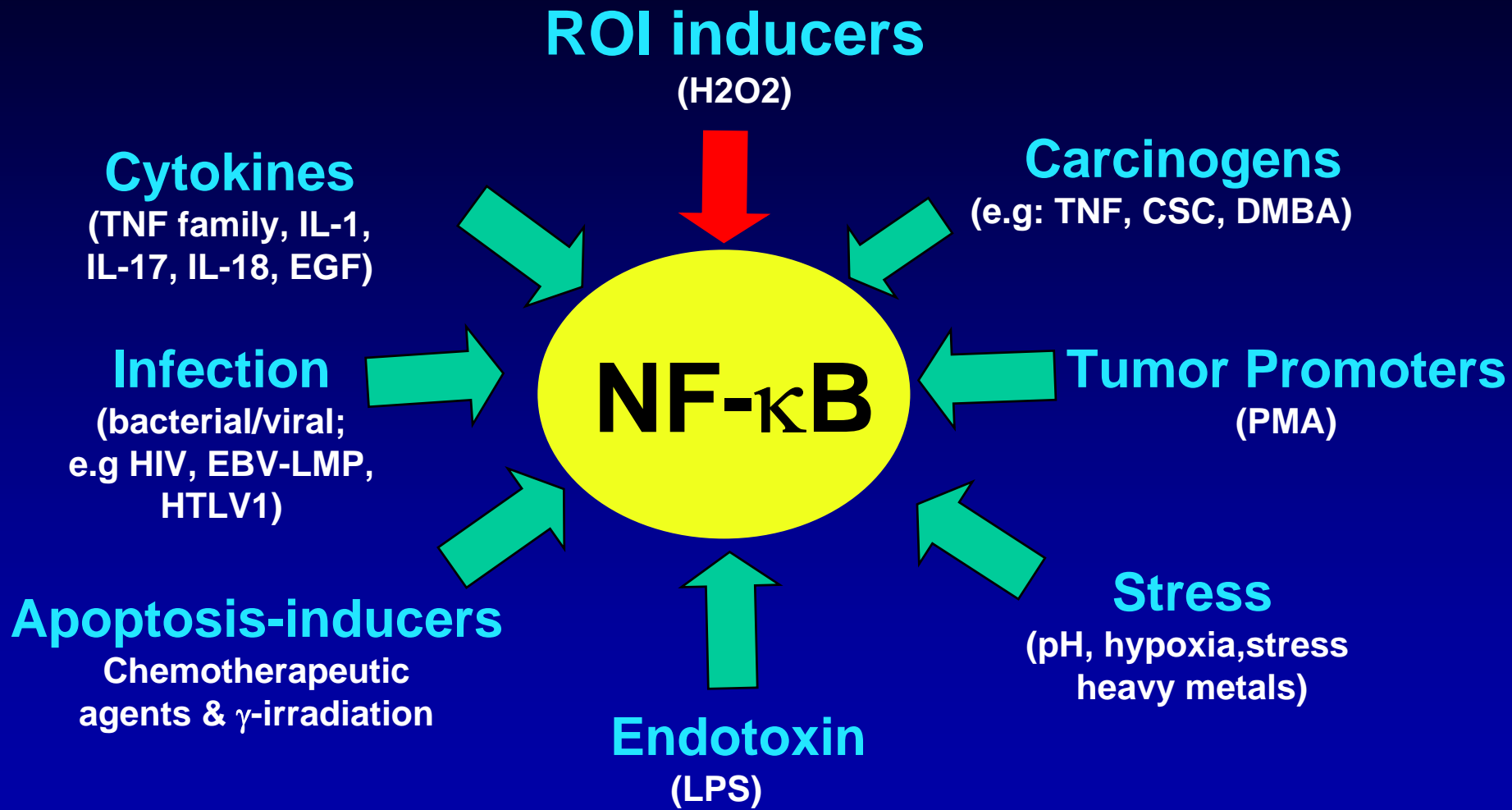


All TNF superfamily members activate NF- κ B

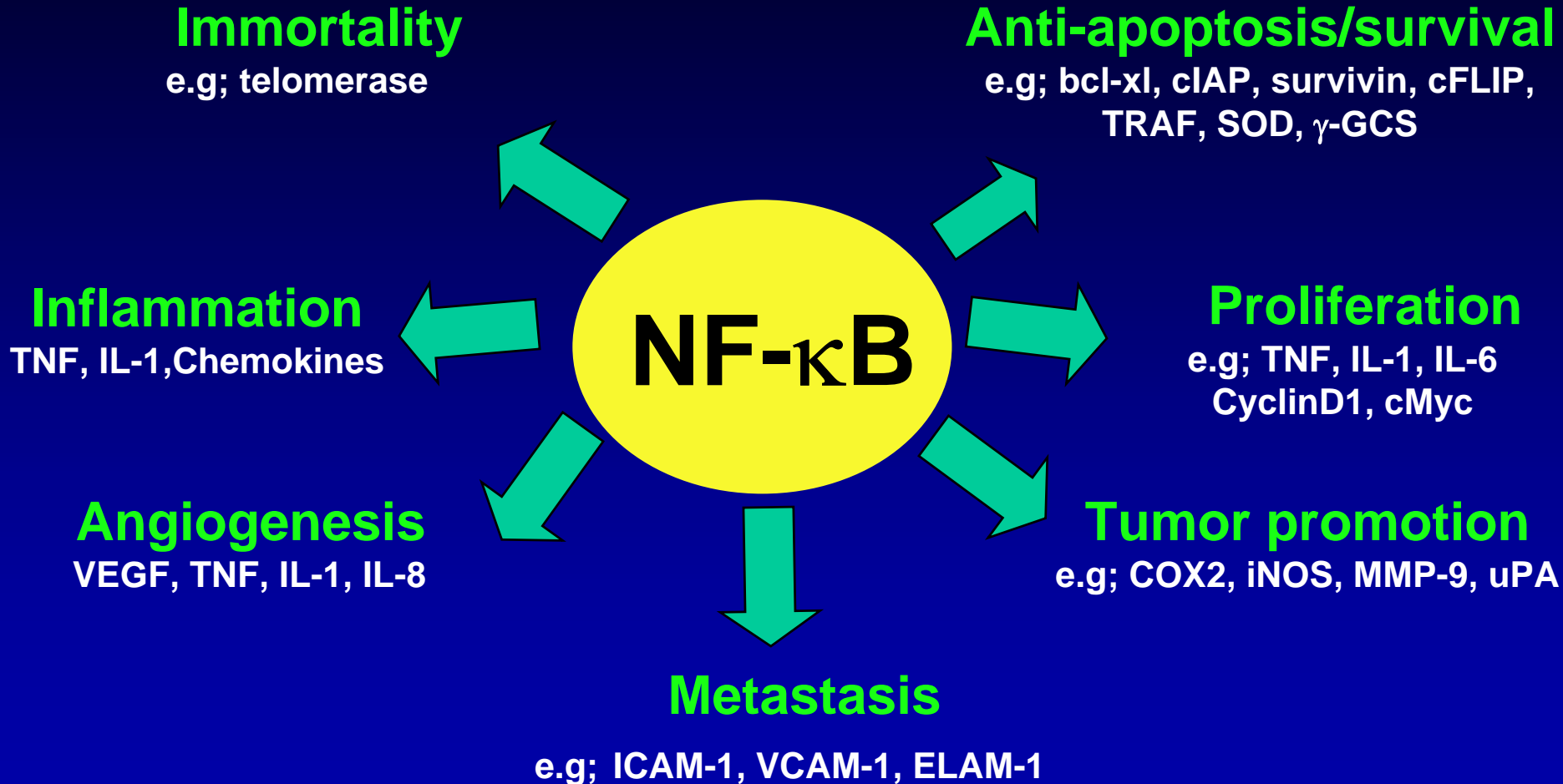


From Aggarwal B. B., Nature Rev. Immunology 2003

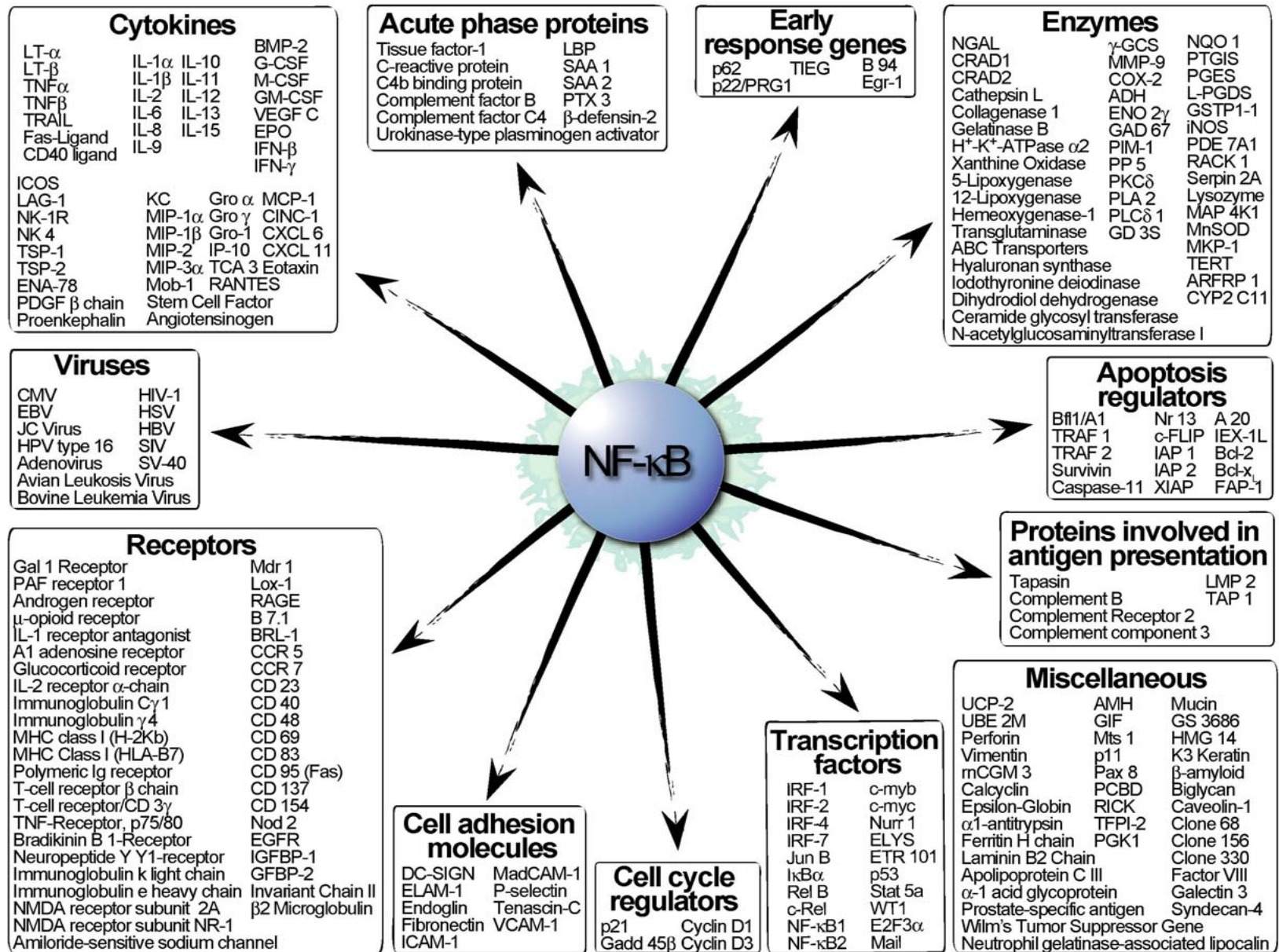
What activates NF- κ B?



Role of NF- κ B in Development of Cancer



NF- κ B -regulated genes



Why NF- κ B is a good targets for cancer drug development?

Activation of NF- κ B blocks apoptosis and mediates tumor cell proliferation

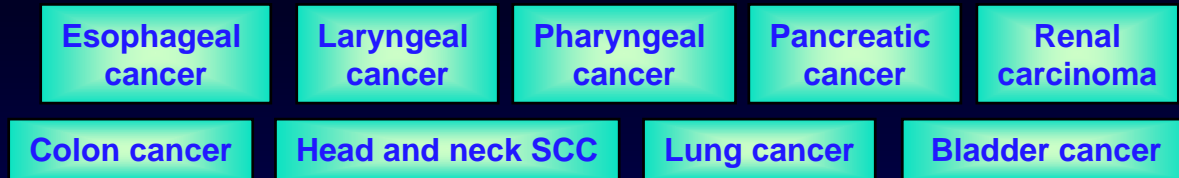
Tumor cells frequently express constitutively activated form of NF- κ B

Tumor microenvironment can induce NF- κ B activation

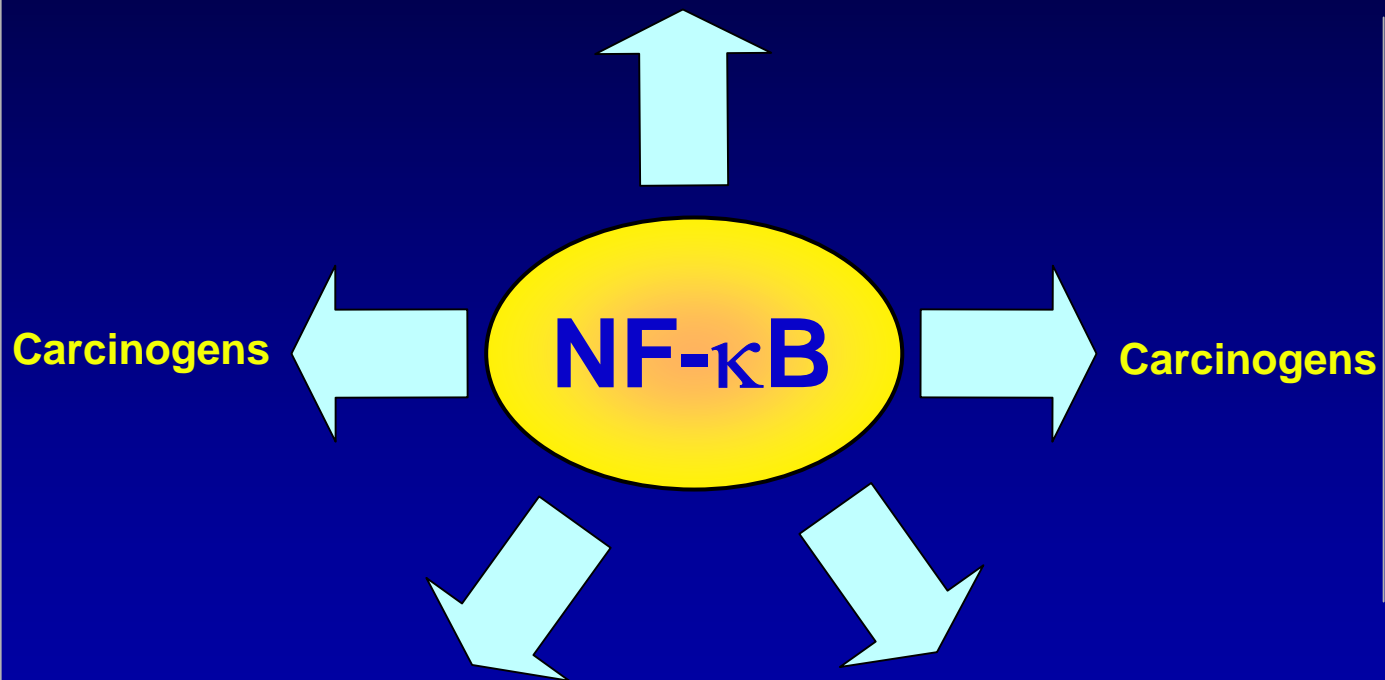
NF- κ B activation induces resistance to chemotherapeutic agents

Several genes involved in tumor initiation, promotion, and metastasis are regulated by NF- κ B.

Cancers linked to constitutive activation of NF- κ B



Tobacco-linked cancers



Acute
Myelogenous
leukemia

Hodgkin's
disease

Non-Hodgkin's
lymphoma

B cell
lymphoma

Adult T cell
leukemia

T cell
lymphoma

Mantle cell
lymphoma

Multiple
myeloma

Thyroid
cancer

Liver
cancer

Breast
cancer

Ovarian
cancer

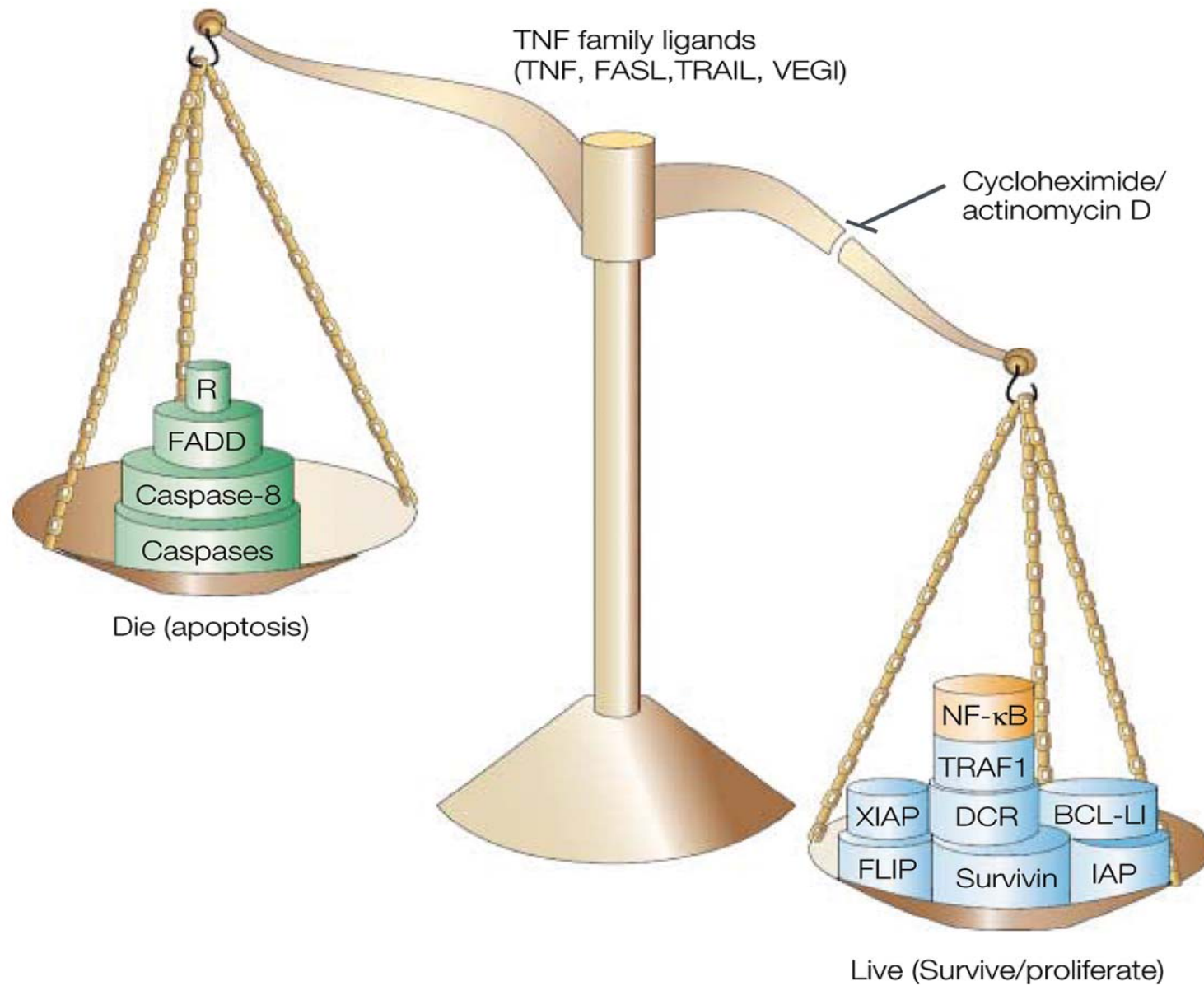
Prostate
cancer

Acute lymphoblastic
leukemia

Cervical
cancer

Nasopharyngeal
carcinoma

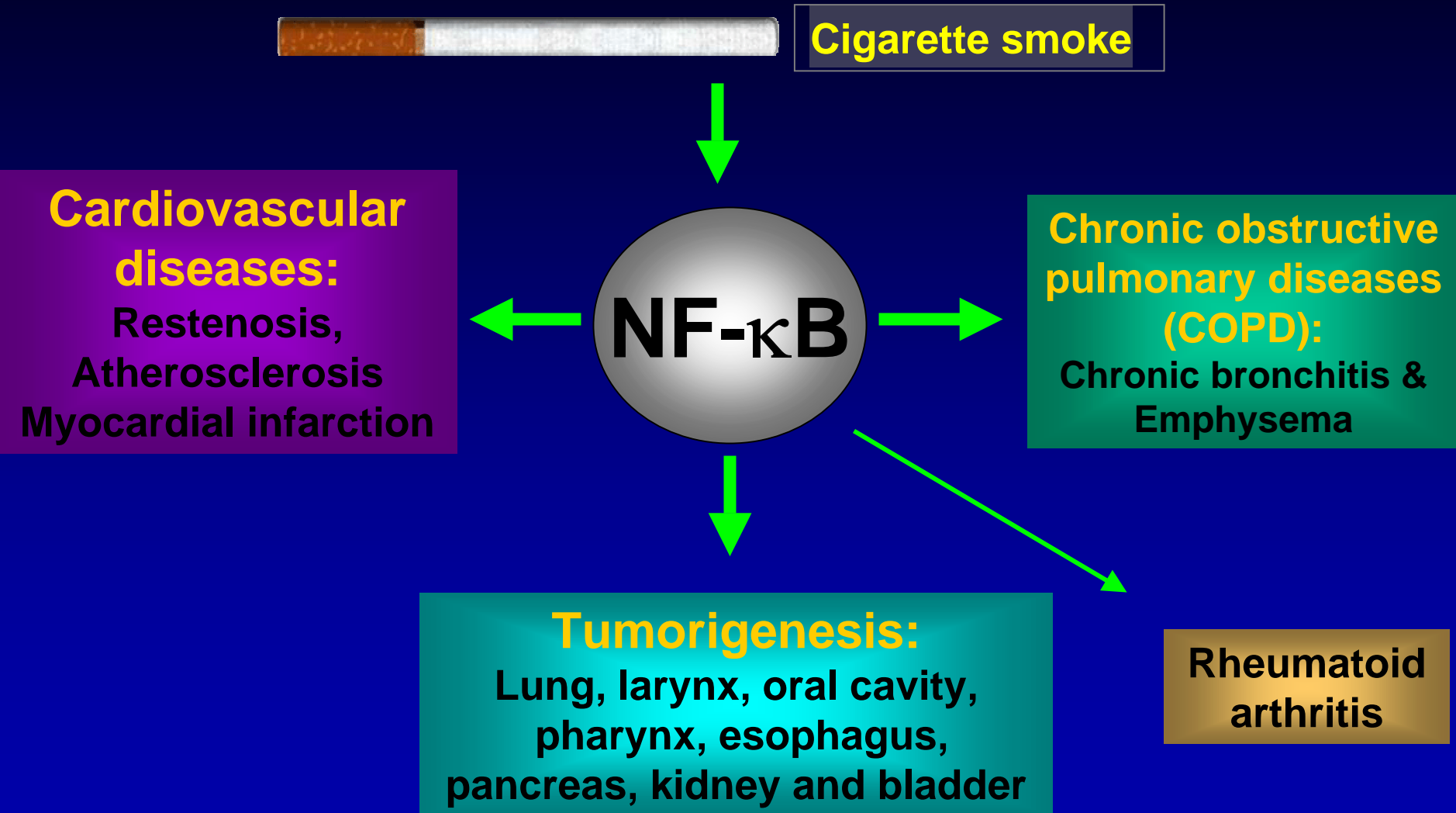
Melanoma



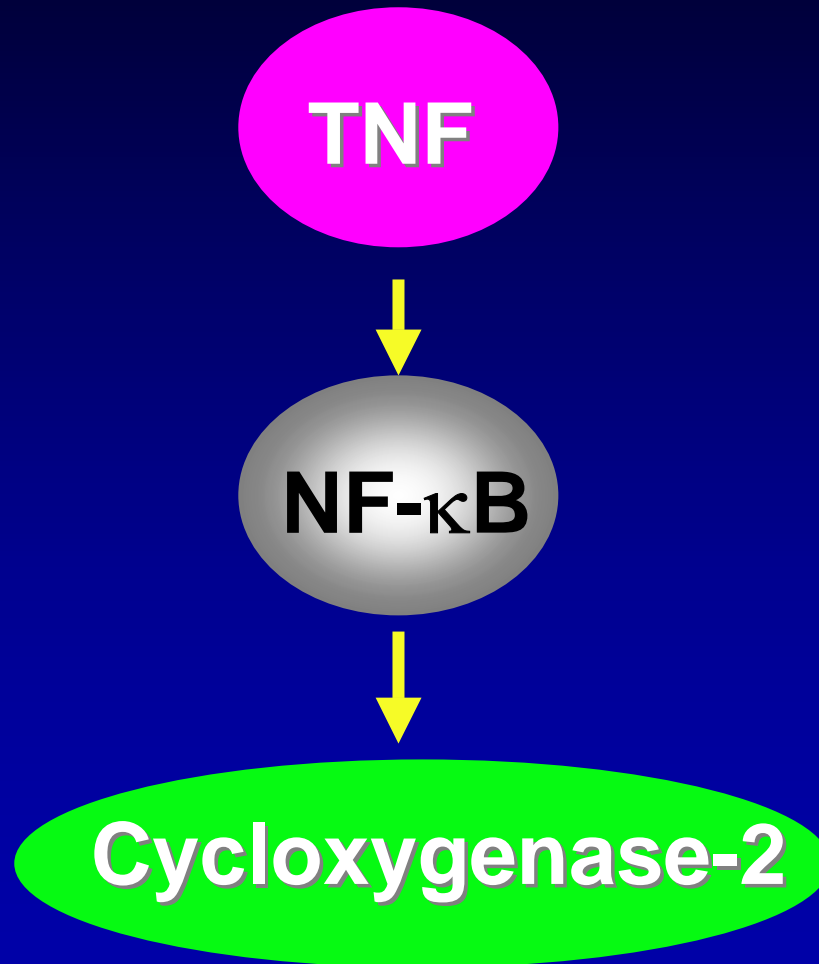
NF- κ B is constitutively active in Human Cutaneous T Cell Lymphoma and Causes Resistance to Apoptosis

Giri and Aggarwal, JBC 273, 1998, 14008-14

Working Model for Cigarette Smoke-Induced Damage



Drug Development for Inflammatory diseases

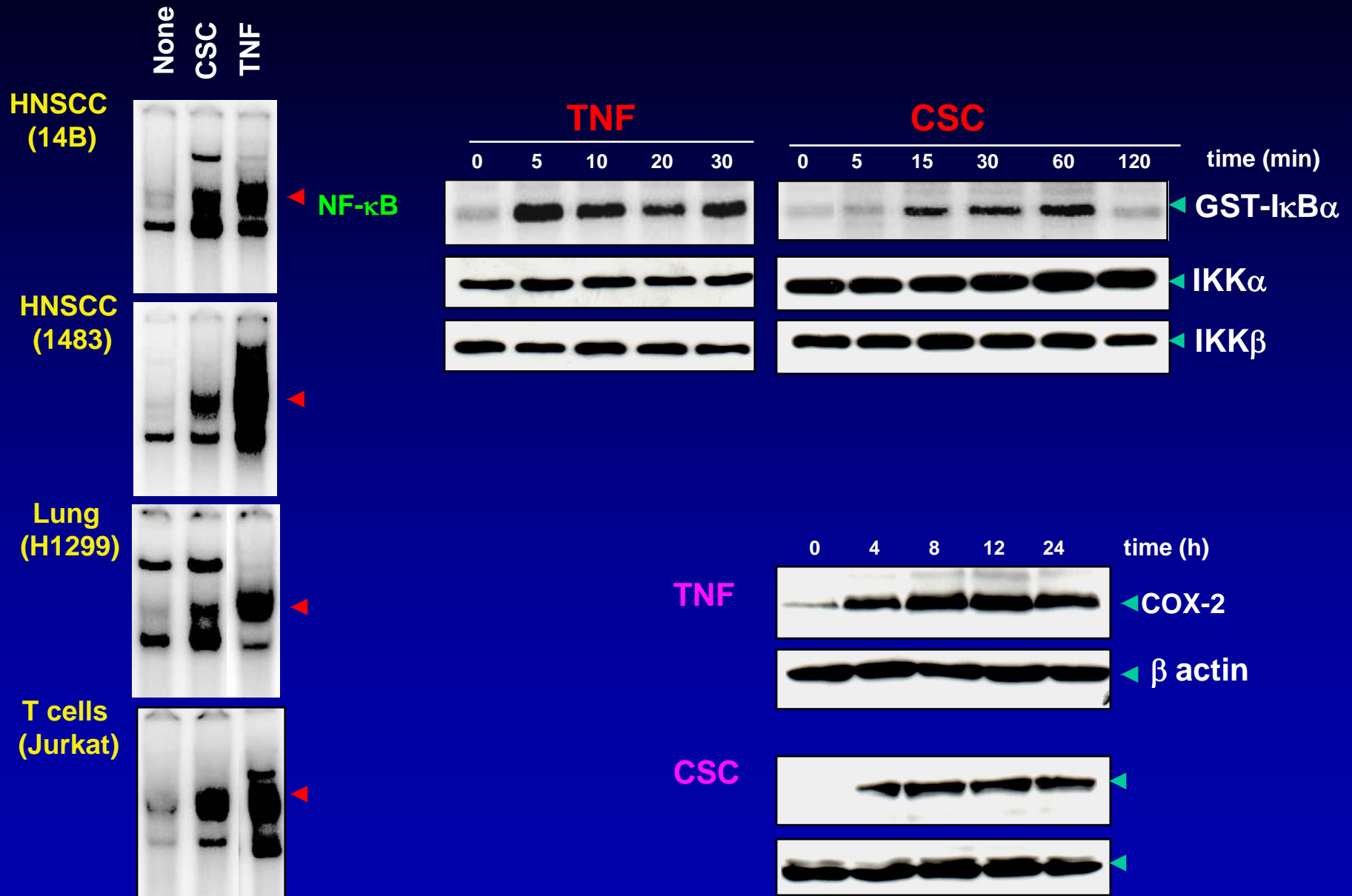


Cigarette Smoke Activates Nuclear Factor- κ B and Induces Cyclooxygenase-2

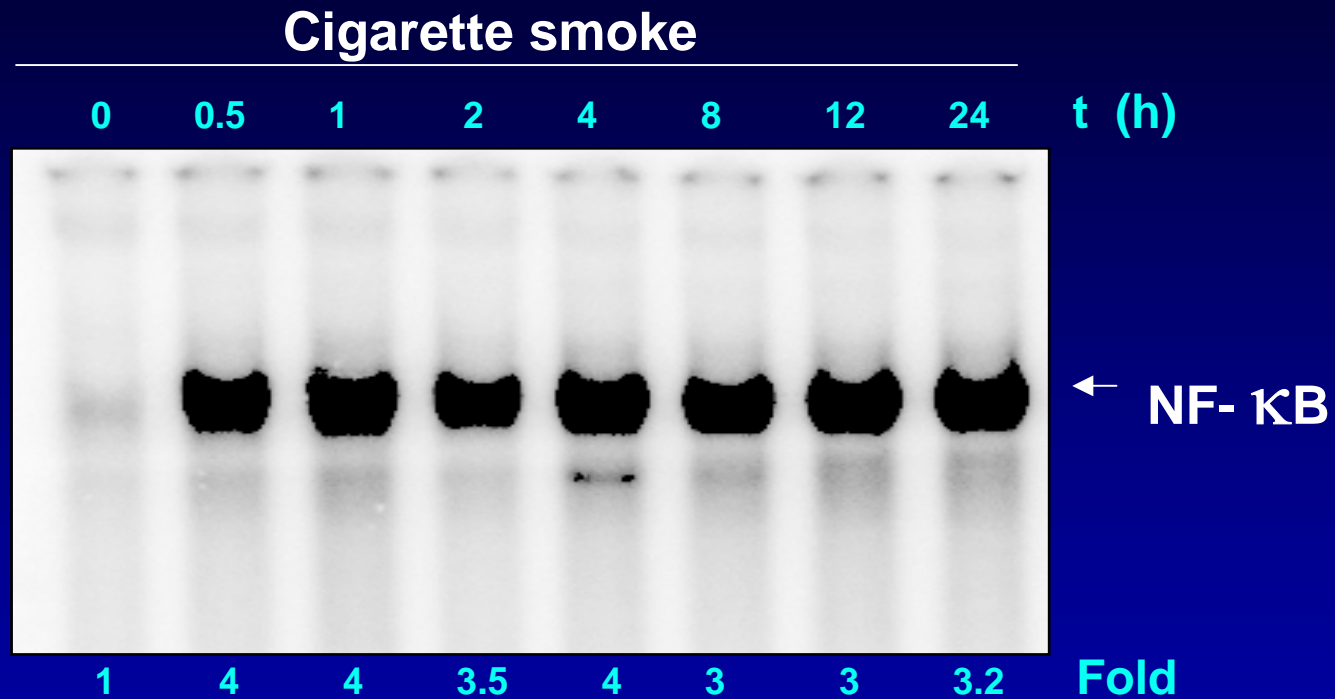
*Anto R. J., Mukhopadhyay A., Gairola C. G. and
Aggarwal B. B.,*

Carcinogenesis, 23, 1511, 2002

CSC activates nuclear factor- κ B



Cigarette smoke-induced NF- κ B activation is persistent



*Shishodia S, and Aggarwal BB.
Cancer Research. 2004;64:5004-12.*

**How to suppress
NF- κ B activation?**

Drug-discovery from natural sources

- **There are 121 prescription drugs in use today, which come from 90 plant species.**

About 74% came from following folklore claims.

(Benowitz S, The Scientist 10, 1996, 1-7).

- **Approximately 25% of the drug prescription in the USA are compounds derived from plants and were discovered through scientific investigation of folklore claims**

(Reynold T, J. Natl. Cancer Inst. 183, 1991, 594-596).

Examples:

Pacific yew
Rosy periwinkle
Foxglove
Meadowsweet

Taxol
Vinblastin and vincristine
Digitalis
Aspirin

Why natural products are good Source of anticancer drugs?

Almost 74% (48/65) of all drugs
approved either were natural products,
were based thereon, or mimicked them
in one form or another (1981-2002)

*Newman DJ, Cragg GM, and Snader KM.,
J. Nat. Prod., 2003, 66, 1022-1037.*

Hippocrates proclaimed
~2500 years ago

**“Let food be thy
medicine
and medicine be
thy food”**

“You are what you eat”

Comparison of Cancer Incidence

Cancer	USA		India		Japan	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Oral cavity	50	11	102	60	29	12
Nasopharynx	4	2	4	3	3	2
Other Pharynx	19	9	57	42	10	7
Oesophagus	31	31	63	59	58	43
Stomach	56	34	43	39	489	225
Colon/Rectum	356	139	40	26	342	143
Liver	30	31	17	16	186	146
Pancreas	72	68	11	11	76	71
Larynx	33	11	35	22	17	5
Lung	463	402	55	51	262	214
Melanoma of skin	113	21	3	1	3	2
Breast	914	212	191	99	314	77
Cervix uteri	78	33	307	174	111	30
Corpus uteri	155	20	17	5	45	13
Ovary etc.	106	62	49	29	66	37
Prostate	1043	179	46	28	111	55
Testis	40	2	6	3	13	2
Bladder	144	28	20	16	56	17
Kidney etc.	86	31	8	6	42	19
Brain, nervous system	54	37	21	16	24	9
Thyroid	46	3	14	4	31	5
Non-Hodgkin lymphoma	135	59	24	19	58	30
Hodgkin's disease	22	4	8	4	3	1
Multiple myeloma	35	26	8	6	16	12
Leukemia	80	54	26	20	48	34
All sites but skin	3223	1391	1017	688	2230	1213

Showing cases were after standardized with world standard population, called World Standardized incidence or mortality rate. It is also expressed per million. J. Ferlay, et al. GLOBOCAN 2000. URL: <http://www-dep.iarc.fr/globocan/globocan.htm>

Identification of inhibitors of NF- κ B from natural sources

Curcumin:
Getting Back
to Our Roots!

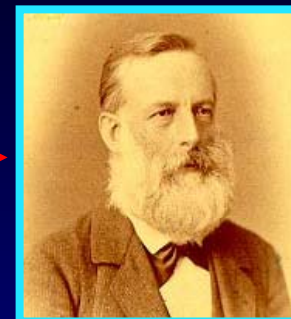


Turmeric

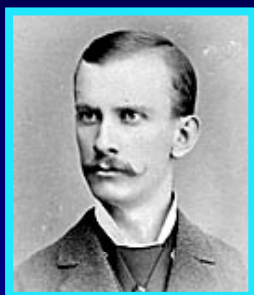


Curcumin is *not* a new molecule

1842 Vogel isolates Curcumin ➡



◀ 1910 Milobedzka determines structure



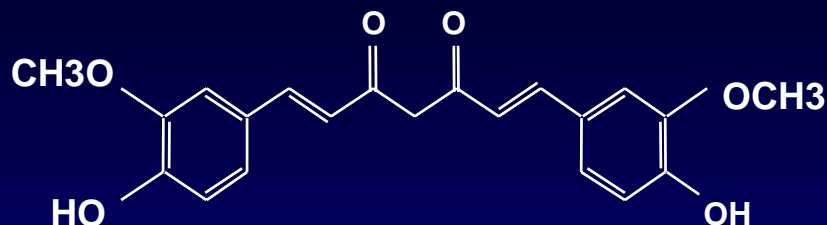
1918 Lampe substantiates structure by synthesis ➡



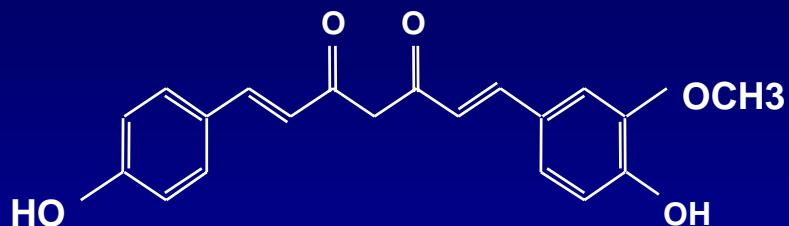
◀ 1953 Srinivasan shows natural curcumin to be a mixture



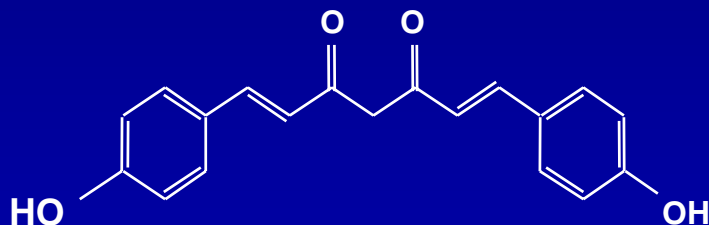
Structure of curcumin



Curcumin I
(77%)



Curcumin II
Demethoxycurcumin
(17%)



Curcumin III
Bis-Demethoxycurcumin
(3%; less active)

Activation of transcription factor Nuclear Factor-kappa B is suppressed by curcumin

Singh S, and Aggarwal BB.

J Biol Chem. 1995 Oct 20;270 (42):24995-5000.

A Typical NF- κ B Activation Pathway

Carcinogens,
Inflammatory stimuli,
Apoptotic stimuli,
Stress stimuli,
Tumor promoters,
Pro-oxidants,
Cytokines

TNF

Production of reactive
oxygen species

Activation of IKK- β

I κ B α phosphorylation

I κ B α ubiquitination

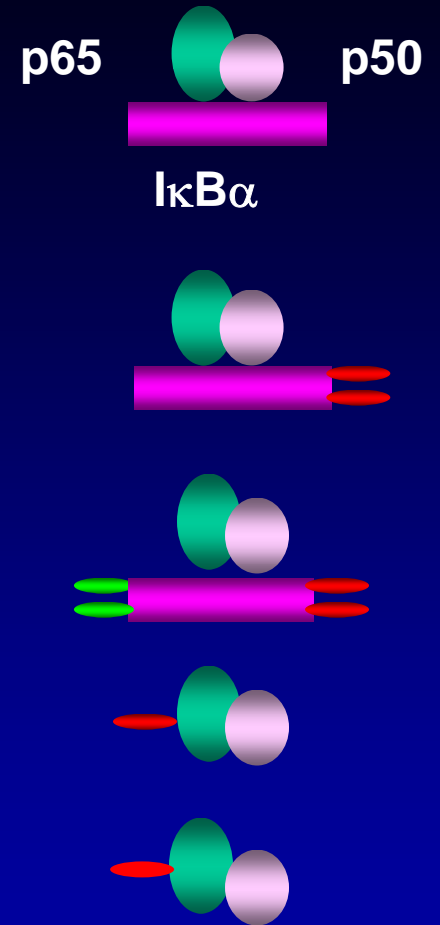
I κ B α degradation
by proteasomes

p65 phosphorylation

p50-p65 nuclear
translocation

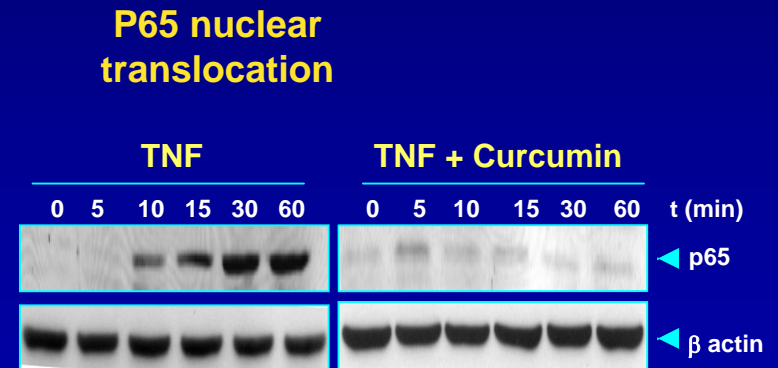
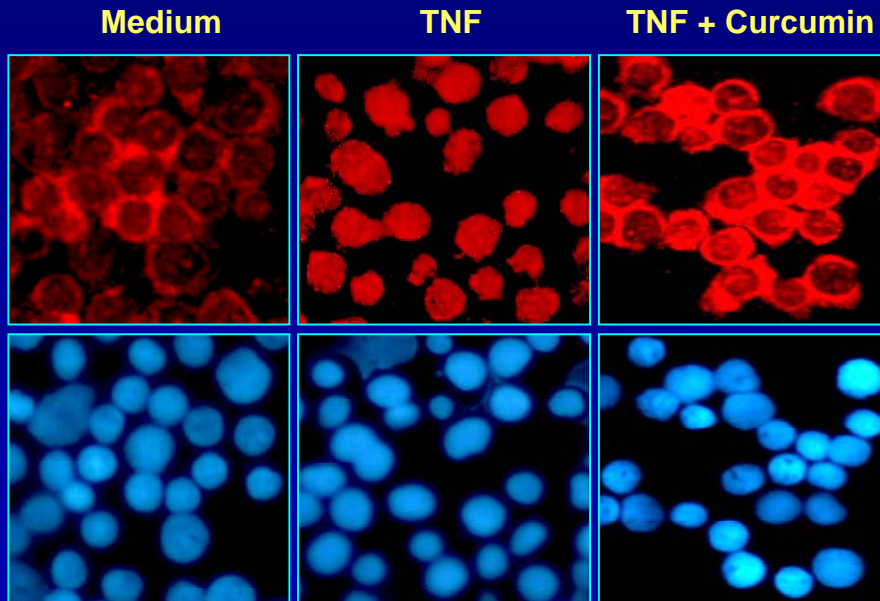
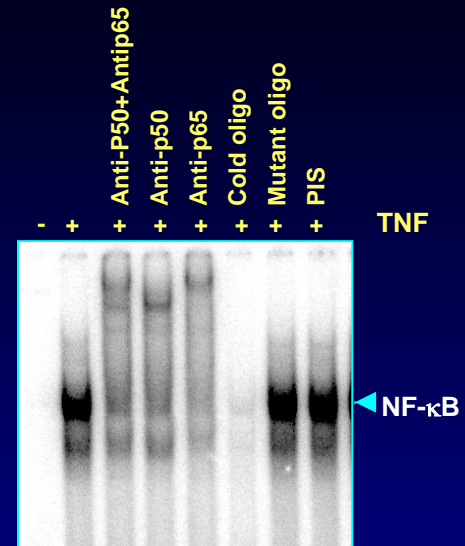
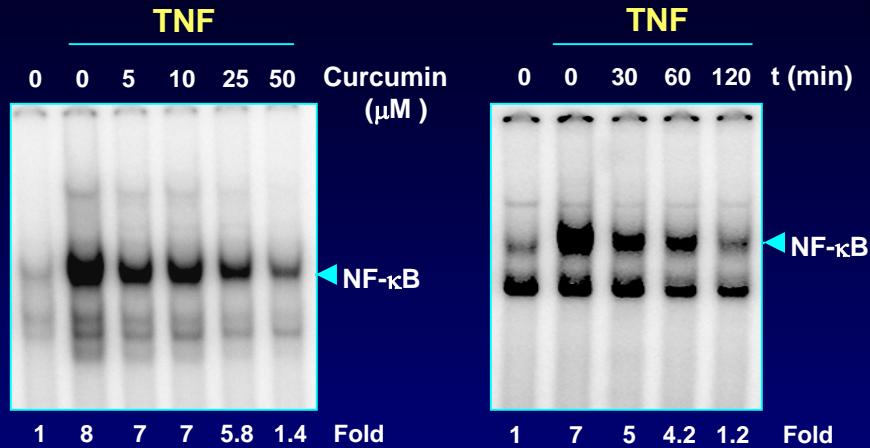
p50-p65 DNA binding

Gene transcription

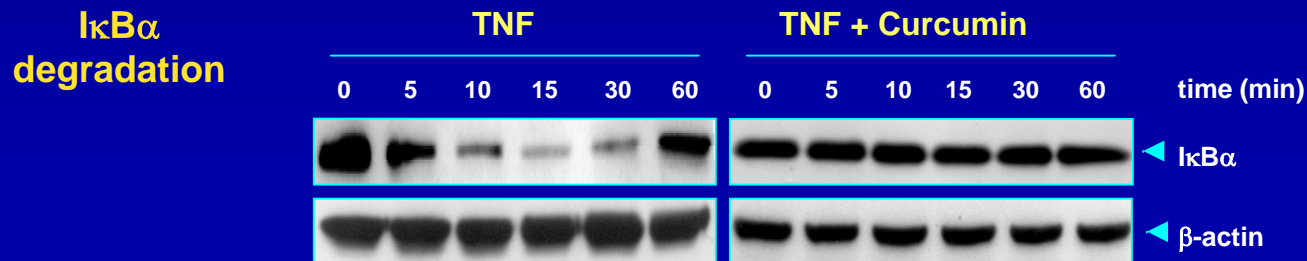
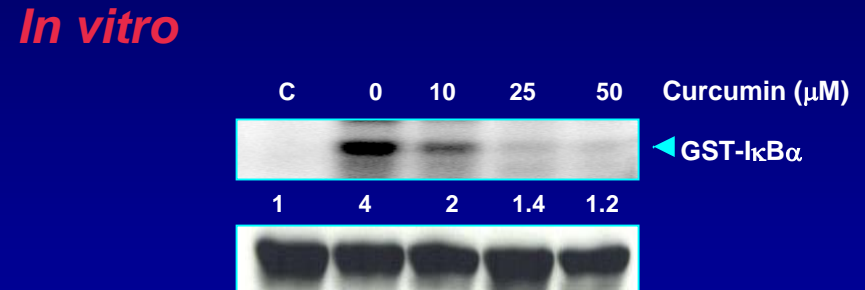
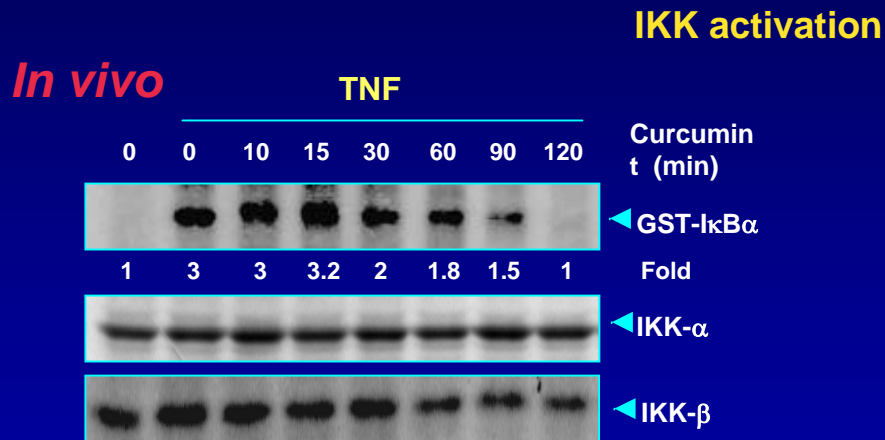
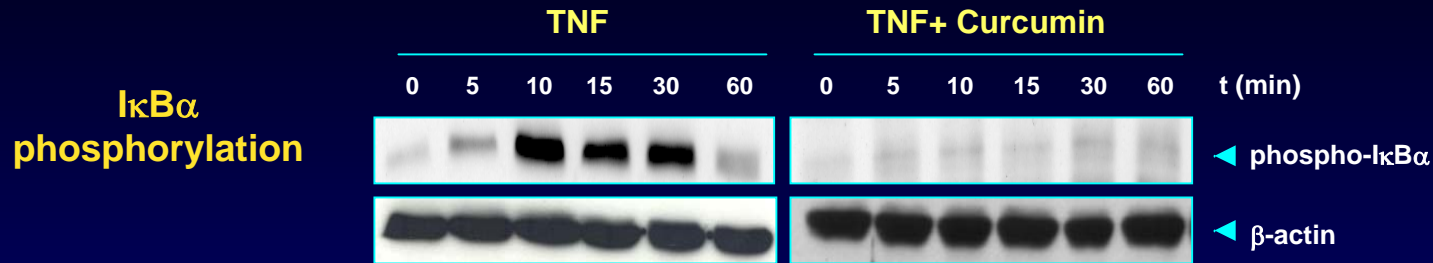


CTC ACT TTCC

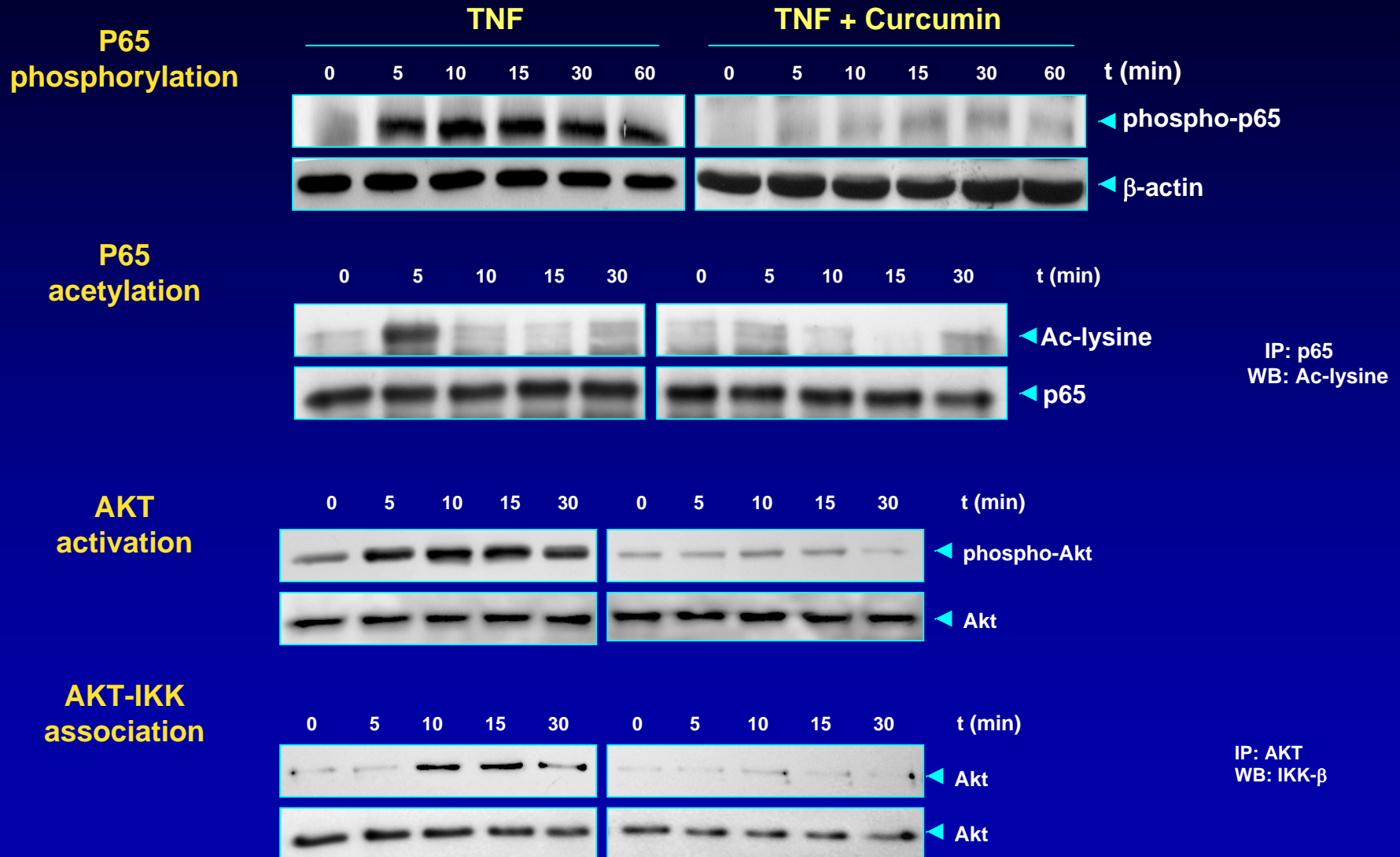
Curcumin inhibits NF- κ B activation



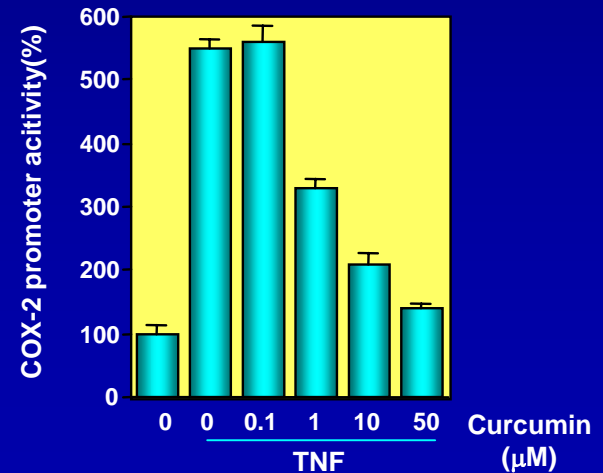
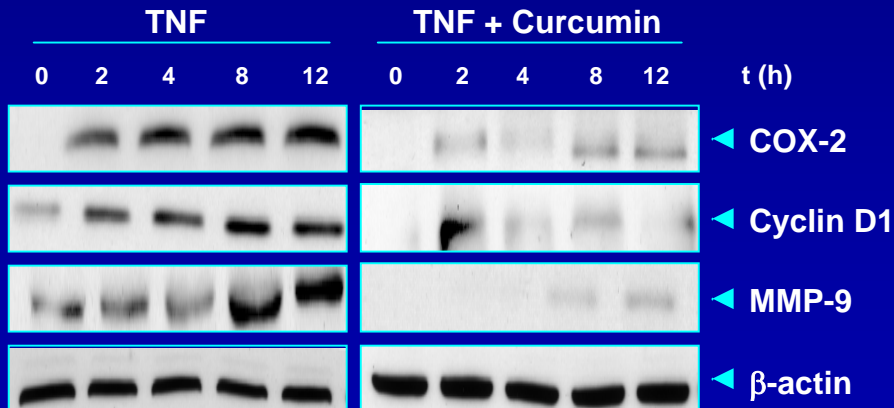
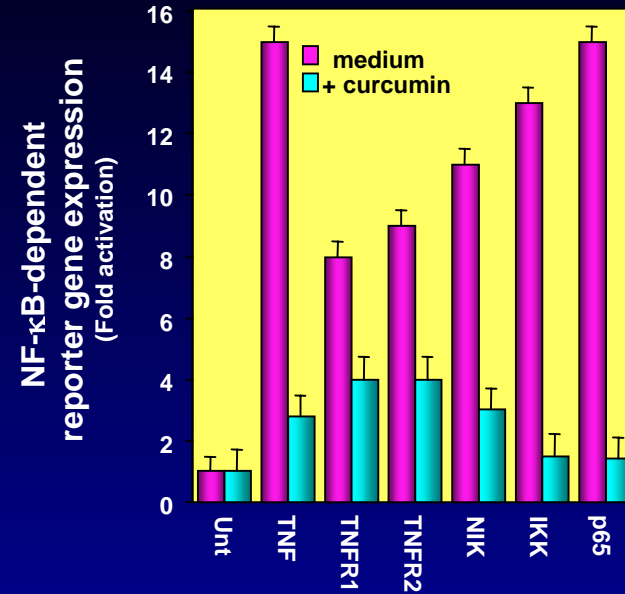
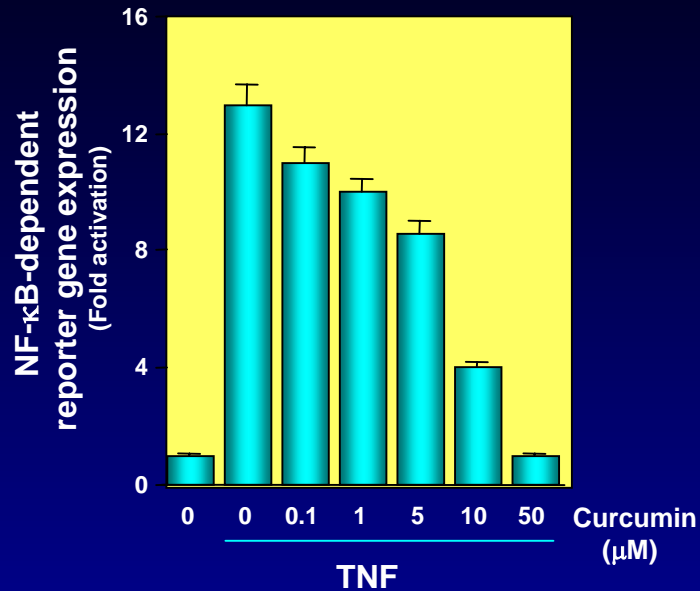
Curcumin inhibits NF- κ B activation



Curcumin inhibits NF- κ B activation



Curcumin inhibits NF- κ B activation



Effect of curcumin on TNF expression and signaling

- Curcumin abrogates LPS-induced **TNF** production
- Curcumin abrogates TNF-induced **NF-κB** activation
- Curcumin abrogates TNF-induced **AP-1** activation
- Curcumin abrogates TNF-induced **JNK** activation
- Curcumin abrogates TNF-induced **AKT** activation
- Curcumin abrogates TNF-induced **PI3K** activation
- Curcumin abrogates TNF-induced expression of **adhesion molecules**
- Curcumin abrogates TNF-induced **COX2** expression
- Curcumin abrogates **STAT3** activation

Curcumin & cancer

Different stages of cancer progression and its suppression by curcumin

Constitutive activation of transcription factors

➤ AP-1 & NF- κ B

➤ Tumor Suppressor genes

Overexpression of

➤ Oncogenes

➤ HER2

➤ Growth factors

(e.g; EGF, PDGF, FGF)

➤ Growth factor receptors

➤ Survival factors

(e.g; Survivin, Bcl-2 and Bcl-xl)

➤ Cyclin D1

➤ Decoy receptor

Overexpression of

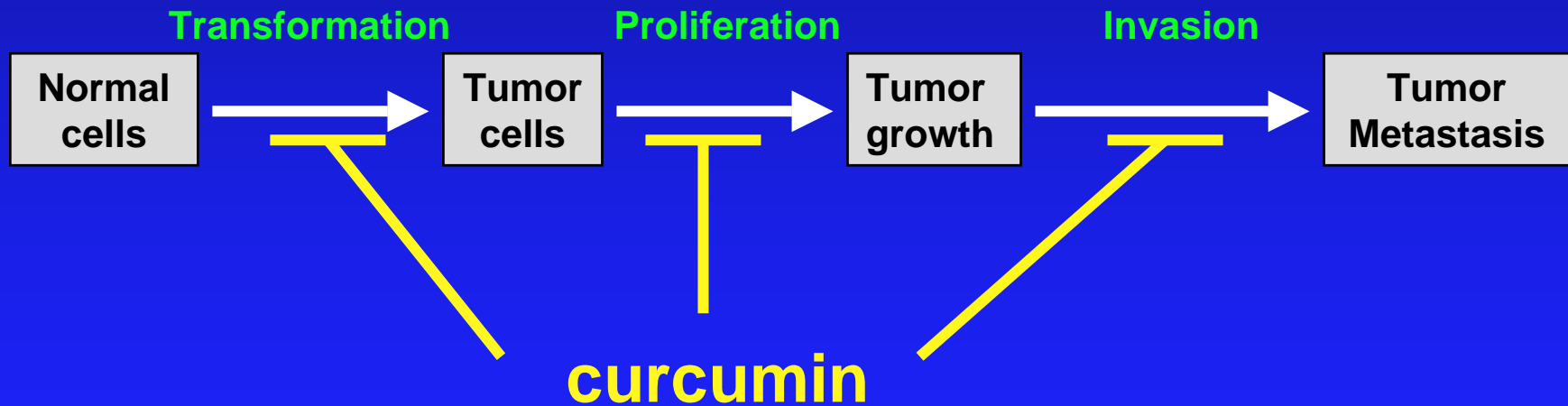
➤ Matrix metalloproteases

➤ Cyclooxygenase-2

➤ Adhesion molecules

➤ Chemokine

➤ TNF



Curcumin & tumor initiation

Inhibitory effects of curcumin
on **tumor initiation** by
benzo[a]pyrene and DMBA.

Huang MT...Conney AH,
Carcinogenesis. 1992 ;13:2183-6.

Curcumin is chemopreventive for various tumors

Tumor initiation

Huang et al, 1992

Tumor promotion in mouse skin

Huang et al. 1988; Conney et al 1991; Huang et al, 1992; Limtrakul et al., 1997;
Huang et al 1997

Forestomach, duodenal, and colon carcinogenesis

Huang et al, 1994; Rao et al, 1995; Singh et al, 1998; Kim et al, 1998; Kawamori et al, 1999

Mammary tumorigenesis

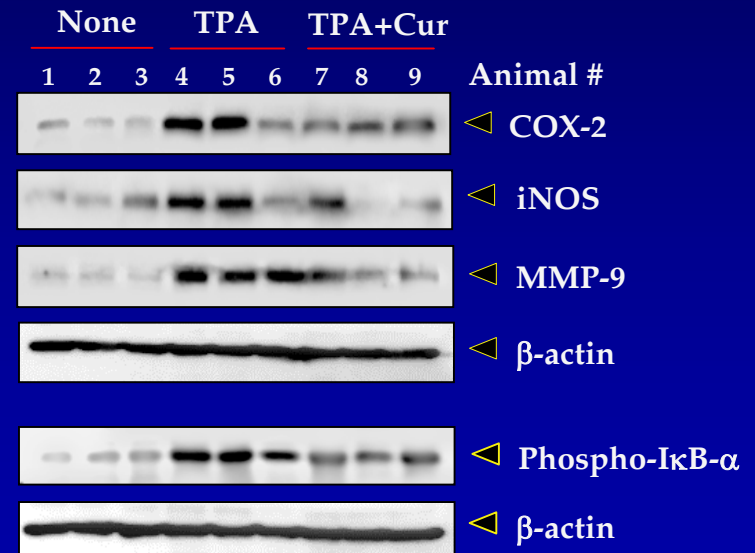
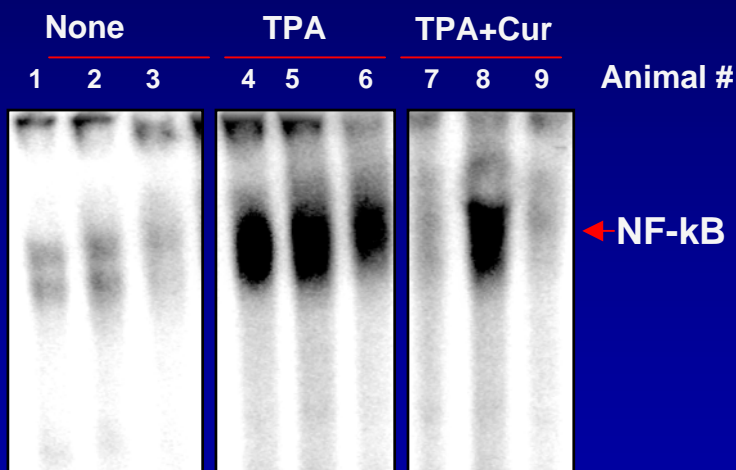
Singletary et al, 1996; Huang, et al, 1998; Lou et al, 1998; Inano et al, 1999

Hepatocarcinogenesis

Chuang et al, 2000

Curcumin suppresses phorbol ester-induced activation of NF- κ B, I κ B α phosphorylation, COX2, MMP9, and iNOS in mouse epidermis.

Female ICR mice (6–7 wks-old) treated topically with curcumin (25 μ M) for 3h followed by TPA (50 nM) for 4h and then biopsied.



Curcumin inhibits proliferation of tumor cells but not of normal cells

Head and neck squamous cell carcinoma

Pancreatic carcinoma

Multiple myeloma

Breast adenocarcinoma

Prostate carcinoma

Acute myelogenous leukemia

Hepatocarcinoma

Chronic myelogenous leukemia

Lung cancer cells

Ovarian carcinoma

Cervical carcinoma

B cell lymphoma

Vascular smooth muscle cells

Scleroderma lung fibroblasts

Bladder cancer

Colon cancer

Melanoma cells

Vascular endothelial cells

Osteoclast cells

Basal cell carcinoma

Aggarwal et al, 2004

Li et al, 2004

Bharti et al, 2003

Mehta et al, 1995

Mukhopadhyay et al, 2001

Anto et al, 2002

Ayng-Ai C et al, 2004

Wu LX et al, 2003

Radhakrishna Pillai, 2004

Chan MM, 2003

Prusty BK, 2005

Han SS et al, 1999

Huang HC, 1992

Tourkina E, 2004

Sindhwani P et al, 2001

Hanif R, 1997

Bush JA, 2001

Singh AK, 1997

Ozaki K, 2000

Jee SH, 1998

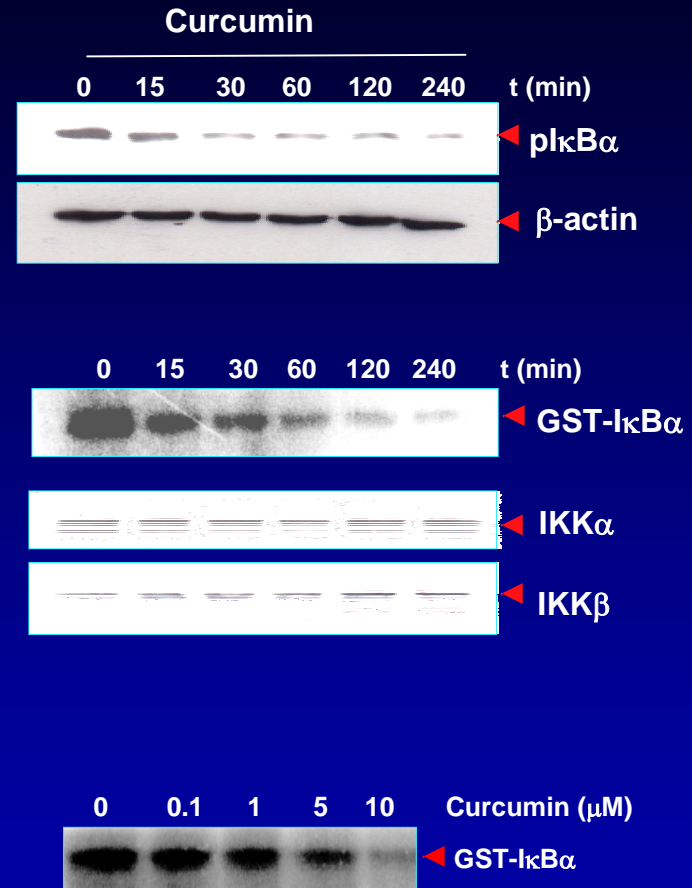
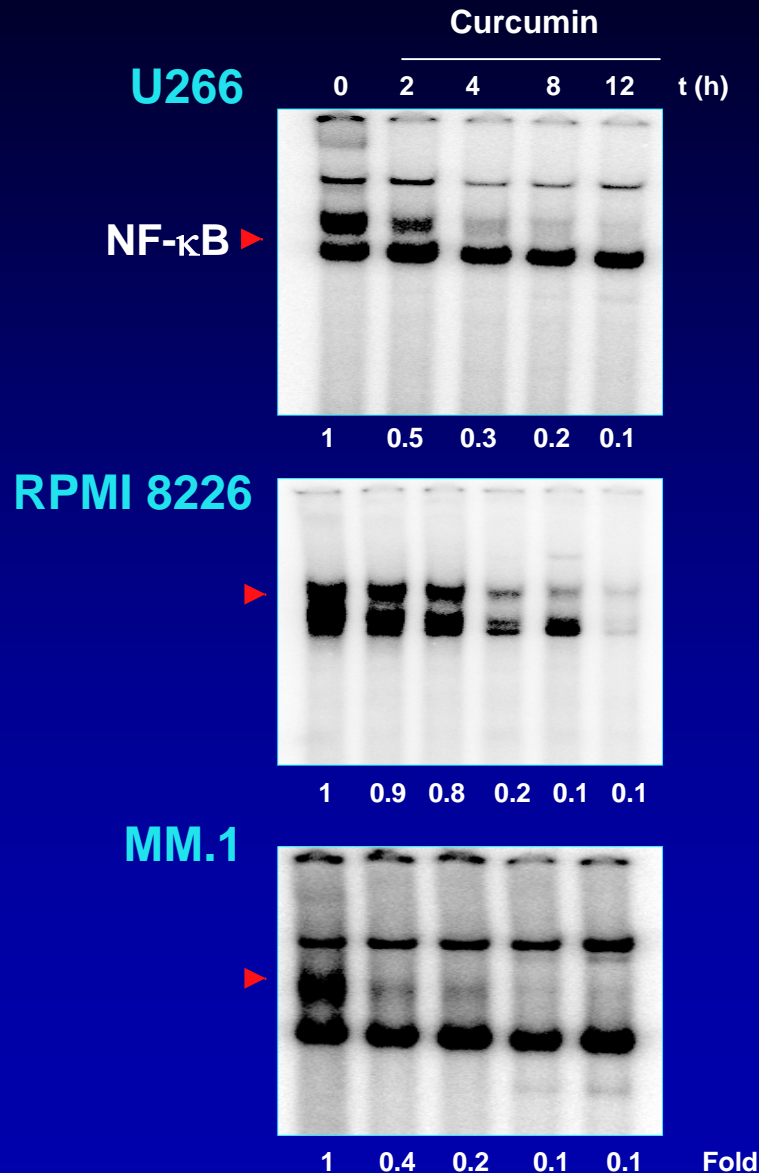
No effect on normal rat hepatocytes, lymphocytes and fibroblasts Ayng-Ai C et al, 2004

Curcumin inhibits constitutive NF- κ B, I κ B α kinase, inhibits proliferation, and induces apoptosis in human multiple myeloma cells

Bharti A., Donato N., Singh S., Aggarwal B.B.,

BLOOD, 101, 2003, 885-61

Curcumin suppresses NF- κ B, I κ B α phosphorylation and I κ B α kinase in multiple myeloma cells

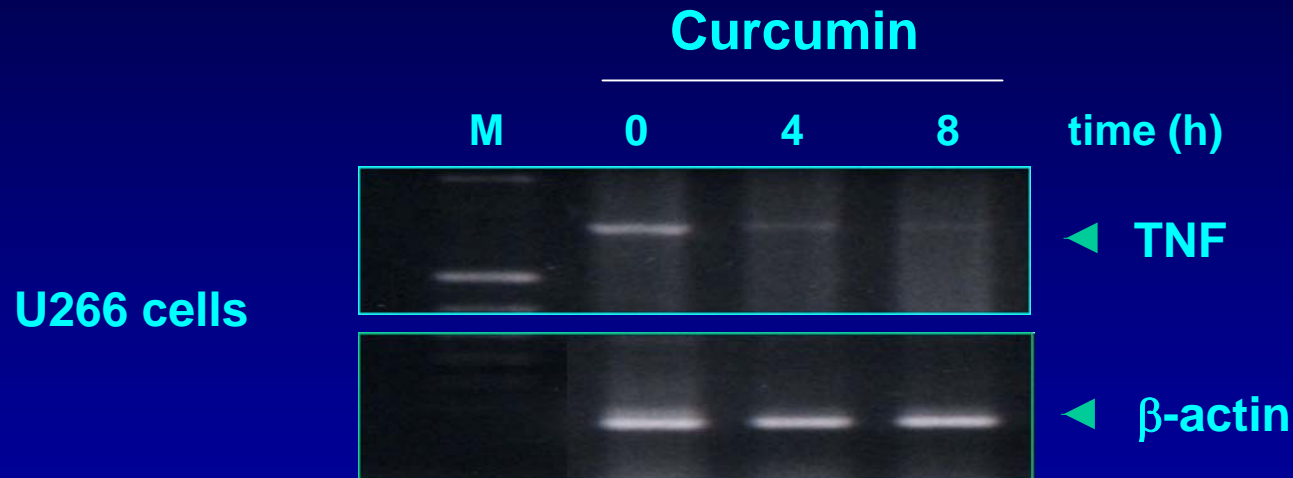


In vitro

Bharti AC, et al Blood. 2004;103:3175-84.

Bharti AC, et al Blood. 2003;101:1053-62.

Curcumin suppresses TNF expression in multiple myeloma cells



Nuclear Factor- κ B and STAT3 are Constitutively Active in CD138+ Cells Derived from Multiple Myeloma Patients and Their Suppression Leads to Apoptosis

Alok C. Bharti, Shishir Shishodia, James M. Reuben,
Donna Weber, Raymond Alexanian, Saroj Raj-Vadhan,
Zeev Estrov, Moshe Talpaz and Bharat B. Aggarwal

BLOOD, 2004, 103: 3175-84

**Curcumin inhibits TNF-
mediated NF- κ B activation
leading to suppression of
expression of cell surface
adhesion molecules in
endothelial cells**

Kumar A. and Aggarwal B. B.,

Biochem. Pharmacol. 55, 775-783, 1998

Curcumin inhibits cyclin D1 expression through transcriptional and post-transcriptional regulation

*Mukhopadhyay A., Banerjee S., Stafford LJ, Xia CX.,
Liu M., and Aggarwal BB,*

ONCOGENE, 21, 8852, 2002

Curcumin induces apoptosis through activation of caspase-8, BID cleavage and cytochrome C release in human acute myelogenous leukemia

*Anto R. J., Mukhopadhyay A., Denning K., and
Aggarwal B.B.,*

Carcinogenesis, 23, 143, 2002

Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines

Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB.

Oncogene. 2001 Nov 15; 20 (52):7597-609.

Curcumin

Dorai T, Gehani N, Katz A.

**Therapeutic potential of curcumin in human prostate cancer-I.
curcumin induces apoptosis in both androgen-dependent and
androgen-independent prostate cancer cells.**

Prostate Cancer Prostatic Dis. 2000;3:84-93.

Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE.

**Therapeutic potential of curcumin in human prostate cancer. III.
Curcumin inhibits proliferation, induces apoptosis, and inhibits
angiogenesis of LNCaP prostate cancer cells in vivo.**

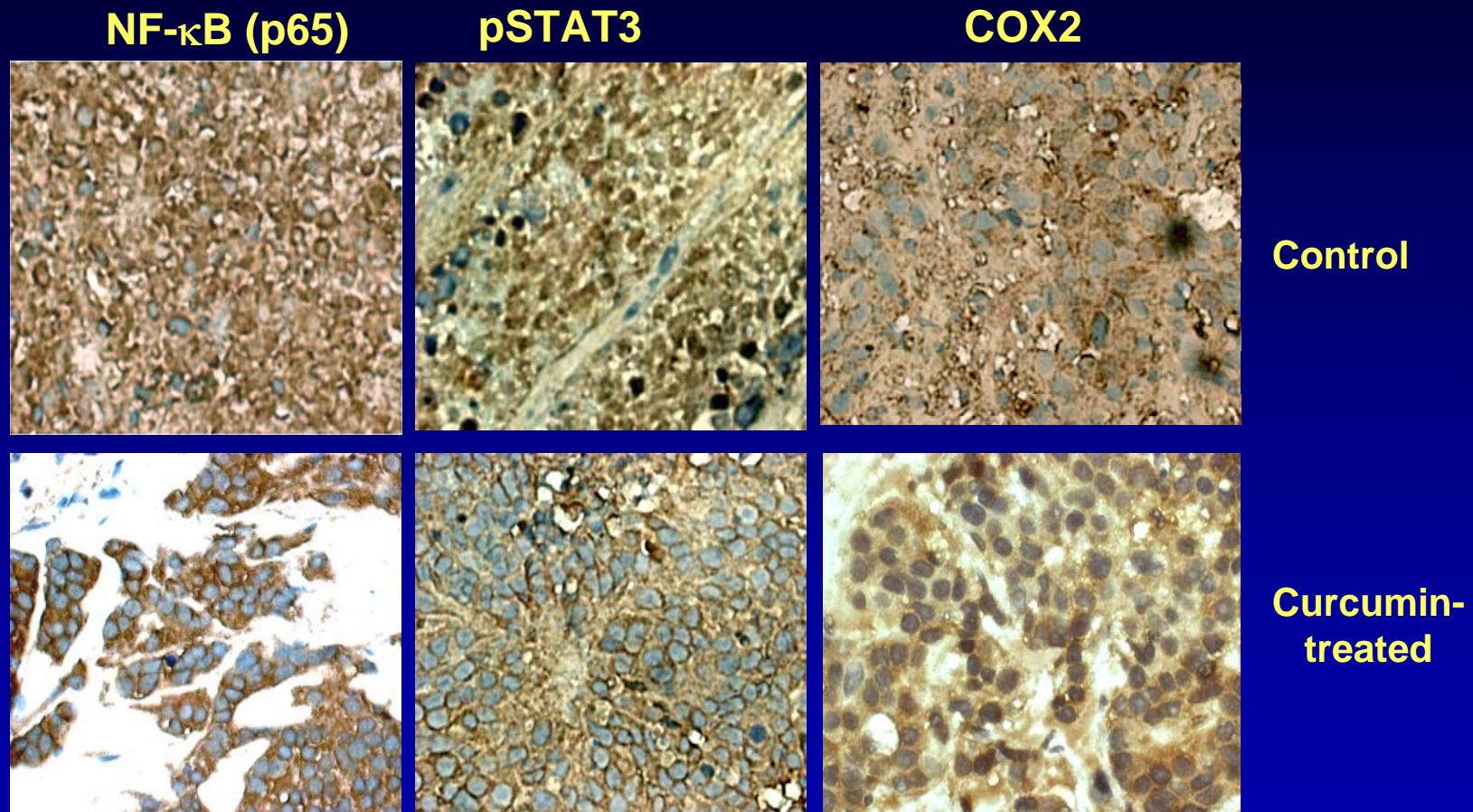
Prostate. 2001;47:293-303.

Dorai T, Gehani N, Katz A.

**Therapeutic potential of curcumin in human prostate cancer. II.
Curcumin inhibits tyrosine kinase activity of epidermal growth factor
receptor and depletes the protein.**

Molecular Urology. 2000;4:1-6.

Curcumin suppresses NF- κ B, pSTAT3 and COX2 in prostate cancer in vivo



Shishodia, Dorai and Aggarwal (unpublished)

Nuclear Factor- κ B and I κ B Kinase are Constitutively Active in Human Pancreatic Cells and their Down- regulation by Curcumin is Associated with Suppression of Proliferation and Induction of Apoptosis

*Lan Li, Bharat B. Aggarwal, Shishir Shishodia, James
Abbruzzese and Razelle Kurzrock*

Cancer, 101:2351-62.

**Curcumin Downregulates the
Constitutive Activation of
NF- κ B and I κ B α Kinase
in Human Head and Neck Squamous
Cell Carcinoma Cells Leading to
Suppression of Proliferation and
Induction of Apoptosis:
Modulation of Cyclin D1, MMP-9 and COX-2**

*S. Aggarwal, Y. Takada, S. Singh, J. Myers and B. B. Aggarwal,
International Journal of Cancer 111, 679-692, 2004*

Curcumin Downregulates Cigarette Smoke-Induced NF- κ B Activation Through Inhibition of I κ B α Kinase in Human Lung Epithelial Cells:

Correlation with Suppression of COX-2, MMP-9 and Cyclin D1

S. Shishodia, P. Potdar, C. G. Gairola and B. B. Aggarwal,

Carcinogenesis 24, 2003, 1269-1279

Curcumin sensitizes tumor cells to chemotherapy

Taxol

Cisplatin

Chemotherapeutic agents

Doxo, 5FU, Cisplatin,taxol

5 FU

Immunization

TRAIL

Vb S etal, 2005

Chan MM, 2003

Hour TC, 2002

Chuang SE etal, 2002

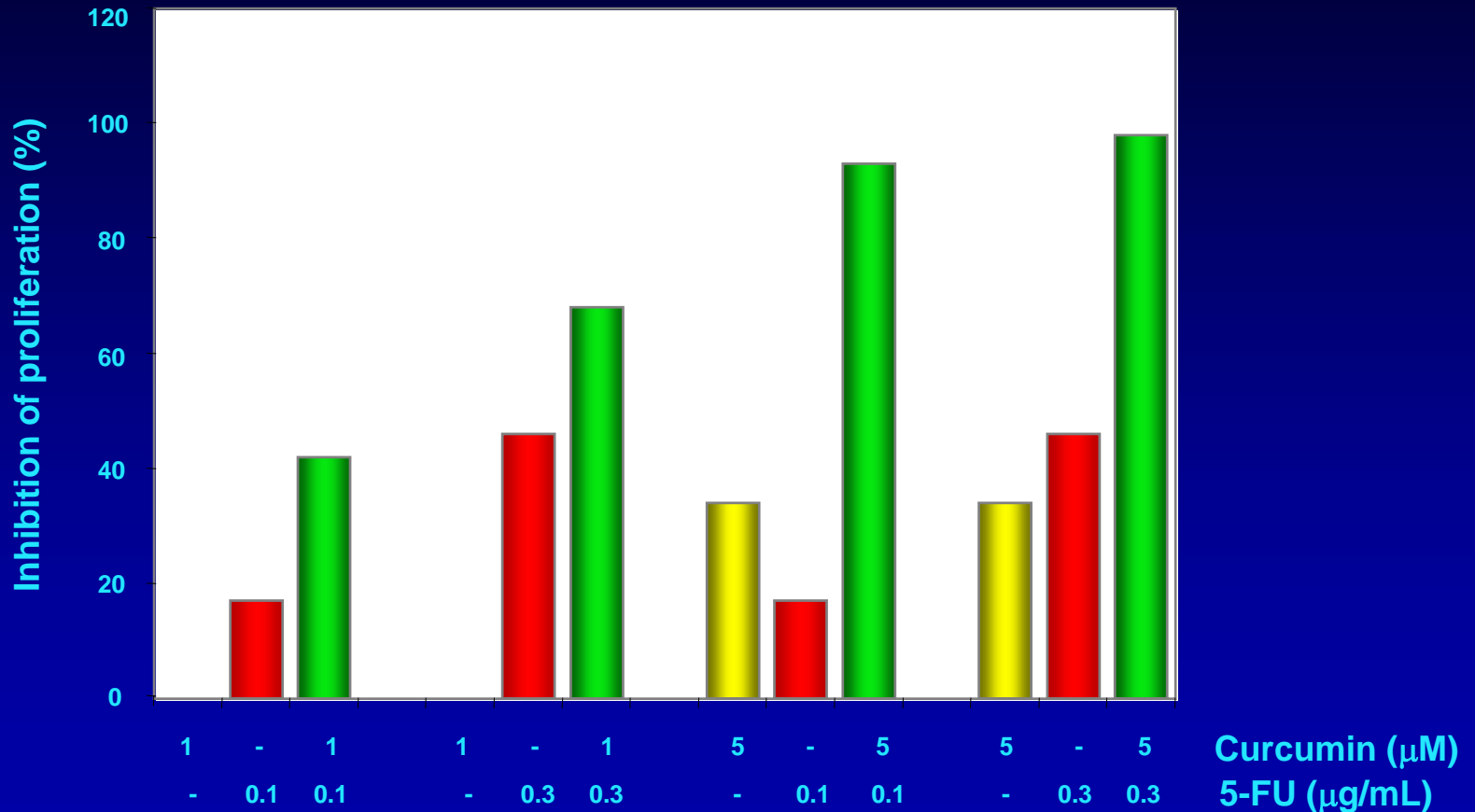
Koo JY etal, 2004

Odor J etal, 2004

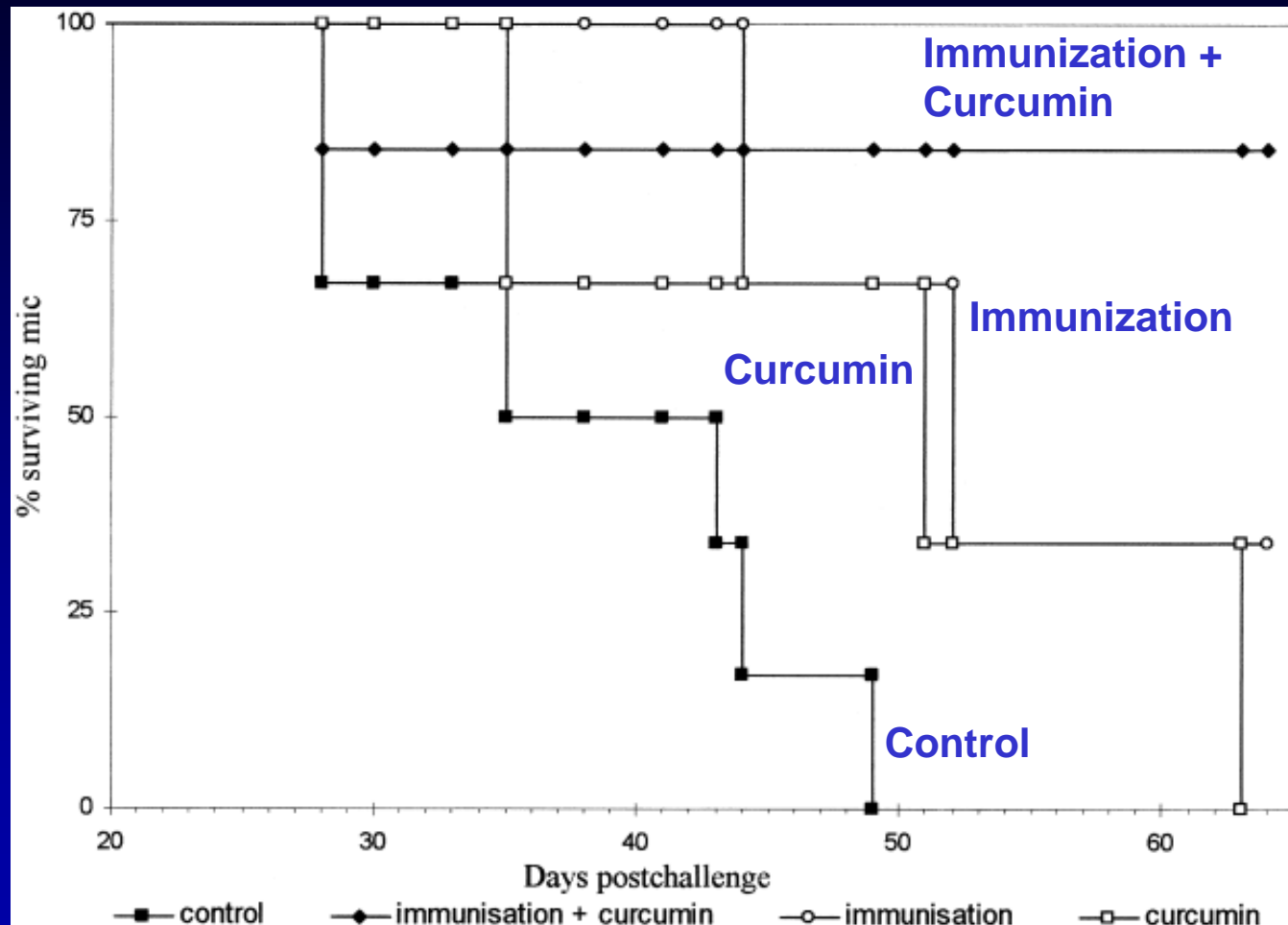
Deeb D etal, 2003, 2004

Decreases adriamycin cardiotoxicity Venkatesan N, 1998

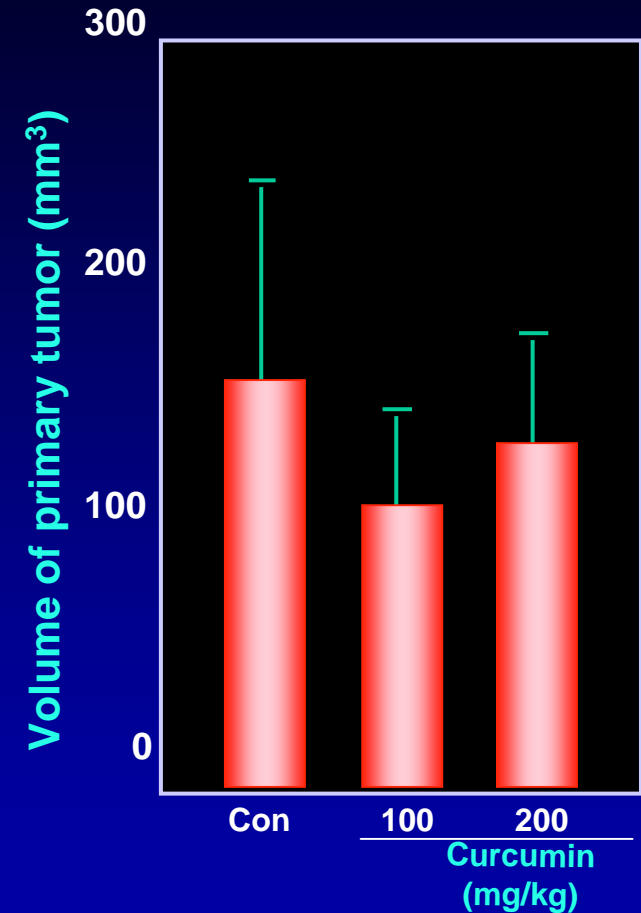
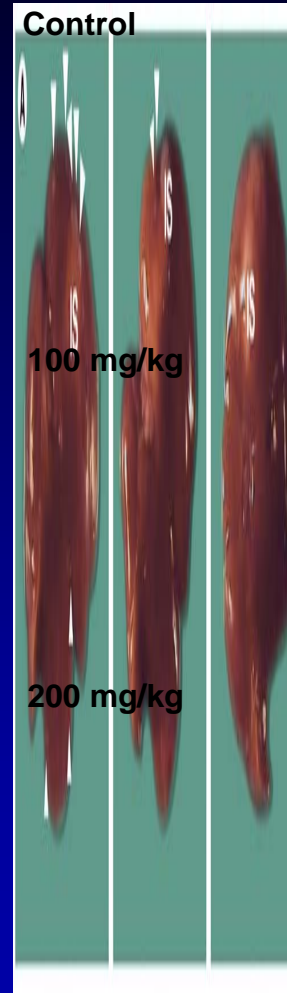
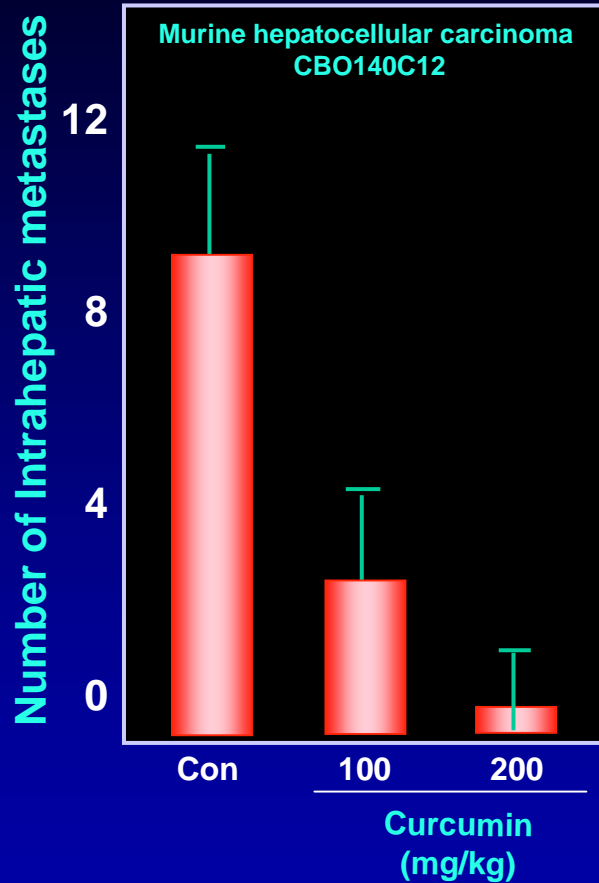
Curcumin synergises with 5-FU for suppression of growth of human gastric cancer AGS cells



Curcumin enhances survival in immunized mice bearing B16-R melanoma



Curcumin inhibits intrahepatic metastasis in an orthotopic implantation model in mice



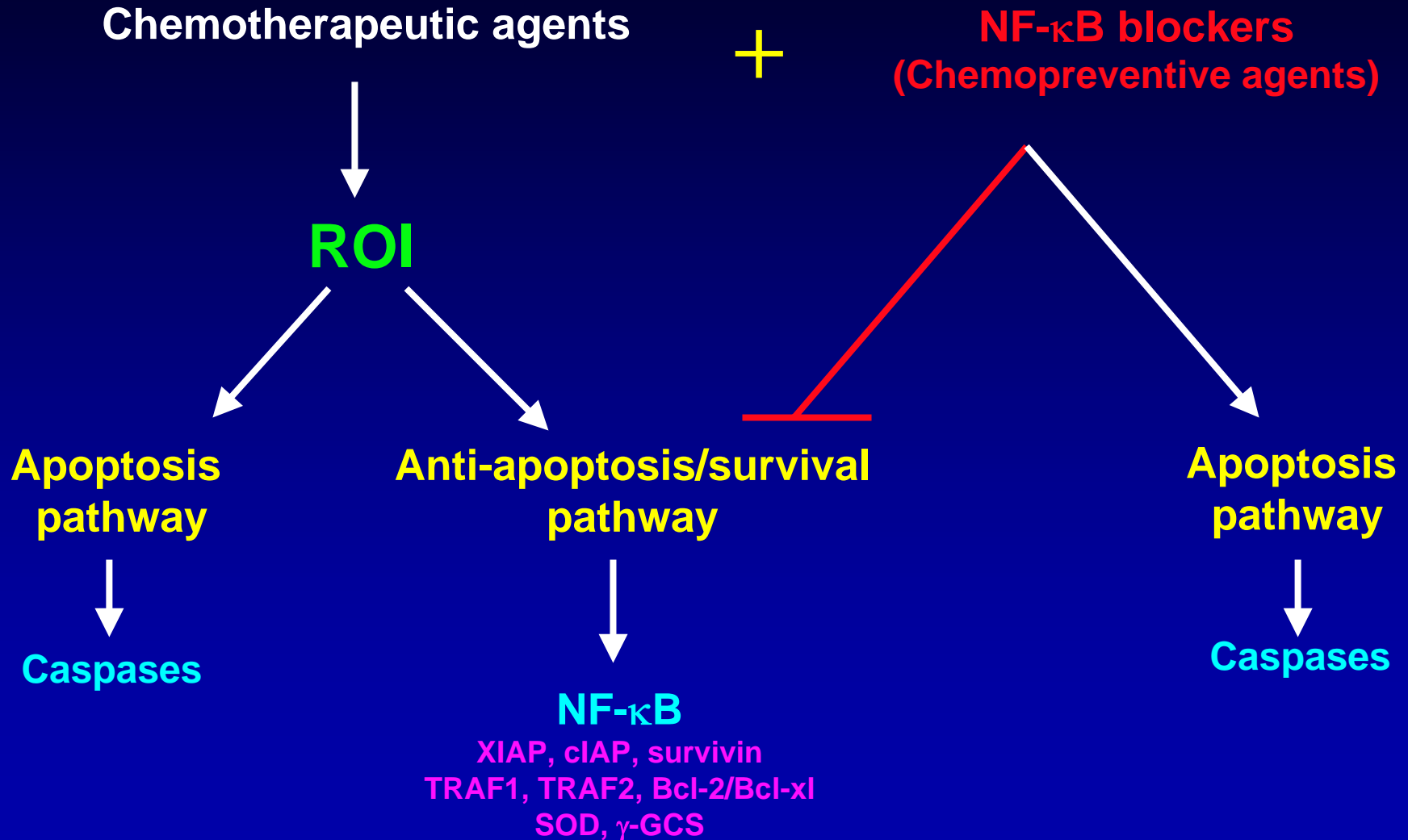
Curcumin Suppresses Metastasis in a Human Breast Cancer Xenograft Model:

Association With Suppression of NF- κ B, COX-2 and MMP-9







*Bharat B. Aggarwal,
Shishir Shishodia, Sanjeev Banerjee, Robert A. Newman,
Carlos E. Bueso-Ramos and Janet E. Price*

(submitted)

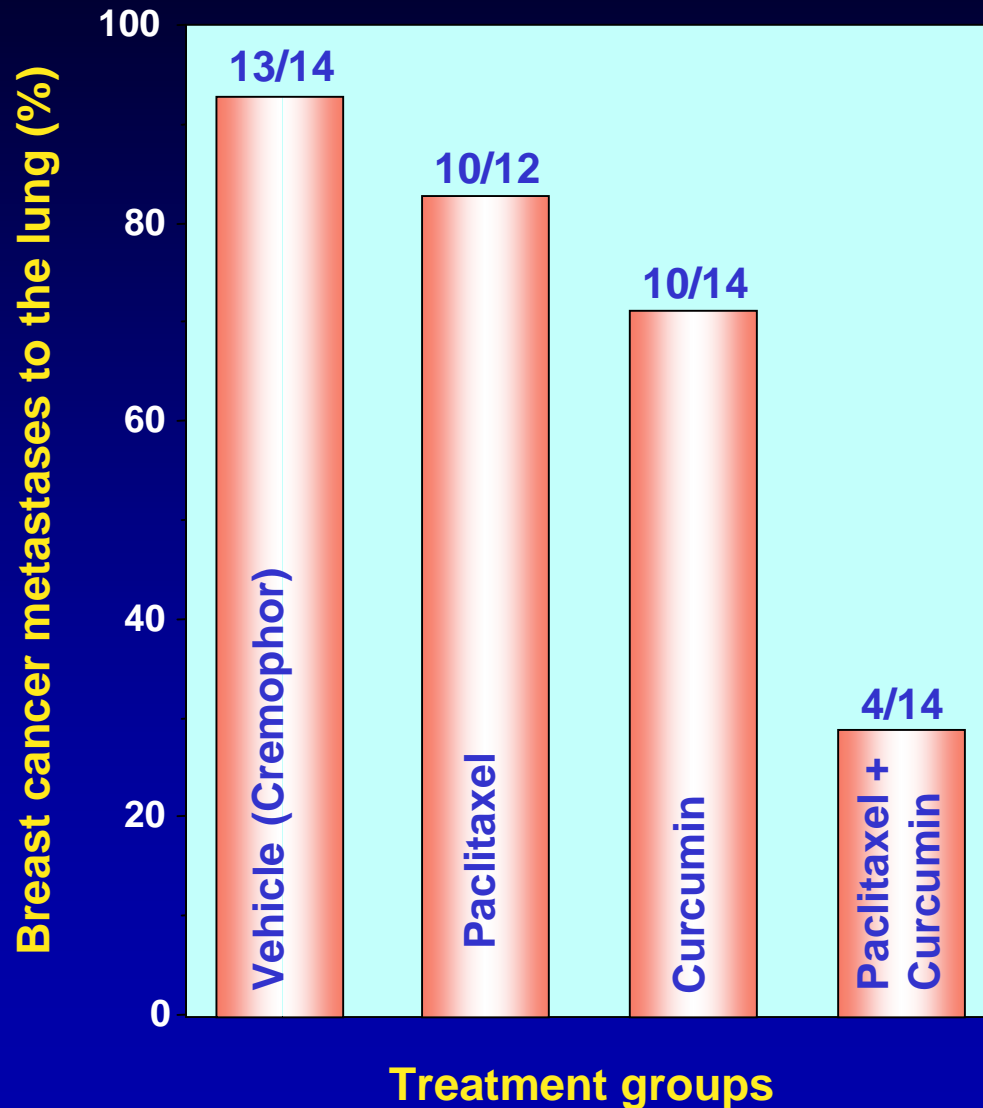
Rationale for a combination therapy of cancer



Curcumin potentiates the effect of paclitaxel by inhibiting the metastasis of the human breast cancer to the lung in mouse xenograft model

- ❖ Inject mammary fat pad of female nude mice with human breast cancer cells (MDA-MB-435, 2 million cells)
- ❖ Allow the tumors to reach to palpable size (10 mm mean diameter)
- ❖ Anesthetize the mice and resect the tumors and close the skin incisions
- ❖ Then randomize the mice into four treatment groups to receive:
 1. Control diet (vehicle injection, i.p.) 
 2. Curcumin diet, (vehicle injection, i.p.) 
 3. Control diet, paclitaxel (10 mg/kg, i.p.)  
 4. Curcumin diet, paclitaxel (10 mg/kg, i.p.)  
- ❖ Paclitaxel was injected on day 10, 17 and 24 after tumor removal
- ❖ Animals were given diet containing 2% curcumin (w/w) 5 day after tumor removal
- ❖ Five weeks after tumor removal, mice were killed and incidence of metastases to the lung and other organs was recorded

Curcumin potentiates the effect of paclitaxel by suppressing the metastasis of the human breast cancer to the lung in mouse xenograft model



Curcumin Inhibits Receptor Activator of NF- κ B Ligand- Induced NF- κ B Activation in Osteoclast Precursors and Suppresses Osteoclastogenesis

A.C. Bharti, Y. Takada, and B. B. Aggarwal

Journal of Immunology; 172, 5940-5947, 2004

Curcumin Inhibits Constitutive and Interleukin-6-Inducible STAT3 Phosphorylation in Human Multiple Myeloma Cells

***Alok C. Bharti, Nicholas Donato, and
Bharat B. Aggarwal***

Journal of Immunology, 171, 2003, 3863-3871

Curcumin

Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3

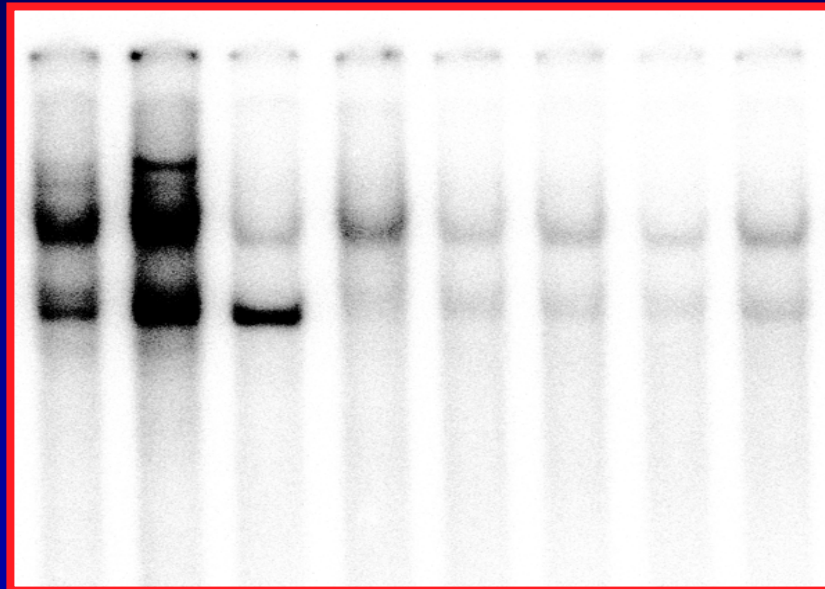
Radiation upregulated TNF leading to an increase in NF- κ B activity resulting in the induction of Bcl-2 protein.

Curcumin in combination with radiation inhibited TNF-mediated NF- κ B activity resulting in bcl-2 protein downregulation.

Chendil D, et al Oncogene 2004, 26:1599-607.

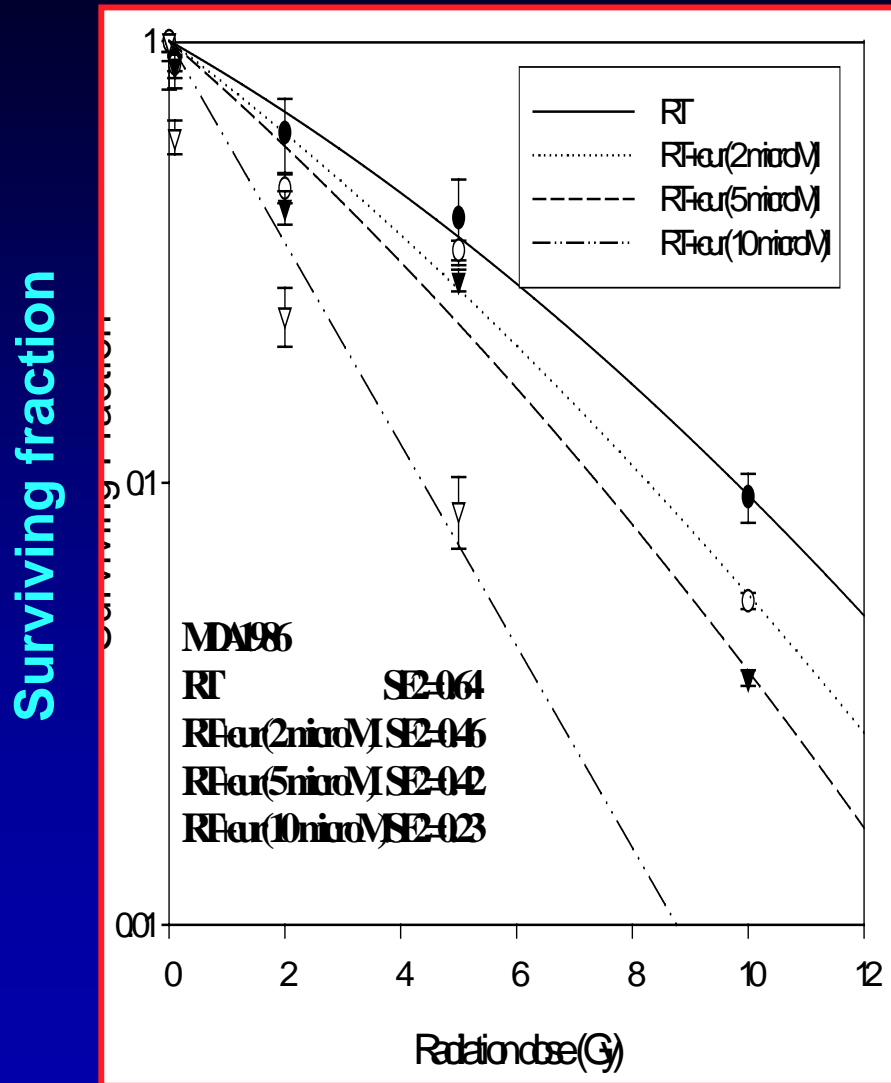
Curcumin inhibits radiation-induced NF- κ B activation in HNSCC

-	-	-	-	-	-	+	+	Wortmannin (2 μ M)
-	-	-	-	+	+	-	-	Ly294002 (25 μ M)
-	-	+	+	-	-	-	-	Curcumin (50 μ M)
-	+	-	+	-	+	-	+	RT (20 Gy)



← NF- κ B

Curcumin sensitizes HNSCC to γ -radiation



**Cancer treatment
requires suppression
of multiple cell-
signaling/survival
pathways!**

Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription

Acetylation of histones and non-histone proteins is involved in the regulation of gene expression in eukaryotes and all viral DNA that integrates into the human genome.

Balasubramanyam K, et al., J Biol Chem. 2004 Dec 3;279(49):51163-71

Curcumin & angiogenesis

Curcumin is an in vivo inhibitor
of angiogenesis

Arbiser JL et al , Mol Med. 1998 Jun;4(6):376-83.

Curcumin & COX2

Curcumin inhibits phorbol ester-induced expression of **cyclooxygenase-2** in mouse skin through suppression of extracellular signal-regulated kinase activity and **NF- κ B** activation

Chun KS et al Carcinogenesis. 2003 Sep;24(9):1515-24.

Curcumin & LOX

Inhibitory effects of curcumin
on in vitro **LOX and COX**
activities in mouse epidermis

Huang MT...Conney AH,
Cancer Res. 1991;51:813-9.

Molecular Targets of curcumin

Structure of curcumin in complex with lipoxxygenase and its significance in cancer

**Skrzypczak-Jankun E, Zhou K, McCabe NP, Selman SH, Jankun J.
Int J Mol Med. 2003 Jul;12(1):17-24**

Curcumin inhibits lipoxxygenase by binding to its central cavity: theoretical and X-ray evidence

**Skrzypczak-Jankun E, McCabe NP, Selman SH, Jankun J.
Int J Mol Med. 2000 Nov;6(5):521-6.**

Department of Urology, Urology Research Center, Medical College of Ohio, Toledo,
OH 43614-5807, USA. ewa@golemxiv.dk.mco.edu

Co-crystalization of curcumin with Lipoxygenase (LOX)

Curcumin inhibits LOX by binding to its central cavity: theoretical and X-ray evidence

**Skrzypczak-Jankun E, McCabe NP, Selman SH, Jankun J.
Int J Mol Med. 2000;6:521-6.**

Structure of curcumin in complex with LOX and its significance in cancer

**Skrzypczak-Jankun E, Zhou K, McCabe NP, Selman SH, Jankun J. Int J
Mol Med. 2003;12:17-24**

Anti-invasive gene expression profile of curcumin in lung adenocarcinoma based on a high throughput microarray analysis.

Using microarray analysis, **81 genes were down-regulated** and **71 genes were up-regulated** after curcumin treatment.

Below sublethal concentrations of curcumin (10 μ M), several invasion-related genes were suppressed, including MMP14, NCAM (0.54-fold), and integrins α 6 and β 4.

In addition, several heat-shock proteins (Hsp) [Hsp27 (2.78-fold), Hsp70 (3.75-fold), and Hsp40-like protein (3.21-fold)] were induced by curcumin.

Real-time quantitative reverse transcription-polymerase chain reaction, Western blotting, and immunohistochemistry confirmed these results in both RNA and protein levels.

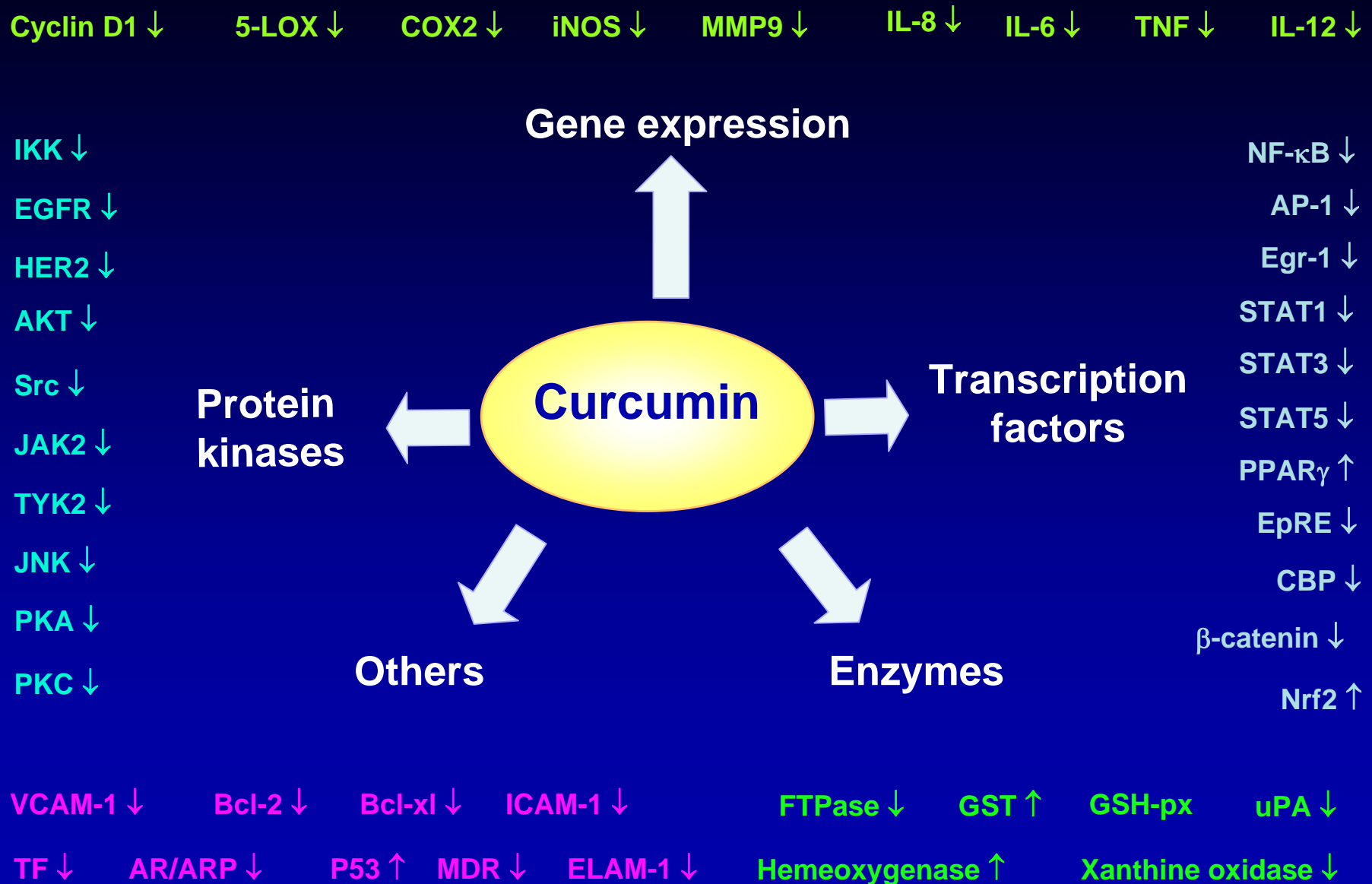
Curcumin (1-10 μ M) reduced the MMP14 expression in both mRNA and protein levels and also inhibited the activity of MMP2, the down-stream gelatinase of MMP14, by gelatin zymographic analysis.

Based on these data, it can be concluded that curcumin might be an effective antimetastatic agent with a mechanism of anti-invasion via the regulation of certain gene expressions.

Curcumin: gene profile

- Performed gene expression profiling study to identify novel targets of curcumin action.
- A cDNA array comprised of 12,625 probes was used to compare total RNA extracted from curcumin-treated, and untreated, MDA-1986 cells for differential gene expression.
- Identified 202 up-regulated mRNAs and 505 transcripts decreased 2 fold or more.
- The pro-apoptotic activating transcription factor 3 (ATF3) was induced over 4 fold. Two negative regulators of growth control (antagonizer of myc transcriptional activity, Mad, and p27kip1) were induced 68 and 3 fold respectively.
- Additionally, two dual-activity phosphatases (CL 100 and MKP-5) which inactivate the JNKs showed augmented expression, coinciding with reduced expression of the upstream activators of JNK (MEKK and MKK4).
- Of the repressed genes, the expression of Frizzled-1, (Wnt receptor), was most strongly attenuated (8 fold).
- Growth control genes (K-sam, encoding the KGF receptor and HER3) as well as the E2F-5 transcription factor, which regulates genes controlling cell proliferation also showed down-regulated expression.
- Treatment of MDA-1986 cells, yielded a rapid, dose-dependent increase in ATF3 protein. Moreover, expression of an exogenous ATF3 cDNA synergized with curcumin in inducing apoptosis.
- In conclusion, we have identified several putative, novel biological targets of curcumin and demonstrated that one (ATF3) contributes to the pro-apoptotic effects of this compound.

Molecular targets of curcumin



**Clinical
trials with
curcumin for
cancer!**

Why curcumin?

- Inhibits proliferation of cancer cells
- Induces apoptosis of cancer cells
- Downregulates EGFR activity
- Downregulates HER2/neu
- Downregulates Bcl-2 expression
- Downregulates NF- κ B activation
- Downregulates AP-1 activation
- Downregulates PI3K-Akt pathway
- Downregulates c-Jun kinase activation
- Suppresses adhesion molecules expression
- Downregulates COX2 expression
- Inhibits angiogenesis
- Downregulates MMP-9 expression
- Downregulates inducible nitric oxide synthase
- Downregulates cyclin D1 expression
- Inhibits taxol-induced NF- κ B activation

Clinical studies with curcumin in human subjects

Study	Patients		Dose	Comments	Ref.
Double blind, cross-over	18 pts. (22-48 yrs)		1200 mg /day x 2wks	Antirheumatic	Deodar et al (1980)
	46 male pts. (15-68)		400 mg; 3x/day x5 days	Inguinal hernia	Satosakar etal (1986)
	111 pts. (40-85yrs.)		Topical	HNSCC, Breast Vulva, Skin	Kuttan etal 1987
	10 volun.		500 mg/day x7 days	Serum cholesterol & LPO	Soni & Kuttan (1992)
	40 pts.		625 mg; 4x/day x 8 wks	well-tolerated	James (1994)
	53 pts.		375 mg; 3x/day x12 wks	Chronic anterior uveitis	Lal etal (1999)
	8 pts.		375 mg; 3x/day 6-22 months	Idiopathic inflamm. orbital pseudotumors	Lal etal (2000)
Prospective Phase I	25 pts.	500 mg-12,000mg/day x3 months		H&N cancers	Cheng etal (2001)
	15 pts.		36-180 mg 4 months	Colorectal Serum GST-down	Sharma etal (2001)

Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions.

Cheng AL, et al Anticancer Res. 2001 Jul-Aug;21(4B):2895-900.

➤ Tested on **25 pts** (13 men & 12 women) with a median age of 60 yrs (36-77)

➤ Curcumin was administered orally **8000 mg/day**

➤ Patients	No.	Histological response
Recently resected bladder cancer;	2	1/2
Oral leukoplakia,	7	2/7
Intestinal metaplasia of the stomach;	6	1/6
CIN	4	1/4
Bowen's disease	6	2/6

➤ All pts (except 2) completed **3 months** treatment regimen

➤ Peak serum conc. of curcumin at 1-2 h after oral intake was **0.4-1.6 uM**

➤ **Conclusion:**

Curcumin is not toxic to humans even at the high dose (8000 mg/day).

Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance.

Sharma RA,Gescher AJ, Steward WP. Clin Cancer Res. 2004 Oct 15;10(20):6847-54.

Background: Curcumin's efficacy appears to be related to induction of glutathione S-transferase enzymes, inhibition of prostaglandin E(2) (PGE(2)) production, or suppression of oxidative DNA adduct (M(1)G) formation.

Objectives: Dose-escalation study to explore the pharmacology of curcumin in humans.

Design: Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies consumed capsules compatible with curcumin doses between 0.45 and 3.6 g daily for up to 4 months. Levels of curcumin and its metabolites in plasma, urine, and feces were analyzed by high-pressure liquid chromatography and mass spectrometry. Three biomarkers of the potential activity of curcumin were translated from preclinical models and measured in patient blood leukocytes: GST activity, levels of M(1)G, and PGE(2) production induced ex vivo.

Results:

- Dose-limiting toxicity was not observed.
- Curcumin and its glucuronide and sulfate metabolites were detected in plasma in the 10 nmol/L range and in urine.
- A daily dose of 3.6 g curcumin engendered 62% and 57% decreases in inducible PGE(2) production in blood samples taken 1 hour after dose on days 1 and 29, respectively, of treatment compared with levels observed immediately predose ($P < 0.05$).
- A daily oral dose of 3.6 g of curcumin is advocated for Phase II evaluation in the prevention or treatment of cancers outside the gastrointestinal tract.
- PGE(2) production in blood and target tissue may indicate biological activity.
- Levels of curcumin and its metabolites in the urine can be used to assess general compliance.

Consumption of Curcumin by Cancer Patients:

Assessment of Curcumin Levels in the Colorectum and their Pharmacodynamic Consequences

Garcea G,Sharma RA, Steward WP, Gescher AJ.. Cancer Epidemiol Biomarkers Prev. 2005;14(1):120-5.

Background: Curcumin has been shown to reduce the adenoma burden in rodent models of colorectal cancer accompanied by a reduction of levels of the oxidative DNA adduct (M(1)G) and of expression of the COX-2.

Hypothesis: Pharmacologically active levels of curcumin can be achieved in the colorectum of humans as measured by effects on levels of M(1)G and COX-2 protein.

Design: Patients with colorectal cancer ingested curcumin capsules (3,600, 1,800, or 450 mg daily) for 7 days. Biopsy samples of normal and malignant colorectal tissue, respectively, were obtained at diagnosis and at 6 to 7 h after the last dose of curcumin. Blood was taken 1 hour after the last dose of curcumin.

Results: The concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3,600 mg of curcumin were 12.7 +/- 5.7 and 7.7 +/- 1.8 nmol/g, respectively.

Curcumin sulfate and curcumin glucuronide were identified in the tissue of these patients. Trace levels of curcumin were found in the peripheral circulation.

M(1)G levels were 2.5-fold higher in malignant tissue as compared with normal tissue ($P < 0.05$ by ANOVA).

Administration of curcumin (3,600 mg) decreased M(1)G levels from 4.8 +/- 2.9 adducts per 107 nucleotides in malignant colorectal tissue to 2.0 +/- 1.8 adducts per 107 nucleotides ($P < 0.05$ by ANOVA).

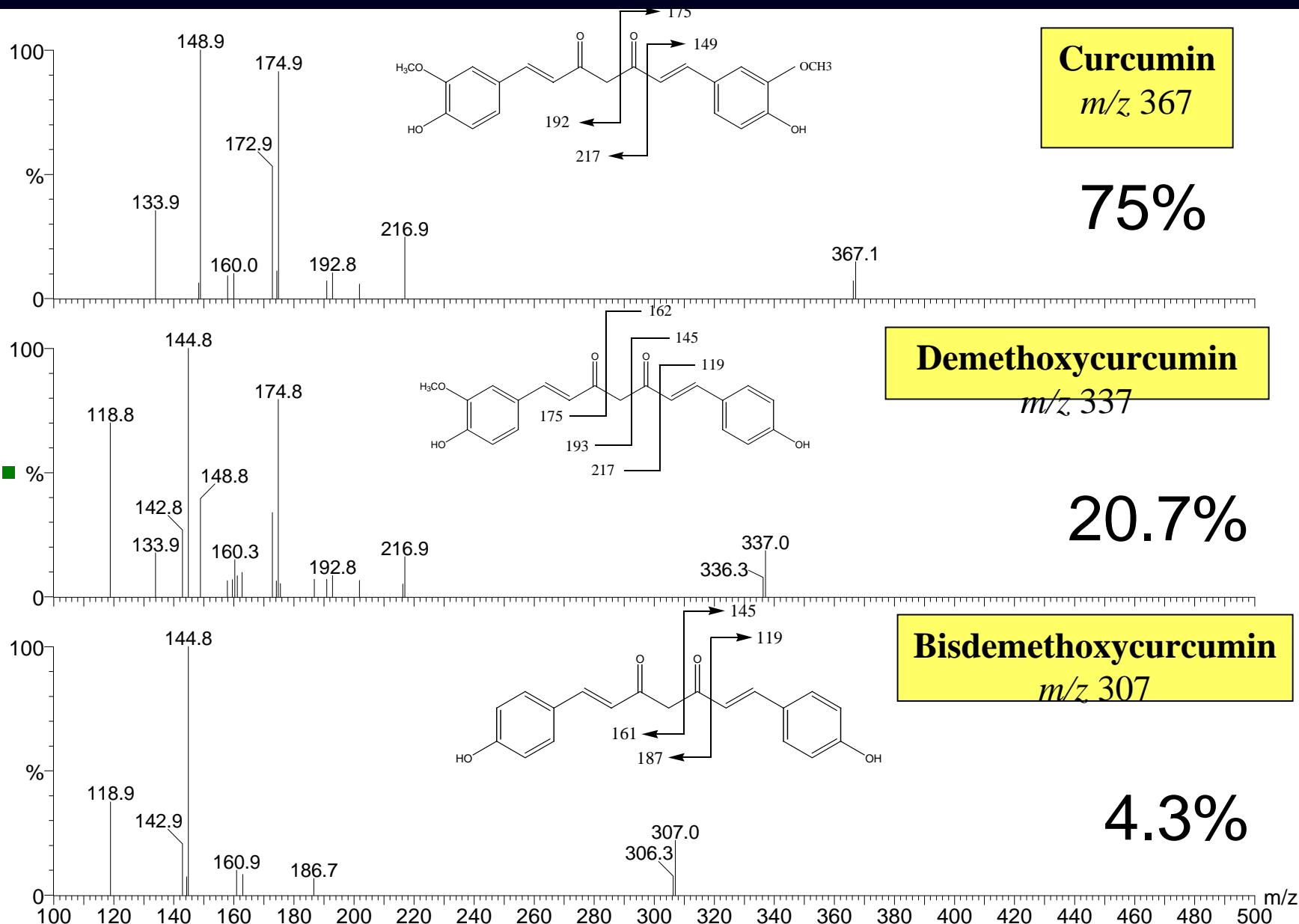
COX-2 protein levels in malignant colorectal tissue were not affected by curcumin.

The results suggest that a daily dose of 3.6 g curcumin achieves pharmacologically efficacious levels in the colorectum with negligible distribution of curcumin outside the gut.

Clinical trials with curcumin for multiple myeloma and pancreatic cancer



Curcumin structure and purity



Ongoing Clinical Trials with Curcumin

Disease	Investigator	Institution
Multiple myeloma	Saroj Raj-Vadhan, MD	UTMDACC, USA
Pancreatic cancer	Razelle Kurzrock, MD	UT MDACC, USA
Pancreatic cancer	Rami Ben Yosef, MD	Ichilov, Israel
Melanoma	Christopher D. Lao, MD	University of Michigan, USA
Colon Cancer	Ernie Hawk, MD	National Cancer Institute, UK
Colon Cancer	Dean Brenner, MD	University of Michigan, USA
Colon Cancer	William P Steward, MD	University of Leicester, UK
Alzheimer's Disease	Milan Fiala, MD	UCLA, USA
Safety Studies	Dean Brenner, MD	University of Michigan, USA
Myelodysplastic syndrome	Azra Raza, MD	University Mass., USA

Curcumin Clinical Trials on Multiple Myeloma Patients

Goal:

To evaluate safety, pharmacodynamics and antitumor potential of **Curcumin** with/without **Bioperine**

Patient population: Previously untreated MM pts who are asymptomatic and without serious or imminent complications, have relapsed or failed treatment with conventional drugs or progressed on or in stable partial remission with residual myeloma protein.









(BM plasma cells >10%; serum M-protein levels >0.5g/dl; urinary M-protein >100 mg/24h)

Drug: 1000 mg curcumin (95% pure) capsule containing 5 mg bioperine (98% pure); divided into 2 doses administered (with water) at around 9AM and 9 PM daily for **12 wks**; with one hour interval without food.

Evaluation:

1. History and physical exam every 4 wks.
2. Blood counts every 2 wks
3. Serum beta-2 microglobulin and serum/urine myeloma protein every 4 wks
4. Plasma drug conc and its metabolites on day 0, 2, 4, and 8 wks
5. NF-kB and NF-kB related genes in BM after 4 and 12 wks.
6. Serum/plasma and PBMC for PGE2 and COX2 evaluation on 4 and 12 wks

Randomized into 3 pts/group

Arm A	Arm B	
		2g/day
		4g/day
		6g/day
		8g/day
Curcumin	Curcumin+Bioperine	

Response:

At least 50% reduction in the paraprotein levels in the serum/urine at least 4 wks apart.

Also 50% decrease in plasma cells in BM.

Curcumin Phase II Trials in Patients with Advanced Pancreatic Cancer

PI: Dr. Razelle Kurzrock; Co-PI: Bharat B. Aggarwal

Objective: Determine the tolerance and response to curcumin in pts (n=50) with advanced pancreatic cancer

Dose: Pts will take oral curcumin daily for eight weeks with starting dose at 8 gm per day

Patient population: Pts with pathologically confirmed adenocarcinoma of the pancreas that is not amenable to curative surgical restriction (includes locally advanced, metastatic, or recurrent disease).

- Evaluations:**
1. Serum samples will be drawn pre-study, at 24 hours, 8 days, and 4 weeks to Assess cytokine levels (IL-8, IL-6, IL-10, and IL 1RA).
 2. Constitutive and TNF- α -induced NF- κ B in PBMC at pre-therapy and on day 8.
 3. Constitutive and TNF- α induced COX-2 protein levels in PBMC and plasma PGE₂ (pre-therapy and day 8).
 4. Tumor (pre-therapy and at 4 weeks) for NF- κ B; COX-2; and apoptosis.
 5. Blood samples (pre-therapy at 1, 2, 6, 24, 48 and 72 h post treatment, and Day 8 and 28), for Curcumin and related compounds.

Response: The primary end point of this study is six-month survival. An increase in 6-month survival (on curcumin) from 46% to 70%.

Curcumin Phase II Trials in Patients with Advanced Pancreatic Cancer

PI: Dr. Razelle Kurzrock; Co-PI: Bharat B. Agarwal

Objective:

- ❖ **To determine the tolerance and response to curcumin in pts with advanced pancreatic cancer**
- ❖ **Assess biologic activity of this molecule in both tumor and surrogate tissues**
- ❖ **(peripheral blood mononuclear cells) including baseline and post-therapy effects on signaling and apoptosis.**
- ❖ **Evaluate time to disease progression and response rates**
- ❖ **Assess pharmacokinetics of curcumin after oral administration in this population**
- ❖ **Evaluate side effects of curcumin in patients with pancreatic cancer.**

Curcumin Phase II Trials in Patients with Advanced Pancreatic Cancer

PI: Dr. Razelle Kurzrock; Co-PI: Bharat B. Agarwal

Dose:

- ❖ **Patients will take oral curcumin daily for eight weeks.**
- ❖ **The starting dose will be 8 gm per day.**
- ❖ **If a patient experiences grade III toxicity, the dose will be held and restarted with a 50% dose reduction after resolution of toxicity.**
- ❖ **Patients with grade IV toxicity will discontinue treatments.**
- ❖ **Patients will continue on treatment until disease progresses, unless Grade II toxicity supervenes.**

Curcumin Phase II Trials in Patients with Advanced Pancreatic Cancer

PI: Dr. Razelle Kurzrock; Co-PI: Bharat B. Agarwal

Patient population:

The patient has pathologically confirmed adenocarcinoma of the pancreas that is not amenable to curative surgical resection (includes locally advanced, metastatic, or recurrent disease).

Curcumin Phase II Trials in Patients with Advanced Pancreatic Cancer

PI: Dr. Razelle Kurzrock; Co-PI: Bharat B. Agarwal

Evaluations:

- Serum samples will be drawn pre-study, at 24 hours, 8 days, and 4 weeks to assess cytokine levels (IL-8, IL-6, IL-10, and IL-1RA).**
- The effect of orally administered curcumin on constitutive and TNF- α --induced binding expression of NF- κ B in peripheral blood mononuclear will be assessed pre-therapy and on day 8 by using EMSAs.**
- Constitutive and TNF- α induced COX-2 protein levels (Western blot; antibody from Transduction Labs) in peripheral blood mononuclear cells and plasma of PGE₂ will be assessed (pre-therapy and day 8).**
- Effect of curcumin on the tumor (pre-therapy and at 4 weeks) will be examined for the following markers:
IHC for NF- κ B activation; COX-2 by IHC ; TUNEL Assay to assess apoptosis**
- For pharmacokinetic studies blood samples (pre-therapy at 1, 2, 6, 24, 48 and 72 hours post-treatment, as well as on Day 8 and 28), will be analyzed for curcumin and related compounds.**

Curcumin trials at the NCI

Dear Dr. Aggarwal,

Our curcumin trial is in the very early stages of development. DCP recently approved a 'letter of intent' from UCI for protocol development in a cohort of current smokers who are age 50+ years. Percent change of PGE2 within rectal ACF will be determined after 30 days of intervention with Curcumin (dose to be determined). I hope that this helps. Sincerely, Bill Anderson

William F. Anderson, MD MPH; Division of Cancer Prevention
DHHS/NIH/NCI

Phone: (301) 594-7672; Fax: (301) 435-6344

Curcumin used: Synthetic made by NCI

PI: Frank Meyskens (University of California, Irvine);
Robert carol (Univ. Chicago, Illinois);
Daniel Turgeon (U. Michigan)

Curcumin & its metabolites

Intravenous injection of 40 mg/kg
b.w. One hour later:

Hexahydrocurcumin (liver)

Hexahydrocurcuminol (liver)

Curcumin glucuronide (plasma)

Curcumin sulfate (plasma)

These metabolites are weak inhibitors of PGE₂ production

Ireson et al, 2001; Cancer Res. 61, 1058-64

Immunomodulatory effects of curcumin

Inhibits neutrophil aggregation, degranulation and superoxide anion generation.

Inhibits LPS-induced production of IL-1 and TNF in macrophages (Chan M, 1995) & increases phagocytosis (Gonda R, 1990).

In vivo increases the proportion of CD4+ splenic T cells and elevates number of B cells (Yasni S., 1993)

Inhibits the production of IL-12 from stimulated murine splenic macrophages and inhibits the secretion of Th1 cytokines from antigen-stimulated murine CD4+T cells (Kan BY, 1999).

Increases mucosal CD4+ T cells and B cells in mice (Churchill M, 2000)

Curcumin & Alzheimer's disease

Curcumin inhibits formation of A β oligomers and fibrils and binds plaques and reduces amyloid in vivo.

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kaye R, Glabe CG, Frautschy SA, Cole GM. J Biol Chem. 2004 Dec 7

Phenolic anti-inflammatory antioxidant reversal of A β -induced cognitive deficits and neuropathology.

Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, Cole GM. Neurobiol Aging. 2001;22(6):993-1005.

Curcumin has potent anti-amyloidogenic effects for Alzheimer's β -amyloid fibrils in vitro.

Ono K, Hasegawa K, Naiki H, Yamada M. J Neurosci Res. 2004;75(6):742-50.

Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models.

Baum L, Ng A. J Alzheimers Dis. 2004;6(4):367-77

Discovery of natural products from Curcuma longa that protect cells from β -amyloid insult: a drug discovery effort against Alzheimer's disease.

Park SY, Kim DS., J Nat Prod. 2002;65(9):1227-31

The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse.

Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. J Neurosci. 2001;21(21):8370-7.

Curcuminoids from Curcuma longa L. (Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from β A(1-42) insult.

Kim DS, Park SY, Kim JK. Neurosci Lett. 2001;303(1):57-61.

Curcumin

Neuroprotective role of curcumin from curcuma longa on ethanol- induced brain damage

Oral administration of curcumin to rats caused a significant reversal in lipid peroxidation, brain lipids and produced enhancement of glutathione in ethanol intoxicated rats

Rajakrishnan V, Viswanathan P, Rajasekharan KN, Menon VP
Phytother Res. 1999 Nov;13(7):571-4

Curcumin

The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse.

Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM.

J Neurosci. 2001;21:8370-7.

Curcumin

**Phenolic anti-inflammatory antioxidant
reversal of A beta-induced cognitive
deficits and neuropathology**

**Frautschy SA, Hu W, Kim P, Miller SA, Chu T,
Harris-White ME, Cole GM.**

Neurobiol Aging. 2001;22:993-1005

Curcumin

**Protective effects of curcumin
against ischaemia/reperfusion
insult in rat forebrain.**

Ghoneim AI, Abdel-Naim AB, Khalifa AE, El-Denshary ES.

Pharmacol Res. 2002;46:273-9.

Curry Spice May Fight Alzheimer's

•By Amy Norton Tue. Jan 4, 2005, 11:58 PM

•NEW YORK (Reuters Health) - The pigment that gives curry spice its yellow hue may also be able to break up the "plaques" that mark the brains of Alzheimer's disease ([news](#) - [web sites](#)) patients, early research suggests.

•Scientists found that curcumin, a component of the yellow curry spice turmeric, was able to reduce deposits of beta-amyloid proteins in the brains of elderly lab mice that ate curcumin as part of their diets.

•In addition, when the researchers added low doses of curcumin to human beta-amyloid proteins in a test tube, the compound kept the proteins from aggregating and blocked the formation of the amyloid fibers that make up Alzheimer's plaques.

•Accumulation of beta-amyloid proteins in the brain is one of the hallmarks of Alzheimer's disease.

•The new findings suggest that curcumin could be capable of both treating Alzheimer's and lowering a person's risk of developing the disease, said study co-author Dr. Gregory M. Cole of the University of California Los Angeles and the Greater Los Angeles Veterans Affairs Healthcare System.

•Cole and his colleagues have gotten funding to begin a small trial in humans suffering from Alzheimer's disease.

•"The big question is how high are the doses we need to fight Alzheimer's and are they really safe in elderly patients?" he told Reuters Health.

•The current findings, published online recently by the Journal of Biological Chemistry, add to the body of research pointing to curcumin's medicinal value. Long used as part of traditional Indian medicine, curcumin is now under study as a potential cancer therapy, and animal research has suggested the compound might serve as a treatment for multiple sclerosis and cystic fibrosis.

•Interest in curcumin as an Alzheimer's therapy grew after studies found low rates of the disease among elderly adults in India, where curry spice is a dietary staple.

•Curcumin is structurally similar to a stain known as Congo red, which is used by pathologists to identify amyloid protein in autopsied brain tissue in order to confirm a diagnosis of Alzheimer's disease after a patient's death.

•Curcumin can also stain amyloid deposits, Cole said, but it has the additional ability, when eaten or injected, to cross into a living animal's brain and bind to amyloid deposits.

•What's more, he explained, curcumin is an antioxidant and anti-inflammatory agent, and it appears to counter the oxidative damage and inflammation that arises in response to amyloid accumulation.

•"It attacks both the amyloid and the response to amyloid," Cole said.

•Because oxidative damage and inflammation mark a number of diseases of aging - such as arthritis and the buildup of plaques in the heart's arteries - Cole said he and his colleagues hope that curcumin eventually proves useful for a range of age-related conditions.

Radioprotective effects of Curcumin

Radioprotective action of curcumin extracted from *Curcuma longa* LINN: inhibitory effect on formation of urinary 8-hydroxy-2'-deoxyguanosine, tumorigenesis, but not mortality, induced by γ -ray irradiation

Inano H, Onoda M. *Int J Radiat Oncol Biol Phys.* 2002;53:735-43.

Prevention of radiation-induced mammary tumors

Inano H, Onoda M. *Int J Radiat Oncol Biol Phys.* 2002;52:212-23

Potent preventive action of curcumin on radiation-induced initiation of mammary tumorigenesis in rats

Inano H, Onoda M, Inafuku N, Kubota M, Kamada Y, Osawa T, Kobayashi H, Wakabayashi K.. *Carcinogenesis.* 2000;21:1835-41.

Chemoprevention by curcumin during the promotion stage of tumorigenesis of mammary gland in rats irradiated with gamma-rays.

Inano H, Onoda M, Inafuku N, Kubota M, Kamada Y, Osawa T, Kobayashi H, Wakabayashi K. *Carcinogenesis.* 1999;20:1011-8.

Protective effect of curcumin, ellagic acid and bixin on radiation induced genotoxicity.

Thresiamma KC, George J, Kuttan R. *J Exp Clin Cancer Res.* 1998;17:431-4.

Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects

- Cystic fibrosis is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR).
- The most common mutation, DeltaF508, results in the production of a misfolded CFTR protein that is retained in the endoplasmic reticulum and targeted for degradation.
- Curcumin is a nontoxic Ca-adenosine triphosphatase pump inhibitor that can be administered to humans safely.
- Oral administration of curcumin to homozygous DeltaF508 CFTR mice in doses comparable, on a weight-per-weight basis, to those well tolerated by humans corrected these animals' characteristic nasal potential difference defect.
- These effects were not observed in mice homozygous for a complete knockout of the CFTR gene. Curcumin also induced the functional appearance of DeltaF508 CFTR protein in the plasma membranes of transfected baby hamster kidney cells.

Egan ME, etal; Science. 2004;304:600-2.

NF- κ B and sunburn

A role for NF- κ B-dependent gene
transactivation in sunburn

*Abeyama K, et al.
Journal of Clinical Investigation
2000;105:1751-9.*

Curcumin & Skin Diseases

Curcumin-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters

MCY Heng, MK Song, J. Harker and MK Heng,
Br. J. Dermatology, 143, 2000, 937-949

Psoriasis, Actinic keratosis, Acne,
Warts, Dermatitis, Eczema
Wound healing, Sunburn
Skin cancer

Psoriasis

Chronic skin disorder characterized by inflammation leading to red, thickened areas with flaky white buildup.

It affects approx. 2% of the US and European population

It is an autoimmune disorder that is mediated by T lymphocytes.

In psoriasis, T lymphocyte adhesion molecule, LFA1/CD11a binds to ICAM-1; thus facilitating the migration of T lymphocytes from circulation into dermal and epidermal tissues, with subsequent reactivation.

Efalizumab is an LFA-1Ab that inhibits the binding of T cells to endothelial cells and their subsequent migration. Other drugs being tested include Alefacept, infliximab. etanercept

Treatment of psoriasis with Psoria-Gold

Before

11-07-2003



R Knee



L Knee



L Leg



L Elbow

After

4 weeks

12-05-2003



Courtesy of Dr. Madeline Heng from UCLA

Curcumin and scleroderma

Curcumin induced apoptosis in scleroderma lung fibroblasts: role of PKC ϵ

Tourkina E, Gooz P, Oates JC, Ludwicka-Bradley A, Silver RM, Hoffman S

Am J Respir Cell Mol Biol.
2004;31:28-35.

Curcumin & Wound-healing

Dermal **wound healing** processes with curcumin incorporated collagen films.

Gopinath D. et al Biomaterials. 2004 May;25(10):1911-7.

Protective effects of curcumin against oxidative damage on skin cells in vitro:
its implication for **wound healing**.

Phan TT et al J Trauma. 2001 Nov;51(5):927-31.

Enhancement of **wound healing** by curcumin in animals.

Sidhu GS et al , Wound Repair Regen. 1998 Mar-Apr;6(2):167-77.

Inhibitory effect of curcumin on PMA-induced increase in **ODC mRNA** in
mouse epidermis.

Lu YP...Conney AH, Carcinogenesis. 1993 Feb;14(2):293-7.

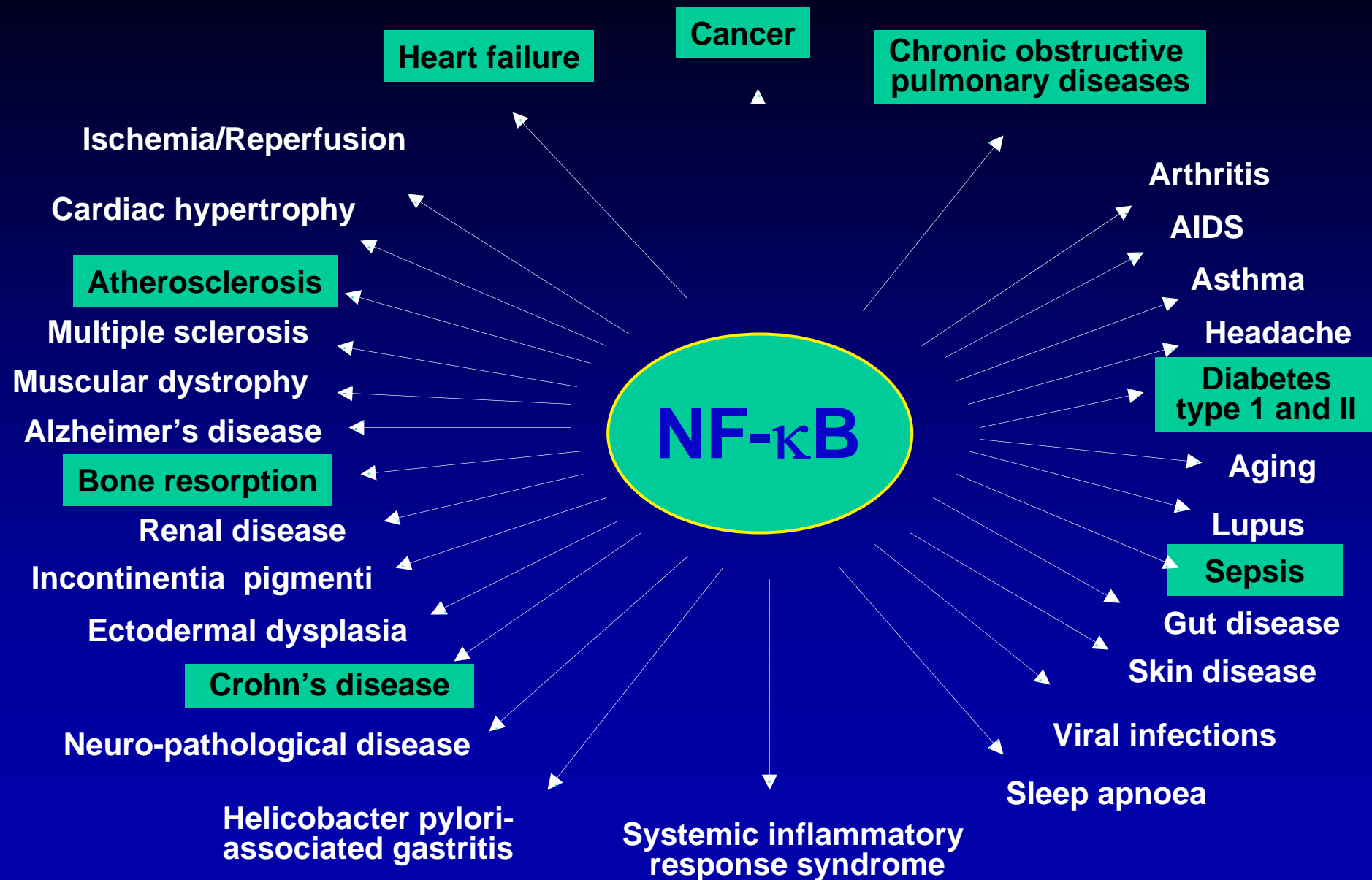
Inhibitory effect of dietary curcumin on **skin carcinogenesis** in mice.

Limtrakul P., Cancer Lett. 1997 Jun 24;116(2):197-203.

Turmeric and curcumin as topical agents in **cancer therapy**.

Kuttan R., Tumori. 1987 Feb 28;73(1):29-31.

NF- κ B has been linked to several diseases



TNF in Health and Disease

Hematopoiesis

Tumor regression

Protection from
Bacterial infection

Innate Immunity

Immune surveillance

AIDS

Alzheimer's disease

Rheumatoid arthritis

Crohn's disease

Diabetes (type II)

Multiple sclerosis

Atherosclerosis

Allergic asthma

GVDH



Osteoporosis/
Bone resorption

Lymphoproliferative
disease

Pulmonary fibrosis

Systemic lupus
erythematosus

Septic shock

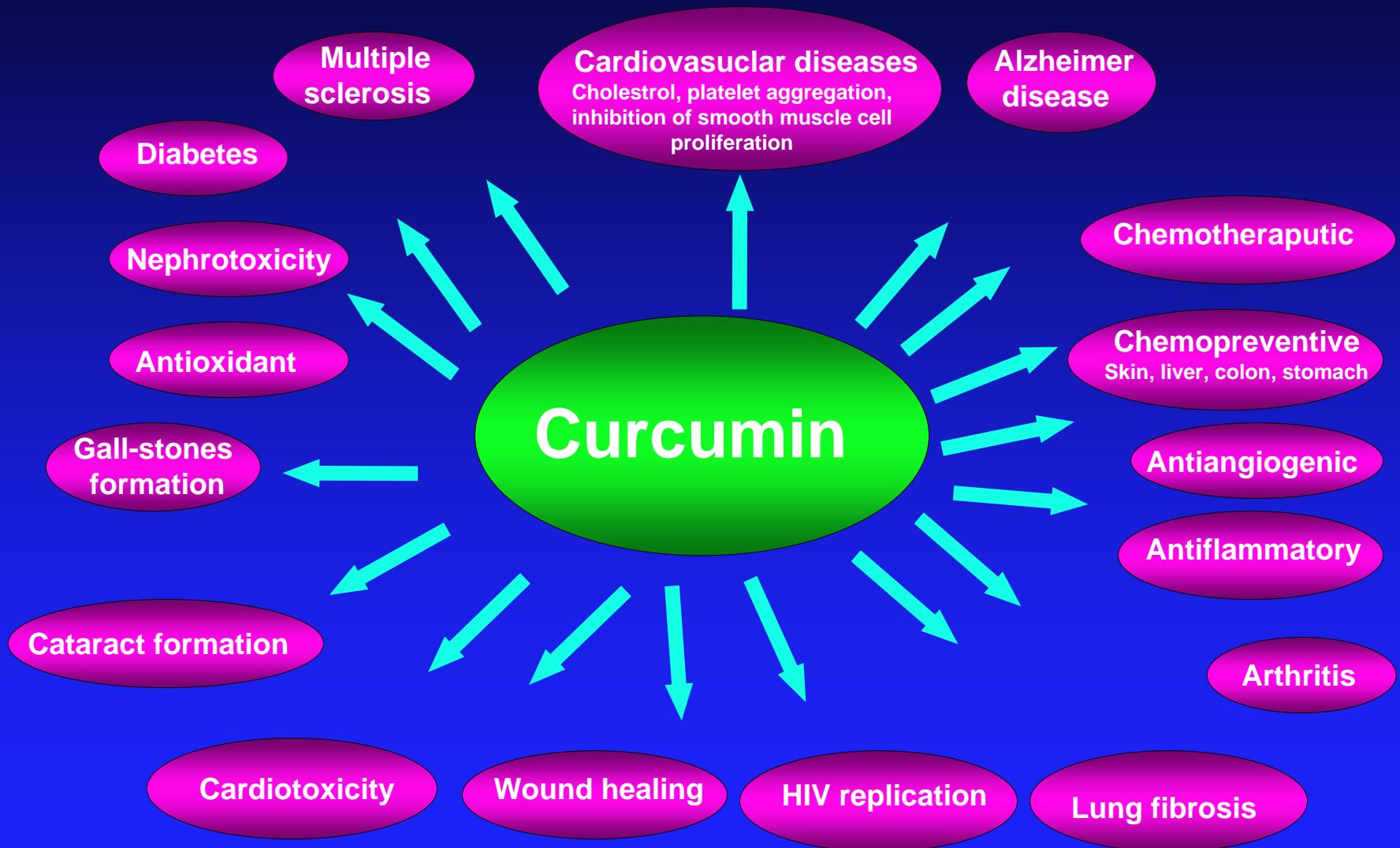
Tumorigenesis

Metastasis

Fever

Aggarwal BB. Signalling pathways of the TNF superfamily:
a double-edged sword. Nat Rev Immunol. 2003; 3: 745-56.

Therapeutic potential of curcumin

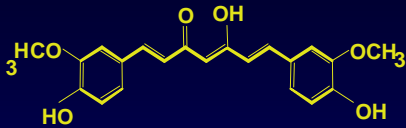


Curcumin use in the Korea

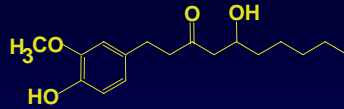


Woolgeum farm at Jindo in Korea

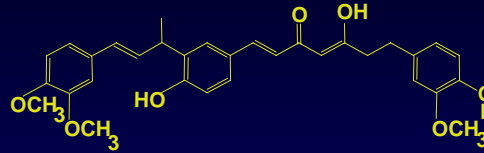
Natural analogs of curcumin



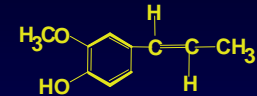
Curcumin



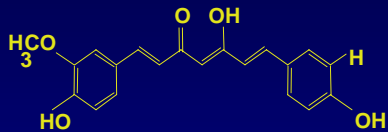
[6]-Paradol



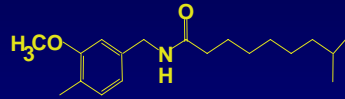
Cassumunin A



Isoeugenol



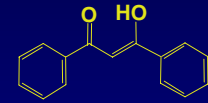
Demethoxycurcumin



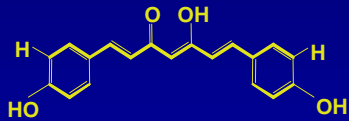
Dihydrocapsaicin



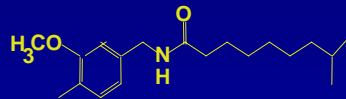
Cassumunin B



Dibenzoylmethane (Licorice)



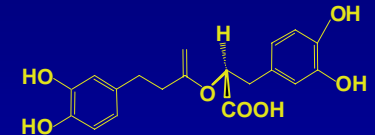
Bisdemethoxycurcumin



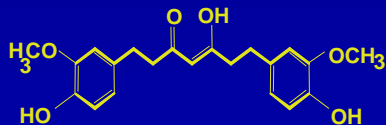
Capsaicin



Yakuchinone A



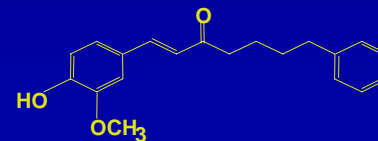
Rosmarinic acid



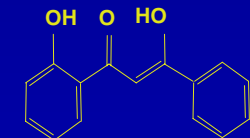
Tetrahydrocurcumin



[6]-Gingerol

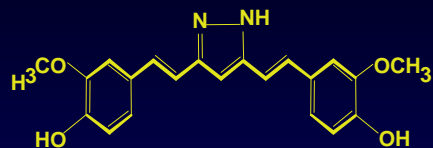


Yakuchinone B

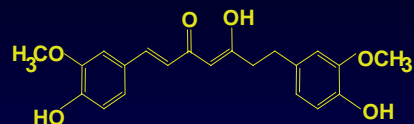


2-Hydroxydibenzoylmethane

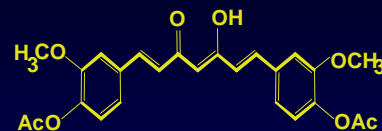
Synthetic analogs of curcumin



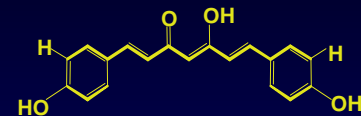
Hydrazinocurcumin



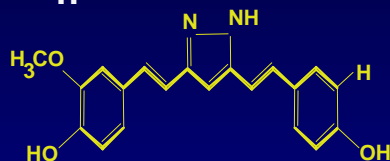
Dihydrocurcumin



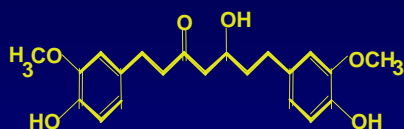
Diacetylcurcumin



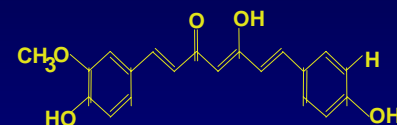
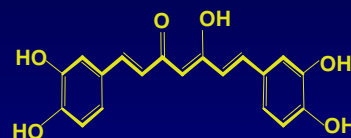
p, p dihydroxydicinnamoyl methane



Hydrazinodemethoxycurcumin



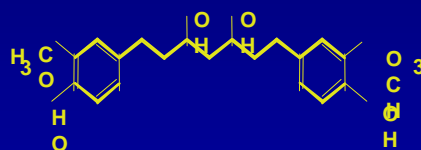
Hexahydrocurcumin 1,7 Bis (3,4-dihydroxyphenyl) -11, 6-heptadiene-3,5-dione



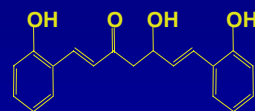
p-dihydroxydicinnamoyl feruloyl methane



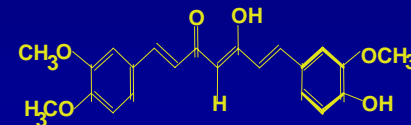
Hydrazinobisdemethoxycurcumin



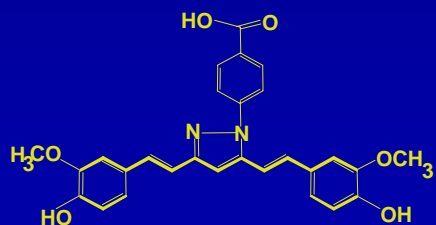
Octahydrocurcumin



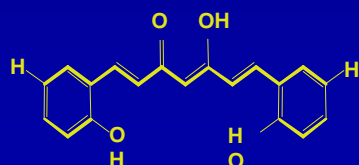
Salicylcurcuminoid



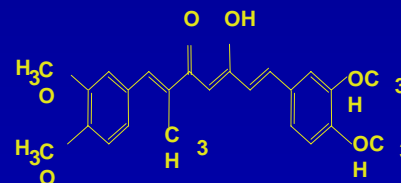
Monomethylcurcumin



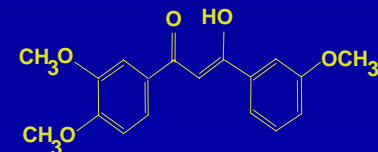
Hydrazinobenzoyl demethoxycurcumin



Bisdemethoxycurcumin analogue



Trimethylcurcumin



Trimethoxydibenzoyl methane

Resveratrol could prevent cancer: Study

RADHIKA JHAMB
India Post News Service

FREMONT, CA: The deadly yet prevalent disease of cancer has long been life-threatening for people all around the world. Researchers have been and continue to be hard at work to get a better understanding of the prevention and cure for this insurmountable disease.

In one such effort, a research team led by Dr Bharat Aggarwal at the University of Texas MD Anderson Cancer Center, made an interesting discovery as a result of their research on Resveratrol. Resveratrol is concluded to be an anti-cancer compound, and the researchers have linked Resveratrol to the prevention of a wide variety of types of cancer.

Dr Aggarwal, in conjunction with Dr Navindra Seeram of the UCLA Center for Human Nutrition, David Geffen School of Medicine, published their review article in a recent issue of the journal *Anti-cancer Research*.

According to the researchers, it is clear from the studies described in the review, that Resveratrol holds great potential in the prevention and therapy of a wide variety of tumors. In vitro (studies conducted in a test tube or outside a living organism) and animal studies comprised the majority of the research reviewed by Aggarwal and Seeram, though several of the leukemia studies were in vivo (inside the animal).

The research points to anti-inflammatory and antioxidant effects

of Resveratrol. According to the review, in vivo studies clearly demonstrate that Resveratrol is pharmacologically safe and can be used for the prevention and therapy of cancer. Also, Resveratrol has potential for treating diseases other than cancer and cardiovascular ailments.

Resveratrol compound can be easily accommodated in our diets, said Dr Seeram. "We reviewed over seventy previous studies examin-



Dr Bharat Aggarwal, Professor, Chief, Section of Cytokine Research at the University of Texas, MD - Anderson Cancer Center

ing Resveratrol's ability to cause cancer cells to stop from spreading and in fact cause cell death in existing cancer cells. Foods containing this compound-like grapes, peanuts, cranberries and other berries-belong in a healthy diet."

In a telephonic interview with *India Post* about the research, Dr Aggarwal observed, "we have been working on this research for past 15 years, it all began when I was working at Genentech, a

biotech research company and found a protein to be toxic. While researching on that we found the capability of Resveratrol to act as an active inhibitor." Dr Aggarwal further added that "Inflammation plays an important role in most diseases if not all- cancer, pulmonary, cardiovascular-for all the common denominator is inflammation and we found that Resveratrol could prevent the onset of the disease.

Studies clearly demonstrate that Resveratrol is pharmacologically safe and can be used for the prevention and therapy of cancer. Also, it has potential for treating diseases other than cancer and cardiovascular ailments

In addition, turmeric used vastly in Indian cooking has an active component curcumin that could work effectively in the anti-inflammation for pancreatic cancer, which is untreatable at the moment."

The clinical trials are presently being conducted at the MD Anderson Cancer Center for finding the dose ranges for effective treatment. Dr Aggarwal informed *India Post* about clinical trials that will soon be taking place in India as well, as

the biotech industry in India has approached him for the same.

The Tata Cancer Center, as well as All India Institute of Medical Sciences (AIIMS) also will soon be conducting its clinical trials. He also avers that "incidence of four common cancers in US is not so common in India, it could be because of the higher consumption of turmeric. Also a study done in UCLA discovered that the rate of Alzheimer's is low in India, another disease for which turmeric could have a non-toxic effect."

When asked from a pharmaceutical standpoint, if Resveratrol could be made available at a certain dose range for it to be prescribed, Dr Aggarwal replied, "there is no patent on natural products, what pharmaceutical companies can do is take the basic structure of the compound and design it into a better molecule.

The approach would be to take the basic structure, redesign it and then patent it. To develop a structural analog, however, will take time." The clinical trials that are being done he said, "would determine the dose range, curcumin for example, can be taken at very high dose range but for the efficacy of a drug we would have to see how the doses could be modified and combined with another for more synergy."

Dr Aggarwal's book titled, *Resveratrol its Role in Health and Disease*, will be coming out this year. The clinical trials in India, including the study would take another two years to end.

Conclusion!

Let us get
back to our
roots

Adverse drug effects of recent FDA-approved drugs

Drug	Target	Use	Approved (Yr)	Withdrawn (Yr)	Reason
Vioxx (Rofecoxib)	COX-2	Rheumatoid arthritis	1999	2004	Heart attack
Celebrex *(Celcoxib)	COX-2	Do	1998	2004	Heart attack
Bextra *(Valdecoxib)	COX-2	Do	2001	2004	Heart attack
Arava (Leflunomide)	Dihydroorotate DH	Do	1997		Peripheral neuropathy
Iressa (Gefitinib)	EGFR TK	NSCLC	2002	2004	No clinical benefit
Remicade (anti-TNF Ab)	TNF	Crohn's disease/RAr	1998	2001**	Lymphoma risk
Prozac (Fluoxetine)	Serotonin	Antidepressant	1986	2004**	Suicidal thoughts
Strattera (atomoxetine)	Norepinephrine	ADHD	2002	2004**	Hepatotoxic
Fen-phen (Phentermine/ Fenfluramine)	Serotonin/ catecholamines	Anti-obesity	1959/1973	1997	Valvular heart disease, PPH
Rezulin (troglitazone)	PPAR γ	Diabetes	1999	2000	Hepatotoxic
Avandia (rosiglitazone)	PPAR γ	Diabetes	1999	2001**	Hepatotoxic
Propulsid (cisapride)	Potassium channels	Heart burn	1993	2000	Cardiotoxic
PPA	ANS	Cold, cough	2000		Hemorrhagic stroke
Baycol (cerivastatin)	HMG CoA reductase	Cholesterol lowering	2000	2003	Rhabdomyolysis
Lotronex (alosetron)	5-HT ₃ RA	Irritable bowel	2000	2000	Ischemic colitis
Serzone (nefazodone)	Serotonin type 2 R	Anti-depressant	2004		Liver injury

* Although celebrex has been linked with cardiotoxicity, no black label warning has yet been issued. **Black box warning; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; EGFR TK, epidermal growth factor receptor tyrosine kinase; NSCLC, non small cell lung carcinoma, TNF, tumor necrosis factor; RAr, rheumatoid arthritis; ADHD, attention deficit hyperactivity disorder; DH, dehydrogenase; RA, receptor antagonist; PPH, primary pulmonary hypertension; PPAR, peroxisome proliferators-activated receptor; PPA, Phenylpropanolamine; ANS, autonomic nervous system; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; rhabdomyolysis, muscle breakdown; 5-HT₃R, serotonin 5-HT_{3A} receptor.

*"Gold is for the mistress-silver for the maid-
copper for the craftsman cunning at his trade."*

*"Good!" said the Baron, sitting in his hall,
but "Iron-Cold Iron-is master of them all."*

Rudyard Kipling

Swaminaryan Temple in Houston



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Anjana Bhardwaj, Ph.D., 2002

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Kazuhiro Ashikawa, M.D., Ph.D.,2000

Goshi Nishimura, M.D., Ph.D., 2000

Sanjeev Banerjee, Ph.D., 2000

Sekhar Majumder, Ph.D., 2000

Betty Lamothe, Ph.D. , 2000

Hong Wang, M.D., Ph.D., 1999

Pedro Lazo, Ph.D., 1999

Nand K. Sah, Ph.D., 1999

Asok Mukhopadhyay, Ph.D., 1998

Ajoy Samanta, Ph.D., 1998

Chitralekha Bhattacharya, Ph.D., 1998

Pramod Rath, Ph.D.,1998

Christines Bezombes, 1997

Anju Shrivastava, Ph.D., 1997

Arjun Singh, Ph.D., 1997

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Dipak Giri, Ph.D., 1997

Gagan B. N. Chainy, Ph.D, 1995

Uma Raju, Ph.D., 1995

Sanjaya Singh, Ph.D., 1994

Bryant Darnay, Ph.D., 1993

Krishnamurthy Natrajan, Ph.D., 1995

Sanjay Kansra, Ph.D., 1996

Valsala Haridas, Ph. D., 1996

Masahiro Higuchi, Ph.D., 1991

Rinee Mukherjee, Ph.D., 1994

Madan M. Chaturvedi, 1993

Shrikanth Reddy, Ph.D., 1993

Lisha Zhang, Ph.D.1993

Eva Poscik, Ph.D., 1991

H. Raghava Reddy, Ph.D., 1989

Venkat Sharma, Ph.D., 1989

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Collaborators:
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Hong WK.

Thank you!

Gracias!

Mercy

Shalom!

Arigato!

Shei-shei!

Gamsa hamnida!

Namaste!

Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription.

- Acetylation of histones and non-histone proteins is involved in the regulation of gene expression in eukaryotes and all viral DNA that integrates into the human genome.
- Dysfunction of histone acetyltransferases (HATs) is often associated with the manifestation of several diseases. HATs are the new potential targets for the design of therapeutics.
- Curcumin is a specific inhibitor of the p300/CREB-binding protein (CBP) HAT activity in vitro and in vivo. Curcumin could also inhibit the p300-mediated acetylation of p53 in vivo.
- Curcumin represses the p300/CBP HAT activity-dependent transcriptional activation from chromatin but not a DNA template.
- Curcumin could inhibit the acetylation of HIV-Tat protein in vitro by p300 as well as proliferation of the virus, as revealed by the repression in syncytia formation upon curcumin treatment in SupT1 cells.
- Curcumin may serve as a lead compound in combinatorial HIV therapeutics.

How to prevent cancer?

- Eliminate smoking
- Exercise regularly
- Eat a balanced diet and stay trim
- Avoid sunburn
- To detect early-stage cancer, undergo check ups: mammography; colonoscopy; prostate exam and PSA
- Practice caloric restriction
- Limit alcohol consumption
- Keep positive attitude and stress-less life

Self-control & discipline is better than pills

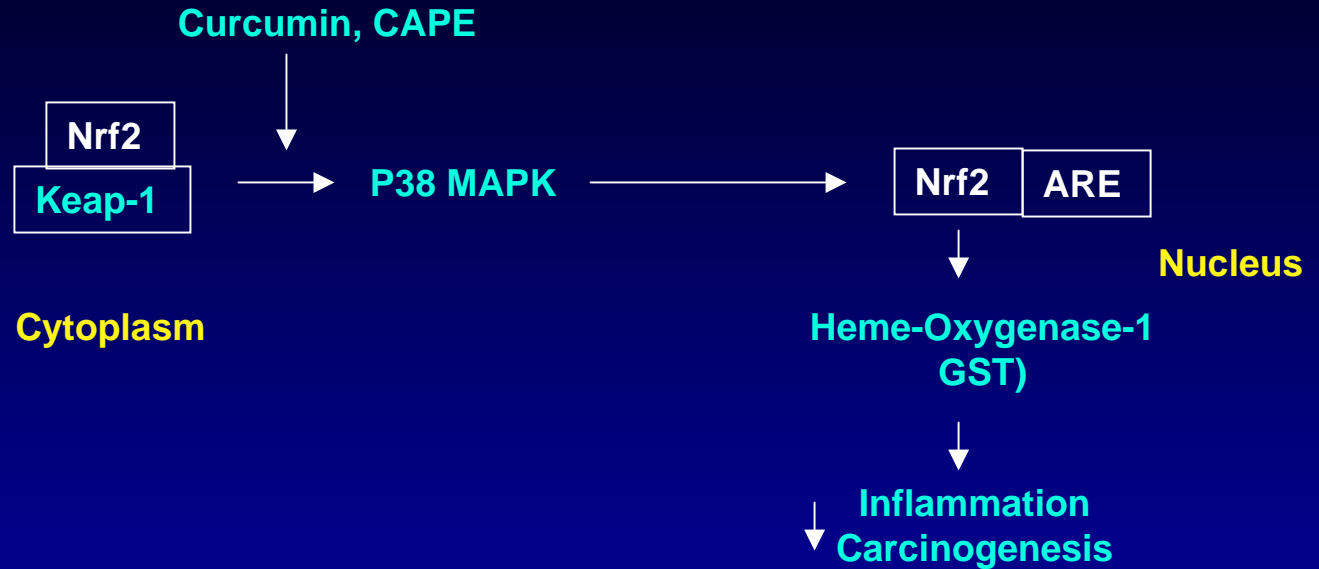
Curcumin and scleroderma

- Scleroderma involves excessive collagen deposition and can be studied using fibroblasts cultured from affected tissues.
- Curcumin causes apoptosis in scleroderma lung fibroblasts (SLF), but not in normal lung fibroblasts (NLF).
- Curcumin induces the expression of the phase 2 detoxification enzymes **heme oxygenase 1** and **glutathione S-transferase P1** (GST P1) in NLF but SLF are deficient in these enzymes.
- Curcumin-induced apoptosis and the expression of GST P1 (but not heme oxygenase 1) are regulated by the **PKC ϵ** .
- SLF, which contain less PKC ϵ and less GST P1 than NLF, become less sensitive to curcumin-induced apoptosis and express higher levels of GST P1 when transfected with wild-type PKC ϵ , but not with dominant-negative PKC ϵ .

Curcumin and scleroderma

- Conversely, NLF become sensitive to curcumin-induced apoptosis and express lower levels of GST P1 when PKC ϵ expression or function is inhibited.
- The subcellular distribution of PKC ϵ also differs in NLF and SLF. PKC ϵ is predominantly nuclear or perinuclear in NLF but is associated with stress fibers in SLF.
- Just as PKC ϵ levels are lower in SLF than in NLF in vitro, PKCepsilon expression is decreased in fibrotic lung tissue in vivo.
- Signaling pathway involving PKC ϵ and phase 2 detoxification enzymes provides protection against curcumin-induced apoptosis in NLF and is defective in SLF.
- **Curcumin may have therapeutic value in treating scleroderma, as it has already been shown to protect rats from lung fibrosis induced by a variety of agents.**

Curcumin



Mustard (*Brassica campestris*)



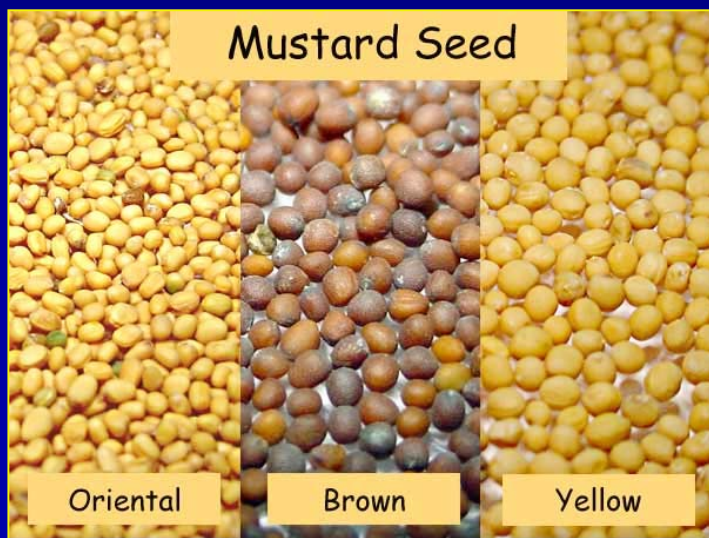
Plant



Flower



Fruit



Seeds



Products

Shikamo/Jambo
Annyeng-Haseyo!

Konnichiwa!

Hello!

Hola!

Bonjour!

Shalom!

Le Hao!

Namaste!

Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration.

Garcea G,Sharma RA, Steward WP, Gescher AJ, Berry DP. Br J Cancer. 2004 Mar 8;90(5):1011-5.

Objective: Investigated whether oral administration of curcumin results in concentrations of the agent in normal and malignant human liver tissue, which are sufficient to elicit pharmacological activity.

Design: In total, 12 patients with hepatic metastases from colorectal cancer received 450-3600 mg of curcumin daily, for 1 week prior to surgery.

Levels of curcumin and its metabolites were measured by HPLC in portal and peripheral blood, bile and liver tissue.

Results: Curcumin was poorly available, following oral administration, with low nanomolar levels of the parent compound and its glucuronide and sulphate conjugates found in the peripheral or portal circulation.

While curcumin was not found in liver tissue, trace levels of products of its metabolic reduction were detected.

In patients who had received curcumin, levels of malondialdehyde-DNA (M(1)G) adduct, which reflect oxidative DNA changes, were not decreased in post-treatment normal and malignant liver tissue when compared to pretreatment samples.

The results suggest that doses of curcumin required to furnish hepatic levels sufficient to exert pharmacological activity are probably not feasible in humans.

Curcumin inhibits formation of Abeta oligomers and fibrils and binds plaques and reduces amyloid in vivo.

•Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM.

•GRECC (VA Medical) and Medicine, University of California Los Angeles, North Hills, CA 91343.

•Alzheimer's disease (AD) involves amyloid (Abeta) accumulation, oxidative damage and inflammation, and risk is reduced with increased antioxidant and anti-inflammatory consumption. The phenolic yellow curry pigment curcumin has potent anti-inflammatory and antioxidant activities and can suppress oxidative damage, inflammation, cognitive deficits, and amyloid accumulation. Since the molecular structure of curcumin suggested potential Ass-binding, we investigated whether its efficacy in AD models could be explained by effects on Ass aggregation. Under aggregating conditions in vitro, curcumin inhibited aggregation ($IC(50) = 0.8$ microM) as well as disaggregated fibrillar Ass40 ($IC(50) = 1$ microM), indicating favorable stoichiometry for inhibition. Curcumin was a better Abeta40 aggregation inhibitor than ibuprofen and naproxen, and prevented Abeta42 oligomer formation and toxicity between 0.1-1.0 muM. Under electron microscopy, curcumin decreased dose-dependently Ass fibril formation beginning with 0.125 microM. Curcumin's effects did not depend on Abeta sequence but on fibril-related conformation. AD and Tg2576 mice brain sections incubated with curcumin revealed preferential labeling of amyloid plaques. In vivo studies showed that curcumin injected peripherally into aged Tg mice, crossed the blood brain barrier and bound plaques. When fed to aged Tg2576 mice with advanced amyloid accumulation, curcumin labeled plaques and reduced amyloid levels and plaque burden. Hence, curcumin directly binds small ss-amyloid species to block aggregation and fibril formation in vitro and in vivo. These data suggest that low dose curcumin effectively disaggregates Ass as well as prevents fibril and oligomer formation, supporting the rationale for curcumin use in clinical trials preventing or treating AD.

•JBC 2004 Dec 7th