Prevention and Treatment of Lung Cancer “Naturally”

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Grand Rounds
Jewish General Hospital
McGill University of Montreal
Thursday, February 23rd, 2011 (12-1:00 PM);
(Host: Drs. Mary Grossman and Jason Agulnik.)
WAR on CANCER

President Richard Nixon signing the National Cancer Act on December 23, 1971
War on Cancer

“I will ask for an appropriation of an extra $100 million to launch an extensive campaign to find a cure for cancer. Let us make a total national commitment to conquer this dread disease. America has long been the wealthiest nation in the world. Now it is time we became the healthiest nation in the world”.

--President Richard Nixon, 1971
State of the Union address
Change in the US Death Rates* by Cause, 1950 & 2002

* Age-adjusted to 2000 US standard population.

Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
....And the death rate from cancer, an indicator that many health experts consider a more accurate measure of progress in fighting the disease, has stayed virtually the same as it was in 1950 — about 200 deaths per 100,000 people a year, and about 1,000 deaths annually per 100,000 people over 65...
Global Lung Cancer Incidence

Age-standardized death from tracheal, bronchial, and lung cancers per 100,000 inhabitants in 2004. [153]

- No data
- ≤ 5
- 5-10
- 10-15
- 15-20
- 20-25
- 25-30
- 30-35
- 35-40
- 40-45
- 45-50
- 50-65
- ≥ 55

From Parkin DM, EJC, 37, 2000, 4-66
Projection for Global Cancer Incidence and Cancer Deaths

- **New Cases**
  - 2002: 10
  - 2020: 16
  - 2030: 20

- **Deaths**
  - 2002: 7
  - 2020: 10
  - 2030: 14
“Forty-one percent of Americans will develop cancer, which means, with very few exceptions, every family will be touched by this disease. The need is urgent,” said John Mendelsohn, M.D., Now Ex-president of M. D. Anderson.

“But the time is optimal because we have more knowledge than ever before about cancer and we have new research tools that position M. D. Anderson to speed progress against this disease.

January, 2010
Cancer Is a Preventable Disease That Requires Major Changes in Life Style

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Reduce your risk of cancer by 30 to 40% by adopting healthier eating habits.

Visit: http://www.mdanderson.org/cancerawareness
Life style Carcinogens/Risk factors
Colorectal cancer is the **second** most common cause of **cancer deaths** in affluent countries.

Processed **red meat** (beef, mutton, lamb, veal, pork, and offal) intake is closely linked with the risk of CRC.

Dietary modification can reduce this cancer burden **by 70%**.

Heterocyclic amines, high saturated fat, carcinogenic N-nitroso compounds, high protein cholesterol and salt contents and heme iron are some of the components of meat linked with CRC.
<table>
<thead>
<tr>
<th>Country</th>
<th>Prostate</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>124.8</td>
<td>66</td>
</tr>
<tr>
<td>China</td>
<td>1.6</td>
<td>45</td>
</tr>
<tr>
<td>India</td>
<td>4.4</td>
<td>3</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.3</td>
<td>?</td>
</tr>
</tbody>
</table>

According to NCI, the median age at diagnosis of lung cancer in the US is 70 y, and the death is 72 y.
# Modern drugs

Published: June 27, 2011

## Promising Treatments for Prostate Cancer Patients

These drugs (and more in the pipeline) have helped extend lives of prostate cancer patients. [Related Article »](#)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Jevtana (cabazitaxel)</th>
<th>Provenge (sipuleucel-T)</th>
<th>Xgeva (denosumab)</th>
<th>Zytiga (abiraterone acetate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPANY</td>
<td>Sanofi</td>
<td>Dendreon</td>
<td>Amgen</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>APPROVED</td>
<td>June 2010</td>
<td>April 2010</td>
<td>November 2010</td>
<td>April 2011</td>
</tr>
<tr>
<td>PRICE</td>
<td>$8,000 every three weeks; $48,000 for a typical course of treatment.</td>
<td>$93,000 for a course of treatment.</td>
<td>$1,650 every four weeks; $21,500 for a typical course of treatment.</td>
<td>$5,000 every four weeks; $40,000 for a typical course of treatment.</td>
</tr>
<tr>
<td>BENEFIT</td>
<td>Median survival of 15.1 months compared to 12.7 months for mitoxantrone, a different drug.</td>
<td>Median survival of 25.8 months versus 21.7 months for a placebo.</td>
<td>Median of 20.7 months until first fracture or other bone-related problem compared to 17.1 months for Zometa, another drug.</td>
<td>Median survival 15.8 months compared to 11.2 months for a placebo.</td>
</tr>
</tbody>
</table>
Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results.

Breathnach OS, Freidlin B, Conley B, Green MR, Johnson DH, Gandara DR, O’Connell M, Shepherd FA, Johnson BE. Lowe Center for Thoracic Oncology, Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA.

Thirty-three phase III trials were initiated between 1973 and 1994. Twenty-four trials (73%) were initiated within the first half of this period (1973 to 1983) and accounted for 5,359 (64%) of the 8,434 eligible patients.

The median number of patients treated per arm of the trials rose from 77 (1973 to 1983) to 121 (1984 to 1994) (P < .001).

Five trials (15%) showed a statistically significant difference in survival between treatment arms, with a median prolongation of the median survival of 2 months (range, 0.7 to 2.7 months).

CONCLUSION: Analysis of past trials in North America shows that the prolongation in median survival between two arms of a randomized study was rarely in excess of 2 months. Techniques for improved use of patient resources and appropriate trial design for phase III randomized therapeutic trials with patients with advanced NSCLC need to be developed.
Breast cancer among immigrants from Japan to USA!

Kolonel, Nature Rev, 2004
Working Hypothesis:

Dysregulated chronic inflammation caused by lifestyle factors mediate chronic diseases including cancer!
What is Inflammation?

Cornelius Celsus, a physician in first century Rome:

Heat *(calor)*

Pain *(dolor)*

Redness *(rubor)*

Swelling *(tumour)*
Inflammation and cancer
Redness, swelling, heat and pain

Rudolf Virchow
(1821-1902; in 1850)

His Pathology laboratory in Wurzburg, Germany

Linked Inflammation with atherosclerosis, rheumatoid arthritis, multiple sclerosis, cancer, asthma, Alzheimer’s

From Heidland A et al, History of Nephrology, 2006
Inflammation is “itis”

Arthritis is inflammation of the joints
Bronchitis............................................ Bronchus
Sinusitis.............................................. Sinus
Gastritis............................................. Stomach
Esophagitis...................................... Esophagus
Pancreatitis..................................... Pancreas
Meningitis....................................... Brain
Rhinitis........................................... Rhina
Gingivitis....................................... Gum
### Inflammation-mediated diseases

<table>
<thead>
<tr>
<th>Adenitis</th>
<th>Endocarditis</th>
<th>Enteritis</th>
<th>Mastitis</th>
<th>Pancreatitis</th>
<th>Salpingitis</th>
</tr>
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<tr>
<td>Adrenalitis</td>
<td>Endotracheitis</td>
<td>Enterococcal</td>
<td>Mastoiditis</td>
<td>Pansinusitis</td>
<td>Salpingo-oophoritis</td>
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<tr>
<td>Allergic rhinitis</td>
<td>Endometritis</td>
<td>Enteritis</td>
<td>Mastitis</td>
<td>Paracolitis</td>
<td>Sialoadenitis</td>
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<td>Appendicitis</td>
<td>Enteritis</td>
<td>Epididymis</td>
<td>Mastitis</td>
<td>Paraglottitis</td>
<td>Sinusitis</td>
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<td>Arachnoiditis</td>
<td>Enteritis</td>
<td>Epididymo-orchitis</td>
<td>Mastoiditis</td>
<td>Paradenitis</td>
<td>Sphenoiditis</td>
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<td>Arteritis</td>
<td>Episcleritis</td>
<td>Fibrositis</td>
<td>Meningitis</td>
<td>Parahepatitis</td>
<td>Splenitis</td>
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<tr>
<td>Arthritis</td>
<td>Esophagitis</td>
<td>Epiglottitis</td>
<td>Meningomyelitis</td>
<td>Parametritis</td>
<td>Spondylitis</td>
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<td>Blepharitis</td>
<td>Ethmoiditis</td>
<td>Epiphysitis</td>
<td>Myelitis</td>
<td>Paramyelitis</td>
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<td>Bronchiolitis</td>
<td>Fascitis</td>
<td>Epithymus</td>
<td>Myeloencephalitis</td>
<td>Paraneuritis</td>
<td>Syndesmositis</td>
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<td>Fibromyositis</td>
<td>Fibrinoid</td>
<td>Myocarditis</td>
<td>Pararteritis</td>
<td>Synovitis</td>
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<td>Bursitis</td>
<td>Funiculitis</td>
<td>Folliculitis</td>
<td>Neuritis</td>
<td>Perianeuritis</td>
<td>Tendonitis</td>
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<td>Capsulitis</td>
<td>Gastritis</td>
<td>Gastric</td>
<td>Neuroretinitis</td>
<td>Periarthritis</td>
<td>Temporal arteritis</td>
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<td>Carditis</td>
<td>Gastroenteritis</td>
<td>Gingivitis</td>
<td>Omphalitis</td>
<td>Periarteritis</td>
<td>Tenosynovitis</td>
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<td>Glottitis</td>
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<td>Tonsillitis</td>
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<td>Optic neuritis</td>
<td>Phlebitis</td>
<td>Urethritis</td>
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<td>Optic neuritis</td>
<td>Pleuritis</td>
<td>Uveitis</td>
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<td>Iritis</td>
<td>Retinitis</td>
<td>Pneumonitis</td>
<td>Vaginitis</td>
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<td>Valvulitis</td>
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<td>Glomerulonephritis</td>
<td>Iritis</td>
<td>Retinitis</td>
<td>Pneumonitis</td>
<td>Vulvulitis</td>
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<td>Glomerulonephritis</td>
<td>Iritis</td>
<td>Retinitis</td>
<td>Poikilodermatomyositis</td>
<td>Vulvovaginitis</td>
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<td>Iritis</td>
<td>Retinitis</td>
<td>Proctitis</td>
<td>Vulvovaginitis</td>
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<td>Iritis</td>
<td>Retinitis</td>
<td>Pyelonephritis</td>
<td>Vulvovaginitis</td>
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<td>Dermatitis</td>
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<td>Iritis</td>
<td>Retinitis</td>
<td>Rheumatoid arthritis</td>
<td>Vulvovaginitis</td>
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<td>Glomerulonephritis</td>
<td>Iritis</td>
<td>Retinitis</td>
<td>Rheumatoid arthritis</td>
<td>Vulvovaginitis</td>
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<td>Retinitis</td>
<td>Rheumatoid arthritis</td>
<td>Vulvovaginitis</td>
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<td>Duodenitis</td>
<td>Glomerulonephritis</td>
<td>Iritis</td>
<td>Retinitis</td>
<td>Rheumatoid arthritis</td>
<td>Vulvovaginitis</td>
</tr>
</tbody>
</table>
# Inflammation as a risk factor for most cancers

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Inflammation</th>
<th>Cancers</th>
<th>% predisposed progress to cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke</td>
<td>Bronchitis</td>
<td>Lung Cancer</td>
<td>11-24</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gastritis</td>
<td>Gastric Cancer</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Cervicitis</td>
<td>Cervical cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepatitis B &amp; C virus</td>
<td>Hepatitis</td>
<td>HCC</td>
<td>10</td>
</tr>
<tr>
<td>Bacteria, GBS</td>
<td>Cholecystitis</td>
<td>Gall bladder cancer</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Gram- uropathogens</td>
<td>Cystitis</td>
<td>Bladder cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tobacco, genetics</td>
<td>Pancreatitis</td>
<td>Pancreatic cancer</td>
<td>≤10%</td>
</tr>
<tr>
<td>GA, alcohol, tobacco</td>
<td>Esophagitis</td>
<td>Esophageal cancer</td>
<td>15</td>
</tr>
<tr>
<td>Asbestos fibers</td>
<td>Asbestosis</td>
<td>Mesothelioma</td>
<td>10–15</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Mononucleosis</td>
<td>Burkitt's lymphoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gut pathogens</td>
<td>IBD</td>
<td>Colorectal cancer</td>
<td>1*</td>
</tr>
<tr>
<td>Ultraviolet light</td>
<td>Sunburn</td>
<td>Melanoma</td>
<td>≤9%</td>
</tr>
<tr>
<td>Infections, STD</td>
<td>PIA</td>
<td>Prostate cancer</td>
<td>?</td>
</tr>
</tbody>
</table>

GA, gastric acid; GBS, gall bladder stones; HCC, hepatocellular carcinoma; STD, sexually transmitted diseases; PIA, prostate inflammatory atrophy.

Most Chronic Diseases Including Cancer are Highly Complex!

Human protein-protein interactions and functional relations from publicly available database contain close to 250,000 interactions among 14,503 unique gene products.

Mishra GR, 2006; Maglott D, 2007; Bader GD, 2001; Kerrien S, 2007

Cancer mutation data base
Bamford S, 2004; Sjoblom T, 2006; Weir BA, 2007; Wood LD, 2007; Jones S, 2008; Parsons DW, 2008
Autophagy Network

Figure 1. Overview of the autophagy interaction network (AIN)
HCIPs within the autophagy network are shown for 32 primary baits (solid squares) and 33 secondary baits (open squares). Sub-networks are color-coded. Interacting proteins are indicated by gray circles.
Hypothesis!

NF-κB activation is a major mediator of inflammation in most chronic diseases (including cancer) & inhibition of NF-κB can prevent/delay the onset of the chronic diseases!
NF-kappa B activation has been linked to most major diseases

Different faces of inflammation and its role in tumorigenesis

**Stress**
(Chemical, physical, and psychological)

**Food Factors**
(Grill, Fried, red meat)

**Environmental pollutants**
(Cigarette smoke, Diesel)

**Viruses**
(HTLV1, HPV, HCV, HBV, EBV)

**Bacteria**
(e.g; Helicobacter pylori)

**Acute inflammation**

- Innate Immunity
- Humoral immunity
- Immune surveillance

**Chronic inflammation**

- Tumor cell survival
- Tumor cell proliferation
- Tumor cell invasion
- Tumor angiogenesis
- Tumor metastasis
- Tumor chemoresistance
- Tumor radioresistance

**Reactive oxygen species**
- Tumor necrosis factor
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Interleukin-18
- Nuclear Factor-κB
- Hypoxia-inducible factor
- Cyclooxygenase-2
- 5-Lipoxygenase
- Inducible nitric oxide-synthase
- Matrix metalloproteinase-9
- Chemokines

**Therapeutic inflammation**

**Pathological inflammation**

Working Hypothesis

- Tobacco
- NF-kappaB
- Inflammation
- Cancer

Graph showing the 20-year lag time between smoking and lung cancer.
Cigarette Smoke Activates Nuclear Factor-κB and Induces Cyclooxygenase-2

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

Carcinogenesis, 23, 1511, 2002
Cigarette smoke-induced NF-κB activation is persistent

Shishodia S, and Aggarwal BB.
NF-κB and Lung cancer

NF-κB fans the flames of lung carcinogenesis.

Tobacco smoke promotes lung tumorigenesis by triggering IKKb- and JNK1-dependent inflammation.

Requirement for NF-κB signalling in a mouse model of lung adenocarcinoma.

Host NF-κB activation potentiates lung cancer metastasis.

Epithelial NF-κB activation promotes urethane-induced lung carcinogenesis.
Here we show that the NF-kappaB pathway is required for the development of tumours in a mouse model of lung adenocarcinoma.

Concomitant loss of p53 and expression of oncogenic Kras(G12D) resulted in NF-kB activation in primary mouse embryonic fibroblasts.

Conversely, in lung tumour cell lines expressing Kras(G12D) and lacking p53, p53 restoration led to NF-kB inhibition.

Furthermore, the inhibition of NF-kB signalling induced apoptosis in p53-null lung cancer cell lines. Inhibition of the pathway in lung tumours in vivo, from the time of tumour initiation or after tumour progression, resulted in significantly reduced tumour development.

Together, these results indicate a critical function for NF-kB signalling in lung tumour development and, further, that this requirement depends on p53 status.

These findings also provide support for the development of NF-kB inhibitory drugs as targeted therapies for the treatment of patients with defined mutations in Kras and p53.
The proteasome inhibitor Bortezomib efficiently induced lung tumor regression in vivo and prolonged the survival of tumor bearing Kras(LSL-G12D/wt); p53(flox/flox) mice. 

In contrast, Kras(G12D/wt) lung tumors, which have low levels of nuclear NF-κB, do not respond to Bortezomib, suggesting that nuclear NF-κB may be a biomarker to predict treatment response to drugs of this class. Following repeated treatment, initially sensitive lung tumors became resistant to Bortezomib.

A second NF-κB inhibitor, Bay-117082, showed similar therapeutic efficacy and acquired-resistance in mice.

Our results using preclinical mouse models support the NF-κB pathway as a potential therapeutic target for a defined subset of lung adenocarcinoma.
NF-kappa B regulates normal and pathological processes, including neoplasia, in a tissue-context-dependent manner. In skin, NF-kappa B is implicated in epidermal homeostasis as well as in the pathogenesis of squamous cell carcinoma; however, its function in the underlying mesenchymal dermis has been unclear. To gain insight into NF-kappa B roles in these two adjacent cutaneous tissue compartments, NF-kappa B effects on expression of 12,435 genes were determined in epidermal keratinocytes and dermal fibroblasts. Although NF-kappa B induced proinflammatory and antiapoptotic genes in both settings, it exhibited divergent effects on growth regulatory genes. In keratinocytes, but not in fibroblasts, NF-kappa B induced p21(CIP1), which was sufficient to inhibit growth of both cell types. Levels of growth inhibitory factor (GIF), in contrast, were increased by NF-kappa B in both settings but inhibited growth only in keratinocytes.

These findings indicate that transcription factors such as NF-kappa B can program tissue-selective effects via both differential target gene induction as well as by inducing common targets that exert differing effects depending on cellular lineage.
Integrative genomic approaches identify IKBKE as a breast cancer oncogene.


The karyotypic chaos exhibited by human epithelial cancers complicates efforts to identify mutations critical for malignant transformation. Here we integrate complementary genomic approaches to identify human oncogenes.

We show that activation of the ERK and phosphatidylinositol 3-kinase (PI3K) signaling pathways cooperate to transform human cells. Using a library of activated kinases, we identify several kinases that replace PI3K signaling and render cells tumorigenic.

Whole genome structural analyses reveal that one of these kinases, IKBKE (IKKepsilon), is amplified and overexpressed in breast cancer cell lines and patient-derived tumors.

Suppression of IKKepsilon expression in breast cancer cell lines that harbor IKBKE amplifications induces cell death. IKKepsilon activates the nuclear factor-kappaB (NF-kappaB) pathway in both cell lines and breast cancers.

These observations suggest a mechanism for NF-kappaB activation in breast cancer, implicate the NF-kappaB pathway as a downstream mediator of PI3K, and provide a framework for integrated genomic approaches in oncogene discovery.
NF-kappaB is frequently expressed in lung cancer and preneoplastic lesions.


NF-κB expression in the pathogenesis of lung cancer

Tang et al, 2006
Obesity and Cancer

- Esophageal cancer
- Colon cancer
- Renal cancer
- Multiple myeloma
- Gastric cancer
- Gall bladder cancer
- Ovarian cancer
- Breast cancer
- Liver cancer
- Endometrial cancer
- Rectal cancer
- Cervical cancer
- Pancreatic cancer
- Non-Hodgkin's lymphoma
- Uterine cancer
- Uterine cancer

Obesity
♂ 14%
♀ 20%

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Circulating mononuclear cells in the obese are in a proinflammatory state

Ghanim H, Aljada A, Hofmeyer D, Syed T, Mohanty P, Dandona P.
Circulation.
Obese subjects express higher levels of activated NF-κB than lean subjects

Modified from Ghanim H, 2004
Obese subjects express elevated levels of Inflammatory cytokines in plasma

Modified from Ghanim H, 2004
Increase in intranuclear NF-κB and decrease in IκB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect.

Expt subjects: (N=9; BMI=25; non-diabetic; 29-38y) fasted overnight, came to clinic between 8-9 AM.

Mixed meals:
Egg muffin,
sausage,
muffin sandwiches,
2 hash browns
(81g CHO, 51g fat; 32 g protein=910 kcal) finished in 15 min.

Control subject: (N=8; BMI=24.3; 26-50 y) given 300ml water

Blood samples: 1, 2, 3 h after the meal.
Evidence that mixed meal activates NF-κB in humans

**Figure:**

- **Panel A:** Western blot analysis comparing NF-κB activity in meal and water intake conditions at different time points (0, 1, 2, 3 hours).
- **Panel B:** Change in NF-κB binding activity over time (0, 1, 2, 3 hours) for meal and water intake.
- **Panel C:** AUC (Area Under the Curve) for NF-κB binding activity for water and meal intake.

**Abbreviations:**
- NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
- IKK: IκB kinase

Aljada A, 2004
NF-κB

NF-κB: the enemy within.

NF-κB: a friend or a foe in cancer?
Shishodia S, Aggarwal BB.

Signalling pathways of the TNF superfamily: a double-edged sword.
Inflammatory networking in cancer

Role of inflammation in tumorigenesis

NF-κB

DNA damage
Oncogenes

Bcl-xl
Bcl-2
Survivin
C-FLIP
cIAP-1
cIAP-2
XIAP

Cyclin D1
C-myc
TNF
IL-1
IL-6
COX2

MMP-9
uPA
ICAM-1
ELAM-1
VCAM-1

VEGF

CXCR4
TWIST

10-20 Years

10 Years

Inflammation

Aggarwal et al, CCR, 2010
More than 1.5 million Americans have Crohn's disease or ulcerative colitis, the most common forms of inflammatory bowel disease.

Nearly 43% of patients with ulcerative colitis develop colorectal cancer after 25-35 years!
Constitutive activation of NF-κB has been linked with most cancers.

NF-κB

Tobacco-linked cancers

Carcinogens

Viral cancers

UV light

- Acute myelogenous leukemia
- Hodgkin’s disease
- Non-Hodgkin’s lymphoma
- B cell lymphoma
- T cell lymphoma
- Mantle cell lymphoma
- Multiple myeloma

- Esophageal cancer
- Laryngeal cancer
- Pharyngeal cancer
- Pancreatic cancer
- Renal carcinoma
- Colon cancer
- Head and neck SCC
- Lung cancer
- Bladder cancer

- Thyroid cancer
- Liver cancer
- Breast cancer
- Ovarian cancer
- Prostate cancer

- Acute lymphoblastic leukemia
- Adult T cell leukemia
- Cervical cancer
- Nasopharyngeal carcinoma
- Melanoma

Shishodia and Aggarwal, Biochemical Pharmacology, 2004
NF-κB addiction and its role in cancer: 
“One size does not fit all”

Chaturvedi MM, Sung B, Yadav VR, Kannappan R, and Aggarwal BB

ONCOGENE 
(2011 Apr 7;30(14):1615-30.)
Cross Talk between NF-κB and other transcription factors

Chaturvedi et al, 2011
Persistently activated Stat3 maintains constitutive NF-κB activity in tumors.


Cancer Cell.
NF-kB and FDA Approved Anticancer Drugs

- Herceptin
- Tykerb
- Erbitux
- Iressa
- Vectibix
- Humira
- Remicade
- Revlimid
- Enbrel
- Sutent
- Sprycel
- Avastin
- Sutent
- Nexavar
- Gleevec
- Sprycel
- Tasigna

- HER2
- EGFR
- TNF
- PDGFR
- VEGFR
- Bcr-Abl

- Proteasome
- mTOR
- Afinitor
- Torisel
- Velcade

Chaturvedi et al., 2011
The NF-kB/bcl-2 pathway correlates with pathologic complete response to doxorubicin-based neoadjuvant chemotherapy in human breast cancer.


NF-kB as a predictor of treatment response in breast cancer.

Inflammatory biomarkers have been linked to survival of breast cancer pts

COX-2
Ahn, 2004; Chow, 2005; Nakopoulou, 2005; Guo, 2008; Haffty, 2008; Younis, 2009; Zeeneldin, 2009

NF-κB
Hou, 2003; Buchholz, 2005

STAT3
Dolled-Filhart, 2003; Wincewicz, 2007
NF-κB-regulated genes

Enzymes
- Collagenase 1 (HD-1)
- HO-1 (NQO1)
- PKC (Protein Kinase C)
- PPI (Protein Phosphatase Inhibitor)
- PK (Protein Kinase)
- MAPK (Mitogen-Activated Protein Kinase)
- ERK (Extracellular Signal-Regulated Kinase)
- JNK (C-Jun N-terminal Kinase)
- p38 (p38 Mitogen-Activated Protein Kinase)
- PI3K (Phosphoinositide 3-Kinase)
- Akt (Protein Kinase B)
- NF-κB (Nuclear Factor κ-light-chain-enhancer of activated B cells)

Stress response genes
- Bcl-2 (B-cell lymphoma 2)
- Bax (Bcl-2-associated X protein)
- Bcl-xL (Bcl-2-like 1)
- Bcl-2 (B-cell lymphoma 2)
- Bcl-2 (B-cell lymphoma 2)
- Bcl-2 (B-cell lymphoma 2)
- Bcl-2 (B-cell lymphoma 2)
- Bcl-2 (B-cell lymphoma 2)
- Bcl-2 (B-cell lymphoma 2)

Early response genes
- C/EBPβ (CCAAT/enhancer binding protein β)
- CREB (CAMP responsive element binding protein)
- AP-1 (Activating protein 1)
- NF-κB (Nuclear Factor κ-light-chain-enhancer of activated B cells)
- IRF (Interferon-regulatory factor)
- JUN (Jun proto-oncogene)
- FOS (Fos proto-oncogene)
- JUN (Jun proto-oncogene)
- FOS (Fos proto-oncogene)
- JUN (Jun proto-oncogene)
- FOS (Fos proto-oncogene)
- JUN (Jun proto-oncogene)

NF-κB-regulated genes

Acute phase proteins
- LPS (Lipopolysaccharide)
- IFN-γ (Interferon-γ)
- TNF (Tumor Necrosis Factor)
- IL-1β (Interleukin-1β)
- IL-6 (Interleukin-6)
- IL-12 (Interleukin-12)

Antigen presentation
- MHC (Major Histocompatibility Complex)
- CD (Cluster of Differentiation)
- CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4)
- PD-L1 (Programmed Death Ligand 1)
- PD-L2 (Programmed Death Ligand 2)

Cell adhesion molecules
- CD44 (Cell-Cadherin)
- ICAM-1 (Intercellular Adhesion Molecule 1)
- VCAM-1 (Vascular Cell Adhesion Molecule 1)

Miscellaneous
- TNF-α (Tumor Necrosis Factor alpha)
- IL-1β (Interleukin-1β)
- IL-6 (Interleukin-6)
- IFN-γ (Interferon-γ)

Gupta et al. (2010) Biochim Biophys Acta 1799 (10-12): 775-87
Here we report the mapping of a protein interaction network around 32 known and candidate TNF-/NF-kB pathway components by using an integrated approach comprising tandem affinity purification, liquid-chromatography tandem mass spectrometry, network analysis and directed functional perturbation studies using RNA interference.

We identified 221 molecular associations and 80 previously unknown interactors, including 10 new functional modulators of the pathway.

This systems approach provides significant insight into the logic of the TNF-/NF-kB pathway and is generally applicable to other pathways relevant to human disease.
How to suppress NF-κB activation safely!
Chronic diseases caused by chronic inflammation requires chronic treatment!
Sloan School of Management at M.I.T. and the Harvard Business School has created Pharmer’s Market, however, we need a Farmer’s Market...

New York Times, November, 2009
Farmer’s Market

Fruits

Spices & condiments

Vegetables

Cereals

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Hippocrates proclaimed ~2500 years ago

“Let food be thy medicine and medicine be thy food”
To treat/prevent most chronic diseases, we need to “dial down” but not “turn off” of “multiple”, not “single” gene
Most diseases including cancer is due to dysregulation of *multiple* genes.

Mono-targeted drugs are unlikely to be an effective therapy.

Multi-targeted drugs are needed

Most natural products are designed for multi-targeting, naturally.
Promiscuity is becoming a virtue in drug development!

(Mencher SK, 2005)
Magic bullets!
Smart drugs!
Targeted therapies!
Multi-targeted drugs!
Promiscuous drugs!
Polypharmacology!
Future of Cancer Treatment

“The future will not be so much going after one pathway, or one gene, but rather co-extinguishing multiple pathways so you can elicit more durable responses with therapy.

……to really cure the disease what we are going to have to do is shut down multiple pathways, which will undo the range of biological capabilities that these cancer cells have”

……Dr. Ronald DePinho, President, M.D. Anderson Cancer Center, Houston
(Houston Chronicle, Scientists find a smarter way to fight cancer, October 2nd, 2011)
Identification of inhibitors of NF-$\kappa$B from natural sources
Drug Development

High Throughput Screen vs. Reverse Pharmacology
Traditional Knowledge
(Traditional Chinese Medicine
Ayurvedic Medicine
Egyptian Medicine
Kampo)

Modern Technology

Modern Knowledge
(Allopathic Medicine)

Ayurveda (Sushruta Samhita)

- Ayurveda means “science of long life”.
- This is an ancient medical system primarily practiced in India for over 6000 years.
Oncologic, Endocrine & Metabolic

From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer

Bharat B Aggarwal†, Haruyo Ichikawa, Prachi Garodia, Priya Weerasinghe, Gautam Sethi, Indra D Bhatt, Manoj K Pandey, Shishir Shishodia & Muraleedharan G Nair

† The University of Texas, MD Anderson Cancer Center, Cytokine Research Laboratory, Department of Experimental Therapeutics, Box 143, 1515 Holcombe Boulevard, Houston, Texas 77030, USA.

Therapeutic Uses of Ayurvedic plants

- **Guggul**
  - Commiphora mukul

- **Salai Guggul**
  - Boswellia Serrata

- **Ashwagandha**
  - Withania Somnifera

- **Amla**
  - EmblicaOfficinalis

- **Grapes**
  - Vitis Vinifera

- **Pipalli**
  - Piper Longum

- **Bala**
  - Sida cordifolia

- **Guduchi**
  - Tinospora cardifolia

- **Hareetaki**
  - Terminalia-chebula

- **Bhumiyaamalaki**
  - Phyllantus amarus

- **Shilajit**
  - Asphaltum

- **Isabgol**
  - Plantago Ovata

- **Punarnava**
  - Spreading Hogweed

- **Basil**
  - Ocimum sanctum

- **Vanshalochan**
  - Bamboosa arundinacea

- **Dalchini**
  - Cinnamomum zeylanicum
Therapeutic Uses of Ayurvedic plants

- **Jeevanti**
  - Leptadenia reticulata
- **Kachur**
  - Curcuma zedoary
- **Karkatakashringi**
  - Pistacia integerrima
- **Laghu Kantakari**
  - Solanum xanthocarpum
- **Mustaka**
  - Cyprus rotundus
- **Patala**
  - Sterospermum suaveolens
- **Kokum**
  - Garcinia indica
- **Clove**
  - Syzygium aromaticum
- **Ashok**
  - Saraca indica
- **Saunf**
  - Foeniculum vulgare
- **Neem**
  - Azadirachta indica
- **Bakul**
  - Erythrina Indica
- **Kushta**
  - Saussurea lappa
- **Yastimadhu**
  - Glycyrrhiza glabra
Antiinflammatory lifestyle

**Spices**
- Asian ginger (Aegle marmelos)
- Cloves (Eugenia caryophyllus)
- Fennel (Foeniculum vulgare)
- Fenugreek (Trigonella foenum-graecum)
- Gamboge (Garcinia hanburyi)
- Holy basil (Ocimum sanctum)
- Onion (Allium cepa)
- Onion seed (Nigella sativa)
- Fennel (Foeniculum vulgare)
- Asian ginger (Alpinia galanga)
- Red chili (Capsicum annum)
- Sesame seed (Sesamum indicum)
- Turmeric (Curcuma longa)
- Gamboge (Garcinia hanburyi)
- Onion seed (Nigella sativa)
- Fennel (Foeniculum vulgare)
- Asian ginger (Alpinia galanga)
- Red chili (Capsicum annum)
- Sesame seed (Sesamum indicum)
- Turmeric (Curcuma longa)

**Fruits & Vegetables**
- Artichoke (Cynara cardunculus)
- Cauliflower (Brassica oleracea)
- Grapes (Vitis vinifera)
- Mulberry (Morus nigra)
- Soybean (Glycine max)

**Traditional Chinese Medicine**
- Evodia (Evodia rutaecarpa)
- Goldenseal (Hydrastis canadensis)
- God of thunder vine (Tripterygium wilfordii)
- Indigo (Polygonum tinctorium)
- Lacquer tree (Rhus verniciflua)
- Magnolia (Magnolia officinalis)
- Smoke tree (Cotinus coggyria)
- Song gen (Picrorhiza kurroa)

**Ayurvedic Medicine**
- Aloe (Aloe vera)
- Ashwagandha (Withania somnifera)
- Boswellia (Boswellia serrata)
- Beauty berry (Colocasia macrantha)
- Chitrak (Plumbago zeylanica)
- False pepper (Embelia ribes)
- Guggulu (Commiphora mukul)
- Himalayan fir (Abies webbiana)
- Indigo (Polybourbon tinctorium)
- Neen (Azadirachta indica)

**Others**
- Cashew nut (Anacardium occidentale)
- Cork bush (Mandecia sejecer)
- Elephant’s foot (Elephantopus scaber)
- Fire lily (Gloriosa superba)
- Ginger lily (Hedychium coronarium)
- Cottonseed oil (Gossypium)
- False pepper (Embelia ribes)
- Pinecone ginger (Zingiber zerumbet)
- Rohitukine (Dysoxylum binectariferum)
- Vegetable ginger (Zingiber officinale)
- Peacock ginger (Kochisia segercg)
- False pepper (Embelia ribes)
- Pinecone ginger (Zingiber zerumbet)
- Rohitukine (Dysoxylum binectariferum)
- Vegetable ginger (Zingiber officinale)
- Peacock ginger (Kochisia segercg)
From exotic spice to modern drug?

Singh S.
Cell. 2007 Sep 7;130(5):765-8.

The global demand for more affordable therapeutics and concerns about side effects of commonly used drugs are refocusing interest on Eastern traditional medicines, particularly those of India and China.
Spicy Approach to Cancer Treatment

By Sowmya Nath

With increasing curiosity into more holistic approaches to disease prevention and treatment, some researchers are rediscovering how an ancient spice may help treat and prevent many types of cancer, revealing curcumin’s antioxidant and anti-inflammatory powers.

Bharat Aggarwal, Ph.D., professor of cancer medicine and cancer research, and chief of the Cytokine Research Laboratory at the University of Texas M. D. Anderson as asthma, and so forth, or immunological diseases, the common denominator in all these diseases is only one, and that is inflammation,” he explained.

Aggarwal said that most cancers are proinflammatory, and chemotherapy and...
Add spices to your life!
Curcumin: Getting Back to Our Roots!
Structure of Curcumin
From turmeric (curry powder)

Diferuloylmethane

Antibacterial action of curcumin and related compounds.

SCHRAUFSTATTER E, BERNT H.

Nature.
1949 Sep 10;164(4167):456.
Activation of transcription factor Nuclear Factor-kappa B is suppressed by curcumin

Singh S, and Aggarwal BB.

Curcumin Downregulates Expression of Cell Proliferation, Antiapoptotic and Metastatic Gene Products Through Suppression of IκBα Kinase and AKT Activation

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

Molecular Pharmacology
[2006 Jan;69(1):195-206]
Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.

Aggarwal BB, Sung B.

Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases.

Aggarwal BB, Harikumar KB.

Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals.

Aggarwal BB.

Annual Reviews in Nutrition
Curcumin

- Chemopreventive
  - Skin, liver, colon, stomach
- Chemotherapeutic
  - Skin, liver, colon, stomach
- Antioxidant
- Antiangiogenic
- Antiflammatory
- Arthritis
- Lung fibrosis
- HIV replication
- Wound healing
- Cardiotoxicity
- Cataract formation
- Multiple sclerosis
- Cardiovascular diseases
  - Cholesterol, platelet aggregation, inhibition of smooth muscle cell proliferation
- Alzheimer disease
- Nephrotoxicity
- Diabetes
- Gall-stones formation

Turmeric in India

Curcumin & cancer
Different stages of cancer progression and its suppression by curcumin

Constitutive activation of transcription factors
- AP-1 & NF-κB
- 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

Transformation
Normal cells → Tumor cells

Proliferation
Tumor cells → Tumor growth

Invasion
Tumor growth → Tumor Metastasis

curcumin

From Aggarwal B etal, Anticancer Research 23, 2003, 363-398
Curcumin in cell culture models!
Preclinical data with curcumin against various cancers

Gynecologic cancers (Cervix, Ovary, Uterus)
Thoracic/ H&N Cancers (Lung, Oral, Thymus)
Breast cancer
Gastrointestinal cancers (Esophagus, Intestine, Liver, Stomach, Pancreas, Colorectal)
Genitourinary cancers (Bladder, Kidney, Prostate)
Brain tumors
Breast cancer
Hematological cancers (Leukemia, Lymphoma, Multiple myeloma)
Melanoma
Gynecologic cancers (Cervix, Ovary, Uterus)

Curcumin down-regulates cigarette smoke-induced NF-kB activation through inhibition of IkBa kinase in human lung epithelial cells: correlation with suppression of COX-2, MMP-9 and cyclin D1.

Shishodia S, Potdar P, Gairola CG, Aggarwal BB.

Carcinogenesis
The objective of these studies was to test our hypothesis in vitro and in vivo in an effort to inform the design of a phase II chemoprevention trial in former smokers. We treated non-tumor-derived, normal (but immortalized) human bronchial epithelial cells (AALE) and lung adenocarcinoma-derived cells (H441) with bioactive curcumin C3 complex. Asynchronous cells in each case were treated with curcumin for 24 h, followed by immunoblotting for Stat3 and activated Stat3-P, prior signal of which was used for normalization.

We also completed a preclinical trial in which 12 mice were randomly divided into three groups and subjected to 3 days or 9 days of curcumin intraperitoneal injections, followed by analysis of lung tissues for Stat3-P changes and growth suppressive effects of the curcumin. The growth suppressive effects were measured using Cyclin D1 and the replicative helicase subunit, Mcm2, as surrogates for the proliferative capacity of the tissues. In-vitro studies with curcuminoid complex demonstrated that the activity of Stat3 in both normal bronchoepithelial cells and lung cancer-derived cells is sensitive to curcumin exposure. In a dose-dependent manner, curcumin treatment resulted in significant suppression of Stat3 phosphorylation and reduction in the proliferative capacity of both cell types. In the preclinical trial with rodent models, curcumin reduced Stat3-P and the proliferative markers CycD1 and Mcm2 in mice lung tissues in vivo. These culture and preclinical studies indicate that the activity of the Stat3 pathway can be suppressed by curcumin treatment, concomitant with a reduction in cell proliferation, supporting our hypothesis that inhibition of the Stat3 pathway represents at least one important mechanism by which curcumin elicits its effects on the bronchoepithelium.

These data provide a rationale for the use of curcumin as a promising chemopreventive agent in high-risk populations such as former smokers.
Targeting constitutive and interleukin-6-inducible STAT-3 signal pathway in head and neck squamous cell carcinoma cells by curcumin.

Chakravarti N, Myers JN, Aggarwal BB.


Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of NF-kappaB signaling.

Aggarwal S, Takada Y, Singh S, Myers JN, Aggarwal BB.


Differential inhibition of protein translation machinery by curcumin in normal, immortalized, and malignant oral epithelial cells.

Chakravarti N, Kadara H, Yoon DJ, Shay JW, Myers JN, Lotan D, Sonenberg N, Lotan R.

Curcumin in animal models!
### Cancer prevention by curcumin in animals

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Carcinogen</th>
<th>Animal</th>
<th>Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal cancers:</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACF</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1993</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Mice</td>
<td>0.5 to 0.2 % w/w</td>
<td>Huang et al, 1994</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>DMH</td>
<td>Mice</td>
<td>0.5%</td>
<td>Kim et al, 1998</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1995</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>0.2 or 0.6% w/w</td>
<td>Kawamori et al, 1999</td>
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<tr>
<td>Colon cancer</td>
<td>PhIP</td>
<td>Apc mice</td>
<td>2000 ppm</td>
<td>Collett et al, 2001</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>1 or 2% w/w</td>
<td>Pereira et al, 1996</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>0.6% w/w</td>
<td>Kwon et al, 2004</td>
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<tr>
<td>Colon cancer</td>
<td>DMH</td>
<td>Rat</td>
<td>0.6%</td>
<td>Shiptz B, 2006</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
<td>Mice</td>
<td>0.5-5%, diet</td>
<td>Sugimoto K, 2002</td>
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<tr>
<td>Colitis</td>
<td>DNB</td>
<td>Mice</td>
<td>0.25%; diet</td>
<td>Salh B, 2003</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
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<td>50mg/kg</td>
<td>Ukil A, 2003</td>
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<tr>
<td>Ulcerative colitis</td>
<td>TNCB</td>
<td>Rat</td>
<td>30-60 mg/kg</td>
<td>Jung H, 2006</td>
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<tr>
<td>Ulcerative colitis</td>
<td>DNCB</td>
<td>Rat</td>
<td>25-100 mg/kg</td>
<td>Venkatarangana MV, 2007</td>
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<td>Duodenal tumor</td>
<td>MNNG</td>
<td>Mice</td>
<td>0.5 to 2.0% w/w</td>
<td>Huang et al, 1994</td>
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<tr>
<td>Esophageal cancer</td>
<td>NMBA</td>
<td>Rat</td>
<td>500 ppm</td>
<td>Usida et al, 2000</td>
</tr>
<tr>
<td>FAD*</td>
<td>AOM</td>
<td>Mice</td>
<td>2%</td>
<td>Huang et al, 1992</td>
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<tr>
<td>FAP*</td>
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<td>Min/+ mice</td>
<td>0.1, 0.2 or 0.5% w/w</td>
<td>Perkins et al, 2002</td>
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<tr>
<td>Forestomach neoplasia</td>
<td>B[a]P</td>
<td>Mice</td>
<td></td>
<td>Azuine et al, 1992</td>
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<tr>
<td>Forestomach cancer</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Singh et al, 1998</td>
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<td>Mice</td>
<td></td>
<td>Nagabhushan et al, 1992</td>
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<td>Stomach cancer</td>
<td>MNNG</td>
<td>Rat</td>
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<td>Ikezaki et al, 2010</td>
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<td><strong>Liver cancers:</strong></td>
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<tr>
<td>Hepatic hyperplasia</td>
<td>DNM</td>
<td>Rat</td>
<td>200 or 600 mg/kg</td>
<td>Chuang et al, 2000</td>
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<tr>
<td>Liver cancer</td>
<td>DNM</td>
<td>Mice</td>
<td>0.2% w/w</td>
<td>Chuang et al, 2000</td>
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<td><strong>Lung cancers:</strong></td>
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<td><strong>Blood cancers:</strong></td>
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<td>Lymphoma/leukemia</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Huang et al, 1998</td>
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</tbody>
</table>
# Cancer prevention by curcumin in animals

<table>
<thead>
<tr>
<th>Cancer</th>
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<td><strong>Breast cancers:</strong></td>
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<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>0.8 to 1.6% w/w</td>
<td>Pereira et al, 1996</td>
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<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>50 to 200 mg/kg</td>
<td>Singletary et al, 1996</td>
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<td>DMBA</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Deshpande et al, 1998</td>
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<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Huang et al, 1998</td>
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<tr>
<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td></td>
<td>Inano et al, 1999</td>
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<td>γ-radiation</td>
<td>Rat</td>
<td>1% w/w</td>
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<td>DMBA</td>
<td>Rat</td>
<td></td>
<td>Lin et al, 2001</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Sencar mice</td>
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<td>Lin et al, 2001</td>
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<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td></td>
<td>Inano et al, 2002</td>
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<td><strong>Oral cancers:</strong></td>
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<td>Oral cancer</td>
<td>MNA</td>
<td>Hamster</td>
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<td>Azuine et al, 1992</td>
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<td>NQO</td>
<td>Rat</td>
<td>500 ppm</td>
<td>Tanaka et al, 1994</td>
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<td><strong>Prostate cancers:</strong></td>
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<tr>
<td>Prostate cancer</td>
<td>DMAB &amp; PhIP</td>
<td>Rat</td>
<td>15 to 500 ppm</td>
<td>Imaida et al, 2001</td>
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<tr>
<td><strong>Skin cancers:</strong></td>
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<tr>
<td>Dermatitis</td>
<td>TPA + UV-A</td>
<td>Mice</td>
<td></td>
<td>Ishizaki et al, 1996</td>
</tr>
<tr>
<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
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<td>Huang et al, 1988</td>
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<tr>
<td>Skin tumor</td>
<td>DMBA</td>
<td>Mice</td>
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<td>Azuine et al, 1992</td>
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<td>Huang et al, 1995</td>
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<td>B[a]P and</td>
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<td>Soudamini, 1989</td>
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<td>Mice</td>
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<td>Huang et al, 1992</td>
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<td>DHPN, EHEN</td>
<td>Rat</td>
<td>1% w/w</td>
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Goel et al, Biochem. Pharm., 2007
Multi-targeted Approach to Prevention of Colorectal Cancer by Curcumin/Turmeric

Curcumin / Turmeric

- c-Myc
- AKT
- NF-κB
- STAT3
- p21
- KRAS
- E-cadherin
- TAK1
- TGFβ/SMAD
- p53
- DNA adducts
- COX-2
- β-catenin
- Notch
- PI3K
- EGFR
- CREB
- IKK
- DNA adducts
- p53
# Treatment of cancer by curcumin in animals

<table>
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<tr>
<th>Tumor</th>
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<th>Dose</th>
<th>Model</th>
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<td>IP</td>
<td>50 mg/kg</td>
<td>Ascites</td>
<td>Kuttan et al, 1985</td>
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<td>Ascites</td>
<td>IP</td>
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<td>Ruby et al, 1995</td>
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<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<td>HCC³</td>
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<td>Lin et al, 2007</td>
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<td>Gavage</td>
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<td>Orthotopic</td>
<td>Kunnumakkara et al, 2007</td>
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<td>Dorai et al, 2001</td>
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<td>5 mg/kg</td>
<td>Orthotopic</td>
<td>Hong et al, 2006</td>
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<tr>
<td>Prostate</td>
<td>Gavage</td>
<td>5 mg/day</td>
<td>Xenograft</td>
<td>Li et al, 2007</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Gavage</td>
<td>1 gm/kg</td>
<td>Orthotopic</td>
<td>Kunnumakkara et al, 2008</td>
</tr>
</tbody>
</table>

1. Lung metastases; 2. Liposomal curcumin; 3. Intrahepatic metastasis; IP, intraperitoneal; IT, intratumoral; IV, intravenous

Goel et al, Biochem. Pharm., 2007
Curcumin attenuates elastase- and cigarette smoke-induced pulmonary emphysema in mice.
Suzuki M, Betsuyaku T, Ito Y, Nagai K, Odajima N, Moriyama C, Nasuhara Y, Nishimura M.
2009 Apr;296(4):L614-23.

Protection from acute and chronic lung diseases by curcumin.
Venkatesan N, Punithavathi D, Babu M.
Curcumin inhibits COPD-like airway inflammation and lung cancer progression in mice.


Carcinogenesis.
Curcumin inhibits proliferation and induces apoptosis in lung cancer cells
Curcumin inhibits infiltration of inflammatory cells and chemokines into BALF in mice exposed to non-typeable Haemophilus influenzae (NTHi)
Curcumin inhibits growth of lung tumors in the mice exposed to non-typeable Haemophilus influenzae (NTHi)
Curcumin inhibits late tumor progression in CCLR mice by suppressing proliferation marker Ki67.
Curcumin as a chemo-sensitizer
Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs.

Goel A, and Aggarwal BB.

Nutrition and Cancer
We evaluated dietary curcumin in radiation-induced pneumonopathy and lung tumor regression in a murine model. Mice were given 1% or 5% (w/w) dietary curcumin or control diet prior to irradiation and for the duration of the experiment. Lungs were evaluated at 3 weeks after irradiation for acute lung injury and inflammation by evaluating bronchoalveolar lavage (BAL) fluid content for proteins, neutrophils and at 4 months for pulmonary fibrosis.

In a separate series of experiments, an orthotopic model of lung cancer using intravenously injected Lewis lung carcinoma (LLC) cells was used to exclude possible tumor radioprotection by dietary curcumin. In vitro, curcumin boosted antioxidant defenses by increasing heme oxygenase 1 (HO-1) levels in primary lung endothelial and fibroblast cells and blocked radiation-induced generation of reactive oxygen species (ROS).

Dietary curcumin significantly increased HO-1 in lungs as early as after 1 week of feeding, coinciding with a steady-state level of curcumin in plasma. Although both 1% and 5% w/w dietary curcumin exerted physiological changes in lung tissues by significantly decreasing LPS-induced TNF-alpha production in lungs, only 5% dietary curcumin significantly improved survival of mice after irradiation and decreased radiation-induced lung fibrosis. Importantly, dietary curcumin did not protect LLC pulmonary metastases from radiation killing.

Thus dietary curcumin ameliorates radiation-induced pulmonary fibrosis and increases mouse survival while not impairing tumor cell killing by radiation.
Thioredoxin reductase-1 mediates curcumin-induced radiosensitization of squamous carcinoma cells.


Stable knockdown of TxnRd1 in both HeLa and FaDu cells nearly abolished curcumin-mediated radiosensitization.

TxnRd1 knockdown cells showed decreased radiation-induced reactive oxygen species and sustained extracellular signal-regulated kinase 1/2 activation, which we previously showed was required for curcumin-mediated radiosensitization.

Conversely, overexpressing catalytically active TxnRd1 in HEK293 cells, with low basal levels of TxnRd1, increased their sensitivity to curcumin alone and to the combination of curcumin and ionizing radiation.

These results show the critical role of TxnRd1 in curcumin-mediated radiosensitization and suggest that TxnRd1 levels in tumors could have clinical value as a predictor of response to curcumin and radiotherapy.
Curcumin Suppresses the Paclitaxel-induced NF-κB Pathway in Breast Cancer Cells and Inhibits Lung Metastasis of Human Breast Cancer in Nude Mice


Clinical Cancer Research
Curcumin potentiates the effect of paclitaxel by suppressing the metastasis of the human breast cancer to the lung in mouse xenograft model.
LETTER

RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis

Eva Gonzalez-Suarez¹*, Allison P. Jacob¹*, Jon Jones¹, Robert Miller¹, Martine P. Roudier-Meyer², Ryan Erwert¹, Jan Pinkas³†, Dan Branstetter² & William C. Dougall¹

Nature, 2010
Curcumin Inhibits RANKL-Induced NF-κB Activation in Osteoclast Precursors and Suppresses Osteoclastogenesis

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

Journal of Immunology; 172, 5940-5947, 2004
Medium

RANKL

RANKL + Curcumin (5 µM)

RANKL + Curcumin (10 µM)

TRAP+ Osteoclasts

Curcumin (µM)

Bharti et al., Journal of Immunology, 2004
Curcumin in human clinical trials!
# Completed clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose/Frequency</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td>2000 mg/day</td>
<td>10</td>
</tr>
<tr>
<td>Phase-I</td>
<td>500-12,000 mg/day x 90 days</td>
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</tr>
<tr>
<td>Phase 1</td>
<td>500-12,000 mg/day</td>
<td>24</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>1200 mg/day x 14 days</td>
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<tr>
<td>Postoperative inflammation</td>
<td>400 mg; 3 x/day x 5 d</td>
<td>46</td>
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<tr>
<td>External cancerous lesions</td>
<td>1% ointment x several months</td>
<td>6</td>
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<tr>
<td>Cardiovascular</td>
<td>500 mg/day x 7 d</td>
<td>10</td>
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<tr>
<td>Atherosclerosis</td>
<td>10 mg; 2x/day x 28 d</td>
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<tr>
<td>HIV</td>
<td>625 mg; 4x/day x 56 d</td>
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<tr>
<td>Gall bladder function</td>
<td>20 mg, single dose (2 h)</td>
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<tr>
<td>Gall bladder function</td>
<td>20-80 mg, single dose (2 h)</td>
<td>12</td>
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<tr>
<td>Chronic anterior uveitis</td>
<td>375 mg; 3x /day x 84 days</td>
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<tr>
<td>Idiopathic Inflamm Orbital pseudo tumors</td>
<td>375 mg; 3x /day x 180-660 days</td>
<td>8</td>
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</tbody>
</table>

Goel et al., Biochem. Pharm., 2007
### Completed clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose/Frequency</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Psoriasis</td>
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<td>Psoriasis</td>
<td>4.5g/day x 84 days</td>
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<tr>
<td>Colorectal cancer</td>
<td>36-180 mg/day x 120 days</td>
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</tr>
<tr>
<td>Colorectal cancer</td>
<td>450-3600 mg/day x 120 days</td>
<td>15</td>
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<tr>
<td>Irritable bowel syndrome</td>
<td>72-144 mg/day x 56 days</td>
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<td>Liver metastasis of CRC</td>
<td>450-3600 mg/day x 7 day</td>
<td>12</td>
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<tr>
<td>Colorectal cancer</td>
<td>450-3600 mg/day x 7 days</td>
<td>12</td>
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<tr>
<td>Cadaveric renal transplantation</td>
<td>480 mg; x1-2/day x 30 days</td>
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<td>Tropical pancreatitis</td>
<td>500 mg/day x 42 days</td>
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<td>Ulcerative proctitis</td>
<td>550 mg; x 2-3/day x 60 days</td>
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<td>Crohn’s disease</td>
<td>360 mg; x 3/day x 30 days</td>
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<td>Ulcerative colitis</td>
<td>2000 mg/day x 180 days</td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>480 mg; x3/day x 180 days</td>
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<td>Cognitive function</td>
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<td>Prostatic intra-epithelial neoplasia (PIN)</td>
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<tr>
<td>Helicobacter pylori infection</td>
<td>300 mg/day x 7 days</td>
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Goel et al, Biochem. Pharm., 2007
### Ongoing clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
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<th>Trial Site</th>
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<tr>
<td>Colorectal cancer, ACF</td>
<td>Phase-I, Randomized</td>
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<td>Rockefeller University Hospital</td>
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<td>Colon cancer</td>
<td>Phase-III, Randomized</td>
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<td>Tel-Aviv Sourasky Med. Center</td>
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<td>Colorectal cancer, ACF</td>
<td>Phase-II, Non-randomized</td>
<td>48</td>
<td>University of Illinois, Chicago</td>
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<tr>
<td>FAP</td>
<td>Phase-II, Randomized</td>
<td>68</td>
<td>University of Pennsylvania</td>
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<td>FAP</td>
<td>Phase-II, Non-randomized</td>
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<td>Johns Hopkins University</td>
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<td>Aberrant crypt foci</td>
<td>Prevention, Randomized</td>
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<td>Cancer Institute of New Jersey</td>
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<td>Pancreatic cancer</td>
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<td>Rambam Medical Center, Haifa</td>
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<td>Pancreatic cancer</td>
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<td>M.D. Anderson Cancer Center</td>
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<td>Pharmacokinetics</td>
<td>Treatment, Non-randomized</td>
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<td>Myelodysplastic syndrome</td>
<td>Phase II</td>
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<td>Univ. Massachusetts, Worcester</td>
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<td>Univ. of California Los Angeles</td>
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<td>Phase-I &amp;II, Randomized</td>
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<td>Multiple myeloma</td>
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<td>Myelodysplastic syndrome</td>
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<td>Hadassah Medical Organization</td>
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Goel et al, Biochem. Pharm., 2007
## Ongoing clinical trials with curcumin

<table>
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<td>Advanced HNSCC</td>
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<td>AIIMS, Delhi</td>
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<td>Cervical cancer (Stage IIb, IIIb)</td>
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<td>AIIMS, Delhi</td>
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<td>Oral premalignant lesions</td>
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<td>Tata Memorial Cancer Ctr</td>
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<td>Oral leukoplakia</td>
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<td>PSC</td>
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<tr>
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<td>Amsterdam Medical Ctr.</td>
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<tr>
<td>Barretts Metaplasia</td>
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<td>MGUS</td>
<td>Phase 1 (3.4 g/day)</td>
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<td>St. George Hospital, Sydney</td>
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</table>

Goel et al., Biochem. Pharm., 2007
Curcumin, the active principle of turmeric, is known to act as an anti-oxidant, anti-mutagen and anti-carcinogen in experimental animals. In the present study, anti-mutagenic effects of turmeric were assessed in 16 chronic smokers.

It was observed that turmeric, given in doses of 1.5 g/day for 30 days, significantly reduced the urinary excretion of mutagens in smokers.

In contrast, in six non-smokers, who served as control, there was no change in the urinary excretion of mutagens after 30 days.

Turmeric had no significant effect on serum aspartate aminotransferase and alanine aminotransferase, blood glucose, creatinine and lipid profile.

These results indicate that dietary turmeric is an effective anti-mutagen and it may be useful in chemoprevention.
We assessed the effects of oral curcumin (2 g or 4 g per day for 30 days) on PGE$_2$ within ACF (primary endpoint), 5-HETE, ACF number, and proliferation in a nonrandomized, open-label clinical trial in 44 eligible smokers with eight or more ACF on screening colonoscopy. We assessed pre- and posttreatment concentrations of PGE$_2$ and 5-HETE by liquid chromatography tandem mass spectroscopy in ACF and normal-tissue biopsies; ACF number via rectal endoscopy; proliferation by Ki-67 IHC; and curcumin concentrations by high-performance liquid chromatography in serum and rectal mucosal samples.

Forty-one subjects completed the study. Neither dose of curcumin reduced PGE$_2$ or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa. A significant 40% reduction in ACF number occurred with the 4-g dose (P < 0.005), whereas ACF were not reduced in the 2-g group. The ACF reduction in the 4-g group was associated with a significant, five-fold increase in posttreatment plasma curcumin/conjugate levels (versus pretreatment; P = 0.009). Curcumin was well tolerated at both 2 g and 4 g.

Our data suggest that curcumin can decrease ACF number, and this is potentially mediated by curcumin conjugates delivered systemically.
Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis.

Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, Giardiello FM.


Five FAP patients with prior colectomy (4 with retained rectum and 1 with an ileal anal pouch) received curcumin 480 mg and quercetin 20 mg orally 3 times a day. The number and size of polyps were assessed at baseline and after therapy. The Wilcoxon signed-rank test was used to determine differences in the number and size of polyps. Treatment side effects and medication compliance also were evaluated. All 5 patients had a decreased polyp number and size from baseline after a mean of 6 months of treatment with curcumin and quercetin. The mean percent decrease in the number and size of polyps from baseline was 60.4% (P < .05) and 50.9% (P < .05), respectively. Minimal adverse side effects and no laboratory abnormalities were noted.

CONCLUSIONS: The combination of curcumin and quercetin appears to reduce the number and size of ileal and rectal adenomas in patients with FAP without appreciable toxicity. Randomized controlled trials are needed to validate these findings.
Currying favor for the heart

Jonathan A. Epstein

Department of Cell and Developmental Biology, Cardiovascular Institute, and Institute for Regenerative Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
Curcumin for clinical trials

Pill (1000 mg)

Capsule (500 mg)

Losegens (100 mg)
Curcumin

4 gram dosage
Constitutive activation of NF-κB in PBMC from MM Patients and its Suppression by Curcumin (2g/day)

Patient #4 (482480)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
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<th>8w</th>
<th>12w</th>
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Patient #6 (337641)

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<th>Pre</th>
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<th>16w</th>
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</table>

A, B, C, D, E, F, and G represents Pre, 4, 8, 12, 16, 20 and 24 wks after curcumin administration.
Adding celecoxib and curcumin to standard therapy has a beneficial effect in patients with metastatic pancreatic cancer.

E. Shacham-Shmueli, L. Galazan, V. Badmaev, M. Inbar, N. Arber, A. Figer;
Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;

Background: Pancreatic cancer, one of the most difficult cancers to treat harbors poor prognosis. The antimetabolite gemcitabine has become the standard treatment. Series of phase III trials examined efficacy of gemcitabine and a second agent, but these doublets demonstrated no survival advantage over single-agent gemcitabine. However, the rationale for continuing to study gemcitabine-based combinations remains compelling. Curcumin derived from the rhizome of Curcuma Longa, commonly called turmeric, has shown to possess potent anti-inflammatory and anti-oxidative properties. Phase I-II studies found curcuminoids to be safe with no dose-limiting toxicity at doses up to 10 g/day PO. Studies showed stabilizing effect of Curcuminoids in some pancreatic cancer patients. COX-2 inhibitors have very broad applications in oncology, from prevention to treatment of advanced malignancies. The COX-2-specific inhibitors celecoxib has anti-inflammatory effect and cancer protection without gastrointestinal toxicity associated with the older non-specific NSAIDs. In vitro combination celecoxib and curcuminoids demonstrated synergistic growth inhibitory effect in several colonic and pancreatic cell lines.

Methods: In a preliminary study that had been performed at Tel Aviv Medical Center, 20 patients with inoperable pancreatic cancer were recruited. They had received gemcitabine + celecoxib (400 mg qd) and curcuminoids (8 g q/d) (13) or placebo (7).

Results: While there were no side effects related to the use of curcuminoids or celecoxib the disease progressed in all subjects receiving gemcitabine and placebo. Stabilization of the disease was achieved in 50% of the patients receiving the combination therapy.

Conclusions: The results in this small study are encouraging. Adding celecoxib and curcuminoids to standard therapy in pancreatic cancer seems to be very promising. A multi center study, with this protocol, has been initiated in Israel.
Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer


Primary Objective: MTD
Secondary Objectives: Tumor markers measurements and assessment of objective and clinical responses to the combination therapy.

RESULTS: Fourteen patients were accrued in this open-label phase I trial. At the last dose level of curcumin, three dose-limiting toxicities were observed and two out of three patients at this dose level refused to continue treatment, leading us to define the maximal tolerated dose of curcumin at 8,000 mg/d. Eight patients out of 14 had measurable lesions according to RECIST criteria, with five PR and three SD. Some improvements as biological and clinical responses were observed in most pts.

CONCLUSION: The recommended dose of curcumin is 6,000 mg/d for seven consecutive d every 3 w in combination with a standard dose of docetaxel. From the encouraging efficacy results, a comparative phase II trial of this regimen plus docetaxel versus docetaxel alone is ongoing in advanced and metastatic breast cancer patients.
Curcumin bioavailability?
# Delivery system for Curcumin

## Nanoparticles
- Bisht, 2007
- Grabovac, 2007
- Tiyaboonchai, 2007
- Zhang, 2007
- Sahu, 2008
- Sahu, 2008
- Sou, 2008
- Chin, 2009
- Gupta, 2009
- Gupta, 2010
- Liu, Z 2009
- Mukerjee, 2009
- Mulik, 2009
- Prajakta, 2009
- Shaikh, 2009
- Shutava, T 2009
- Sou, 2009
- Anand, 2010
- Bisht, 2010
- Cartiera, 2010
- Dandekar, 2010a
- Dandekar, 2010b
- Wu, 2010
- Ganta, 2010
- Ghosh, 2010
- Das, 2010
- Duan, 2010
- Gao, 2010*
- Kakkar, 2010
- Konwarh, 2010
- Koppolu, 2010
- Kumar, 2010
- Mohanty, 2010
- Mulik, 2010
- Mulik, 2010
- Nair, 2010
- Onoue, 2010
- Padhye, 2010
- Ray, 2010
- Tang, 2010
- Yallapu, 2010
- Yallapu, 2010
- Yen, 2010
- Zhu, 2010
- Song, 2010

## Bioconjugates
- Kumar, 2000
- Kumar, 2001
- Sun, 2006
- Salmaso, 2007
- Marczylo, 2007
- Yadav, 2009
- Yadav, 2010
- Kim, 2010
- Sneharani, 2010
- Manju, 2010b
- Simoni, 2010
- Wan, 2010

## Soild Dispersion
- Paradkar, 2004
- Xu, 2008

## Collagen film
- Gopinath, 2004
- Dai, 2009

## Stents/films
- Pan, 2009
- Patel, 2009

## FDDS
- Shishu, 2008

## Liposomonal
- Li, 2005a
- Jung, 2006
- Li, 2005b
- Jung, 2006

## Hydrogels/ Gelatin
- Vemula, 2006
- Cao, 2009
- Vemula, 2009
- Wu, 2010a
- Wu, 2010b

## Micro-emulsion
- Lee, 2008
- Cui, 2009
- Zheng, 2010

## Guar gum
- Elias, 2010
- Liu, 2011

* (IV); FDDS, floating drug delivery system
Effect of NCB-02 (Curcumin), atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study.

Curcumin decreases serum inflammatory biomarkers in DM2 Patients

Biomarkers level

**ET-1** (pg/ml)

Placebo

Atorvastatin (10 mg/day)

Curcumin (NCB-02 150 mg x 2 daily)

**8 wks**

**Pre** **Post**

**IL-6** (pg/ml)

**TNF-α** (pg/ml)

**MDA** (nmol/ml)

N=21

N=23

Usharani, 2008
Uveitis

- Uveitis is the inflammation of uvea.
- Symptoms include red eye, injected conjunctiva, pain and decreased vision.
- Uveitis is estimated to be responsible for approx 10% of the blindness in the USA.
- Treated with steroids, topical cycloplegics, such as atropine or homatropine, methotrexate, anti-TNFs' infusions.


- Administered 600 mg curcumin, twice a day, orally.
- Consisted of 106 patients.
- More than 80% of patients responded.
- Benefits in eye inflammatory and degenerative conditions, such as dry eye, maculopathy, glaucoma, and diabetic retinopathy.
Curcumin & CRC patients
126 pts; 360 mg curcumin; thrice/day

Body weight

TNF-α

Apoptosis

p53

(He et al, 2011)
Curcumin

Transcriptional factors
- AP-1
- CREB-BP
- STAT-1
- STAT-3
- STAT-4
- STAT-5
- Nrf-2
- β-catenin
- EGR-1
- PPAR-γ
- HIF-1
- ERE
- NF-κB

Inflammatory cytokines
- IL-1
- IL-2
- IL-5
- IL-6
- IL-8
- IL-12
- MCP
- MIP
- MaIP
- TNF-α
- IL-18

Enzymes
- GCL
- iNOS
- COX-2
- 5-LOX
- Desaturase
- DNA pol
- FPT
- GST
- GluCl
- MPH
- XMP

Growth factors
- CTGF
- FGF
- HGF
- TGF-β1
- VEGF
- IL-1R AK
- ERK
- PhK
- MAPK
- PAK
- PKA
- PKB
- PTK
- PTP

Receptors
- EPCR
- IR
- EGFR
- HER-2
- Fas R
- H2R
- ER-α
- AHR
- AR
- TF
- PDGF
- NGF
- ITR
- CXCR4
- LDLR
- DR-5
- IL-8 R
- AHR
- ITR
- MDRP

Kinases
- uPA
- Bcl-xL
- p53
- Hsp-70
- DEF-40
- ICAM-1
- ELAM-1
- Cyclin D1
- IAP-1
- MDRP
- ER-α
- Fas R
- H2R
- EGFR
- HER-2
- DR-5
- IL-8 R
- AHR
- AHR
- AR
- TF
- PDGF
- NGF
- ITR
- CXCR4
- LDLR
- DR-5
- IL-8 R
- AHR
- ITR
- MDRP

Others
- JAK
- JNK
- MAPK
- PhK
- PAK
- PKA
- PKB
- PTK
- PTP

Molecular targets upregulated
- Bcl-2
- Bcl-xL
- uPA
- Notch-1
- EGR-1
- WT-1
- β-catenin
- p53
- Nrf-2
- NF-κB
- HIF-1
- ERE
- STAT-1
- IL-1
- IL-2
- IL-5
- IL-6
- IL-8
- IL-12
- MCP
- MIP
- MaIP
- TNF-α
- IL-18
- AATF-1
- ATFase
- ATPase
- COX-2
- 5-LOX
- Desaturase
- DNA pol
- FPT
- GST
- GluCl
- MPH
- XMP

Molecular targets downregulated
- Cyclin D1
- IAP-1
- MDRP
- ER-α
- Fas R
- H2R
- EGFR
- HER-2
- DR-5
- IL-8 R
- AHR
- AHR
- AR
- TF
- PDGF
- NGF
- ITR
- CXCR4
- LDLR
- DR-5
- IL-8 R
- AHR
- ITR
- MDRP

Anand et al, CL, 2008
Multi-targeted

Inflammatory cytokines
IL-1, IL-2, IL-5, IL-6, IL-8, IL-12, IL-8, MCP-1, MIP-1, MaIP

Enzymes
ATFase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, iNOS, MMPs, NQO-1, ODC, PhPD, TIMP-3, 5-LOX, Telomerase

Growth factors
TGF β, FGF, HGF, PDGF, TF

Receptors
AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R

Adhesion molecules
ELAM-1, ICAM-1, VCAM-1

Anti-apototic proteins
Bcl-2, BclxL, IAP-1

Protein Kinases
IKK, AAPK, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, Phk, PK, PKA, PKB, PKC, pp60c-src tK, PTK

Transcriptional factors
AP-1, β-Catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Nrf-2, NF-κB, PPAR-γ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1

Others
Cyclin D1, Cyclin E, HsP 70, MDR

Curcumin Targets

Mono-targeted

COX-2
Celecoxib

EGFR
Erbitux

TNF
Remicade
Humira
Enbrel

HER-2
Herceptin

Bcr-Abl
Gleevac

VEGF
Avastin

Tubulin
Paclitaxel

Topoisomerase
Camptothecin

Kunnumakkara et al, CL, 2008
Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo

Anand P, Nair HB, Sung B., Kunnunakkara AB, Yadav VR., Tekmal RR and Aggarwal BB; Biochemical Pharmacology, 2009
## Comparison of Cancer Incidence in USA and India

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<th>Cancer</th>
<th>USA</th>
<th>India</th>
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<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
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<tr>
<td>Breast</td>
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<td>160</td>
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<tr>
<td>Prostate</td>
<td>690</td>
<td>130</td>
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<tr>
<td>Colon/Rectum</td>
<td>530</td>
<td>220</td>
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<tr>
<td>Lung</td>
<td>660</td>
<td>580</td>
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<tr>
<td>Head &amp; Neck SCC</td>
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<tr>
<td>Liver</td>
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<td>Pancreas</td>
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<td>Stomach</td>
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<td>Colon/Rectum</td>
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<td>Melanoma</td>
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<td>Testis</td>
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<td>Bladder</td>
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<td>Kidney</td>
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<td>Brain, Nervous system</td>
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<td>Thyroid</td>
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<td>Endometrial Cancers</td>
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<tr>
<td>Ovary</td>
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<td>40</td>
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<tr>
<td>Multiple myeloma</td>
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<td>Leukemia</td>
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<td>90</td>
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<td>Non-Hodgkin lymphoma</td>
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Showing cases per 1 million persons calculated on the basis of current consensus: Endometrial cancers include Cervix uteri and Corpus uteri.

Thank you!

A scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it.

-Max Planck