INCON / 10° ICMAA, Guarujà, Brazil, September 26-29, 2010

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MECHANISTIC APPROACHES TO THE PREVENTION OF MUTATION AND CANCER

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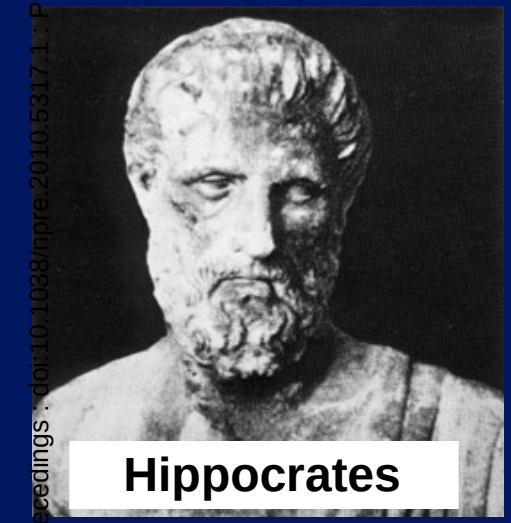
Department of Health Sciences

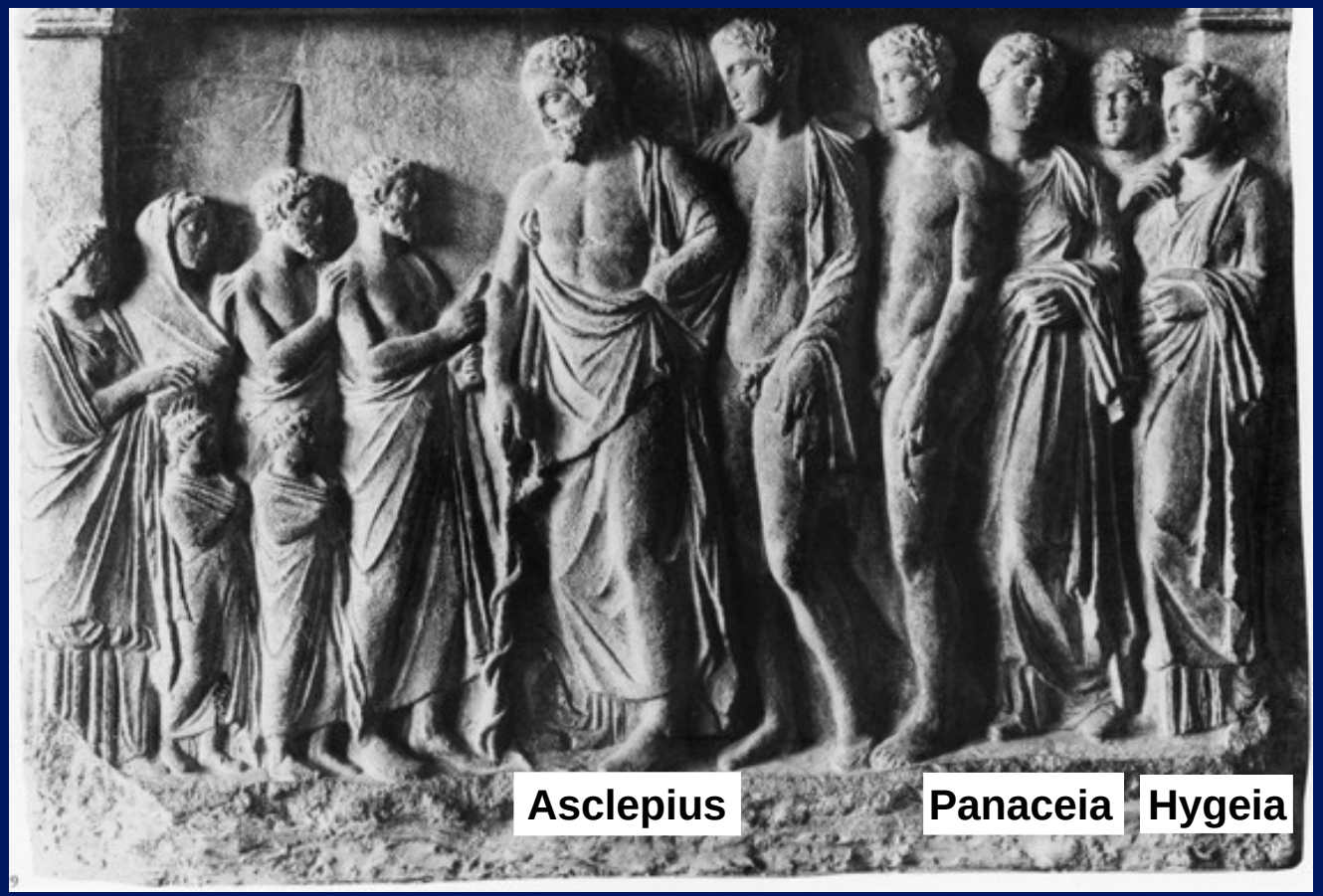
Section of Hygiene and Preventive Medicine

THE HIPPOCRATIC OATH

I swear by Apollo the Physician and Asclepius and Hygeia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath……



Hippocrates



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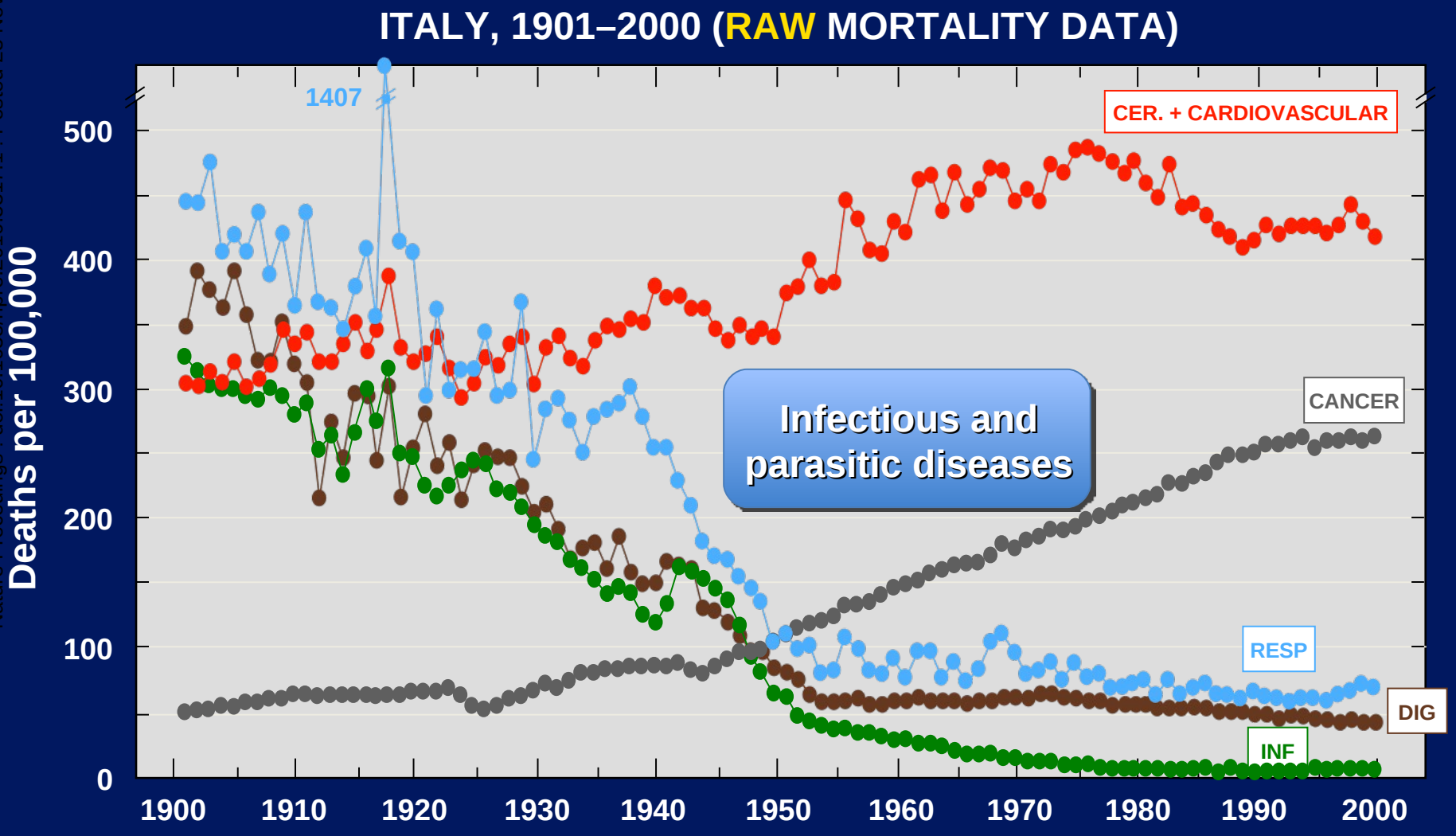

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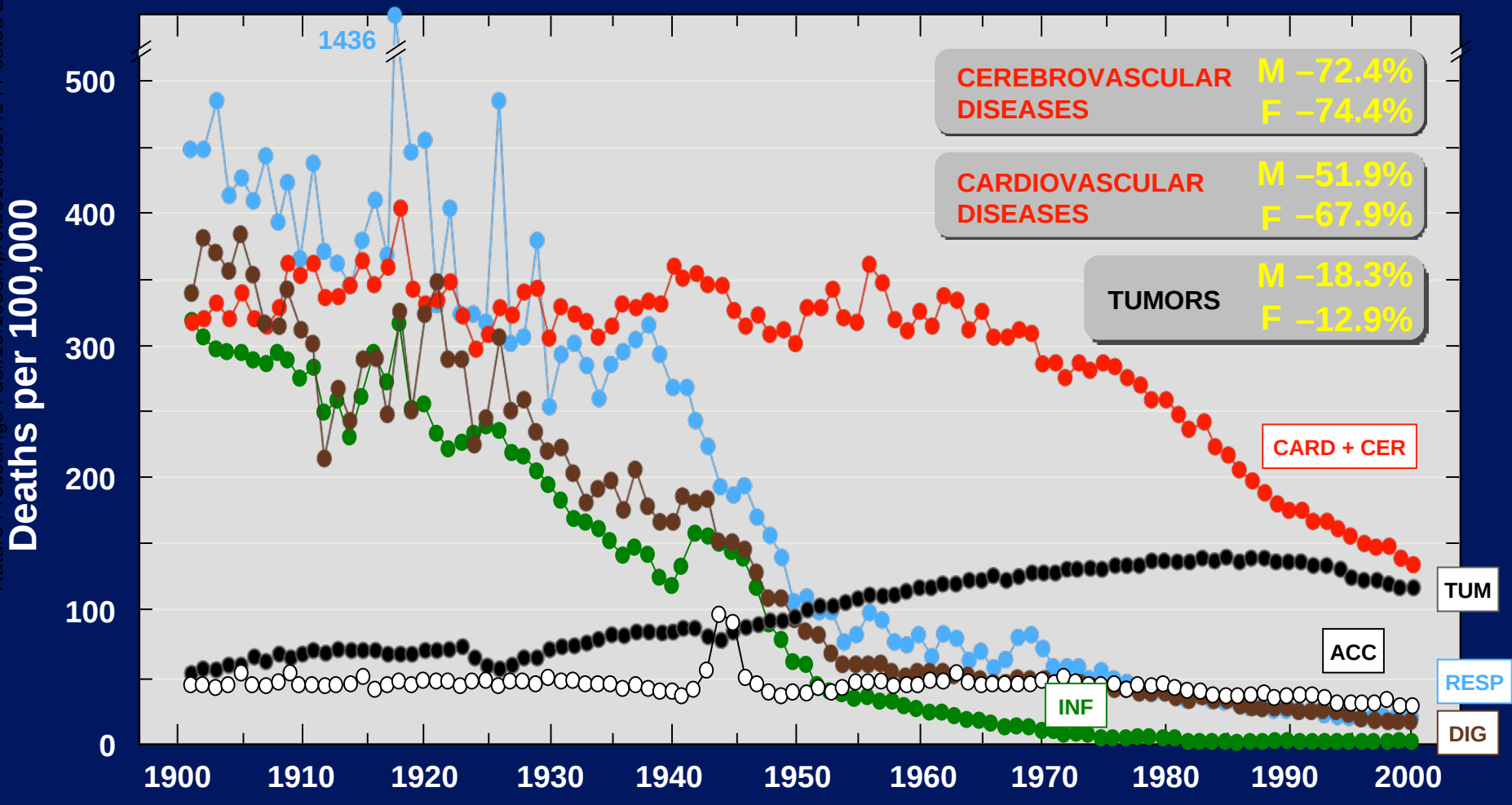

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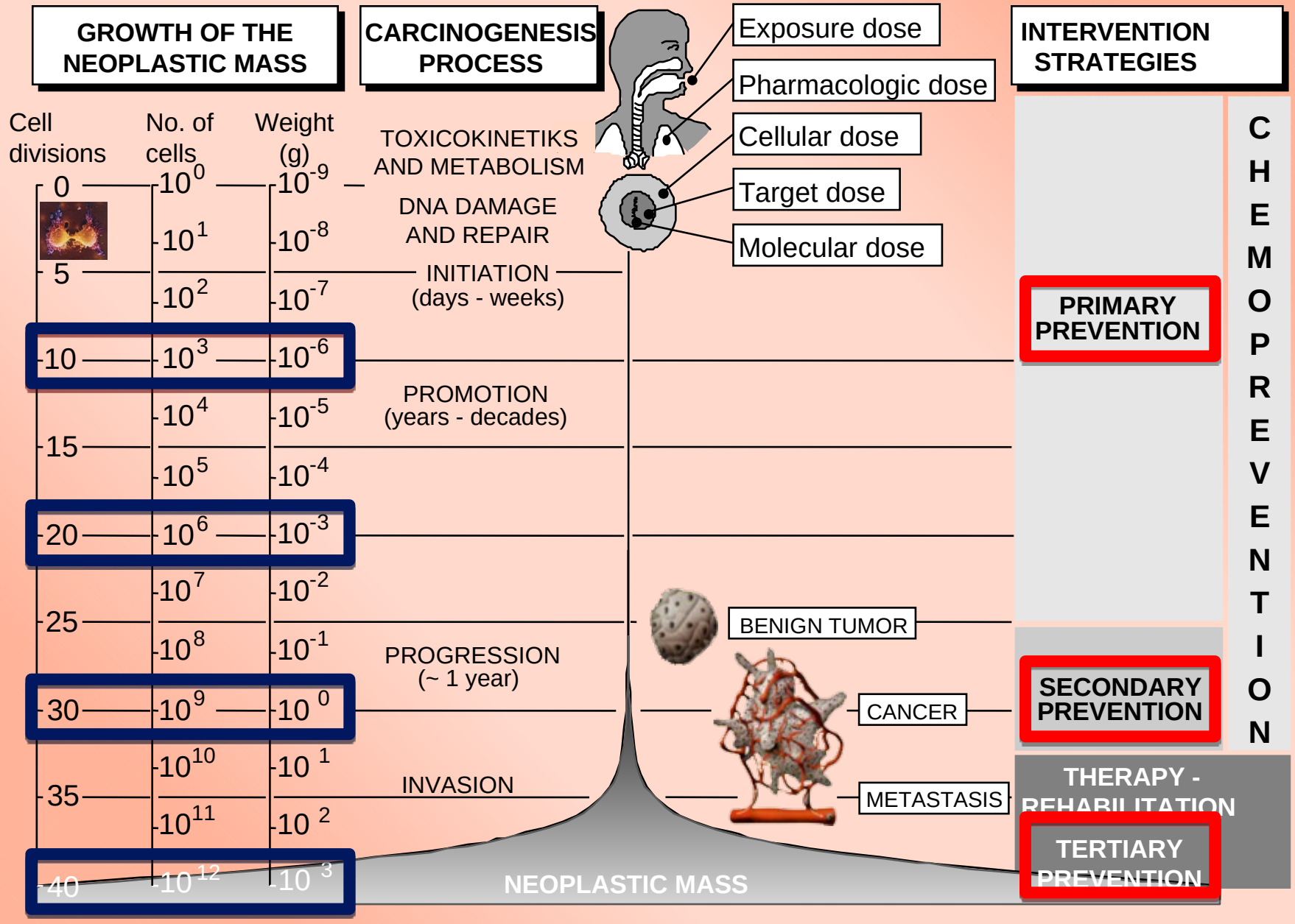

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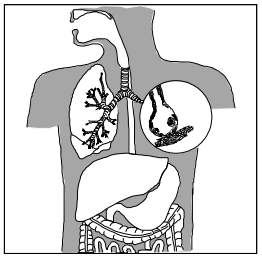
PRIMARY PREVENTION

1. *Inhibition of mutation and cancer initiation in the extracellular environment or in nontarget cells*



1.1. Inhibition of uptake of mutagens/carcinogens
- 1.1.1. Inhibition of penetration
- 1.1.2. Removal from the organism

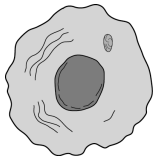
1.2. Inhibition of the endogenous formation of mutagens and carcinogens
- 1.2.1. Inhibition of the nitrosation reaction
- 1.2.2. Modification of the intestinal microbial flora

1.3. Complexation, dilution and/or deactivation of mutagens/carcinogens outside cells
- 1.3.1. By physical or mechanical means
- 1.3.2. By chemical reaction
- 1.3.3. By enzyme–catalyzed reaction

1.4. Favoring absorption of protective agents

1.5. Stimulation of trapping and detoxification in nontarget cells

2. *Inhibition of mutation and cancer initiation in target cells*



2.1. Modification of transmembrane transport
- 2.1.1. Inhibition of cellular uptake
- 2.1.2. Stimulation of extrusion outside cells

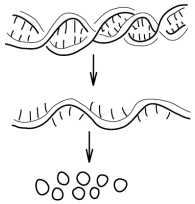
2.2. Modulation of metabolism
- 2.2.1. Inhibition of activation of promutagens/ procarcinogens by Phase I enzymes
- 2.2.2. Induction of Phase I detoxification and Phase II conjugation pathways, or acceleration of decomposition of reactive metabolites
- 2.2.3. Stimulation of activation, coordinated with detoxification and blocking of reactive metabolites

2.3. Blocking or competition
- 2.3.1. Trapping of electrophiles by either chemical reaction or enzyme–catalyzed conjugation
- 2.3.2. Antioxidant activity and scavenging of reactive species
- 2.3.3. Protection of DNA nucleophilic sites

2.4. Inhibition of cell replication

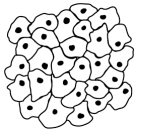
2.5. Maintenance of DNA structure and modulation of DNA metabolism and repair
- 2.5.1. Increase of fidelity of DNA replication and repair

2.5.2. Stimulation of repair and/or reversion of DNA damage
- 2.5.3. Inhibition of error-prone repair pathways
- 2.5.4. Correction of hypomethylation
- 2.5.5. Inhibition of histone deacetylation
- 2.5.6. Blocking of telomerases or inhibition of their activity



2.6. Control of gene expression
- 2.6.1. Targeted inactivation of oncogenes
- 2.6.2. Inhibitionofoncogene expression
- 2.6.3. Inhibition of oncogene sequences or activity
  - 2.6.3.1. Inhibition of translation targeted to oncogene mRNA
  - 2.6.3.2. Inhibition of transcription of specific DNA sequences
  - 2.6.3.3. Blocking of target genes
  - 2.6.2.4. Farnesyltransferase inhibition
- 2.6.4. Neutralization or post–translational modification of oncogene products
- 2.6.5. Replacement of deleted tumor suppressor genes
- 2.6.6. Mimicking the DNA binding of tumor suppressor genes by antiidiotypic antibodies
- 2.6.7. Killing of cells lacking tumor suppressor genes

3. *Inhibition of tumor promotion*



3.1. Inhibition of genotoxic effects (see 1 and 2)

3.2. Antioxidant activity and scavenging of free radicals

3.3. Antiinflammatory activity
- 3.3.1. Cyclooxygenase inhibition
- 3.3.2. Lipooxygenase inhibition
- 3.3.3. Inhibition of inducible nitric oxide synthase
- 3.3.4. Leukotriene receptor antagonism

3.4. Inhibition of proteases

3.5. Inhibition of cell proliferation
- 3.5.1. Inhibition of ornithine decarboxylase
- 3.5.2. Promoting proteasomal degradation of cyclins
- 3.5.3. Interference with multiple signaling pathways

3.6. Induction of cell differentiation

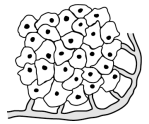
3.7. Modulation of cell apoptosis

3.8. Signal transduction modulation

3.9. Protection of intercellular communications

SECONDARY PREVENTION

4. *Inhibition of tumor progression*



4.1. Inhibition of genotoxic effects (see 1 and 2)

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- 4.5.1. Selective estrogen receptor modulation
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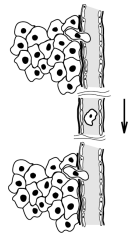
4.6. Effects on the immune system

4.7. Inhibition of angiogenesis

4.8. Antineoplastic activity by either mechanical, physical, chemical, or biological means

TERTIARY PREVENTION

5. *Inhibition of invasion and metastasis*



5.1. Antioxidant activity and scavenging of free radicals

5.2. Signal transduction modulation

5.3. Inhibition of cell proliferation (see 3.4)

5.4. Modulation of cell apoptosis

5.5. Induction of cell differentiation

5.6. Inhibition of angiogenesis

5.7. Effect on cell-adhesion molecules

5.8. Inhibition of proteases involved in basement membrane degradation and modulation of the interaction with the extracellular matrix

5.9. Activation of antimetastasis genes

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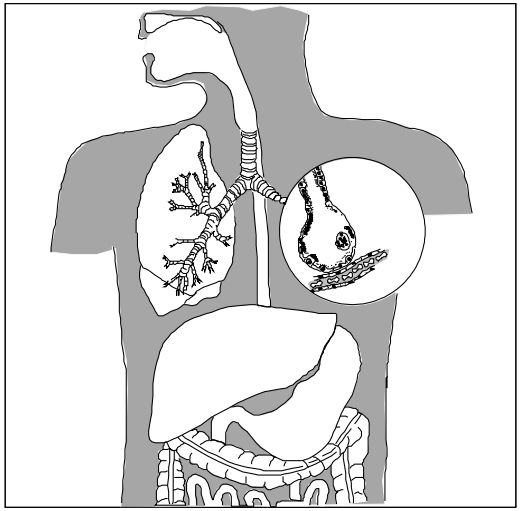

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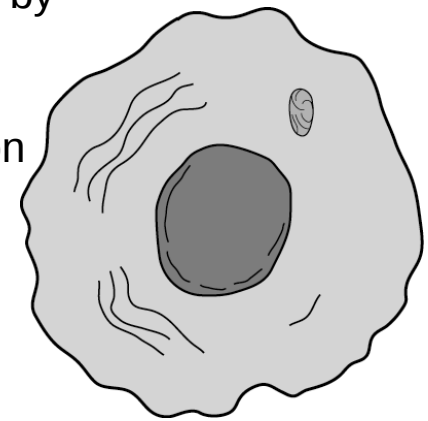

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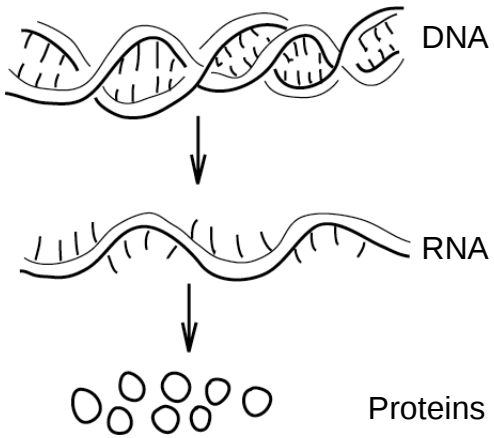

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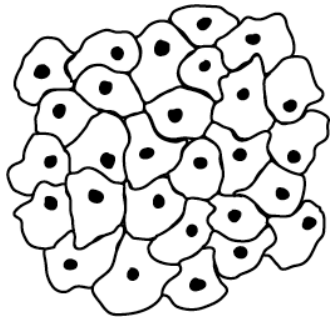

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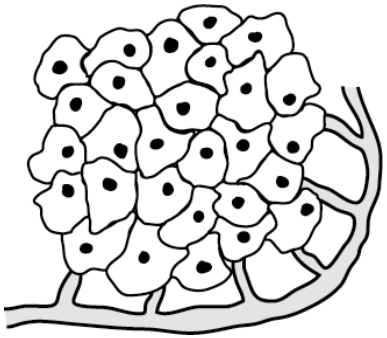

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TERTIARY PREVENTION

5. Inhibition of invasion and metastasis

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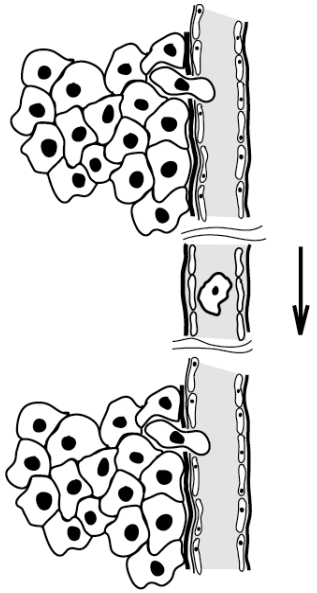

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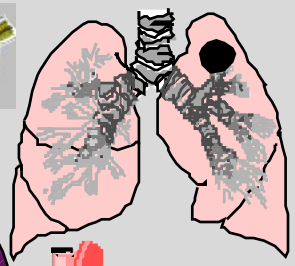
DECODING THE BLACK BOX

DISEASES



YEARS - DECADES

DAYS - WEEKS

EARLY BIOLOGICAL DAMAGE

BIOLOGICALLY EFFECTIVE DOSE

EXPOSURE MARKERS

RISK FACTORS

Analysis of metabolites

Mutagenicity of escreta

Protein adducts

DNA adducts 8-oxo-dG

Metabolic alterations

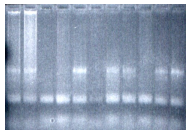
DNA damage and repair

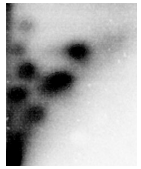
Cytogenetic effects

Activation of oncogenes

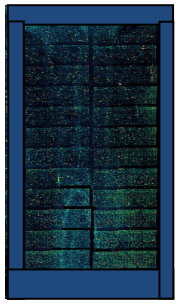
Deletion/mutation of oncosuppressor genes

Proliferation, differentiation, apoptosis, etc.





GENOME



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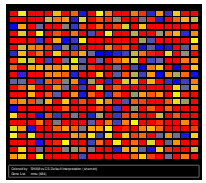
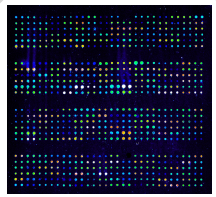


MIRNOME



PROTEOME

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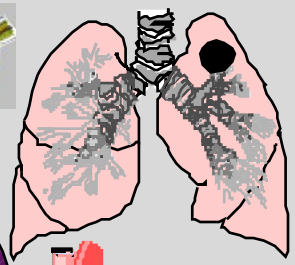
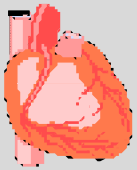
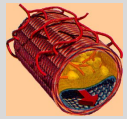
PROTECTIVE FACTORS

DISEASES







DAYS - WEEKS

YEARS - DECADES

BIOLOGICALLY EFFECTIVE DOSE

EARLY BIOLOGICAL DAMAGE

RISK FACTORS

STOP

EXPOSURE MARKERS

Analysis of metabolites

Mutagenicity of escreta

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DNA damage and repair

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Activation of oncogenes

Deletion/mutation of oncosuppressor genes

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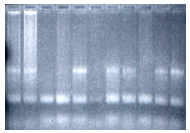

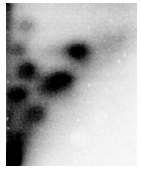

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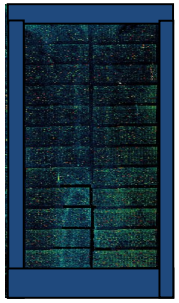
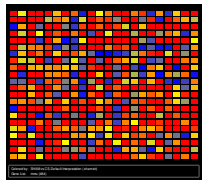
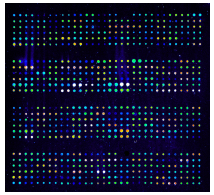


TRANSCRIPTOME



MIRNOME



PROTEOME

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Cancer / Physical agents

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

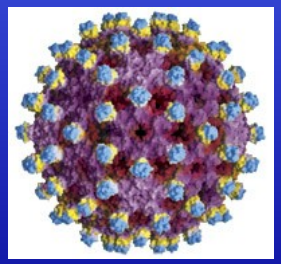
Pathological conditions

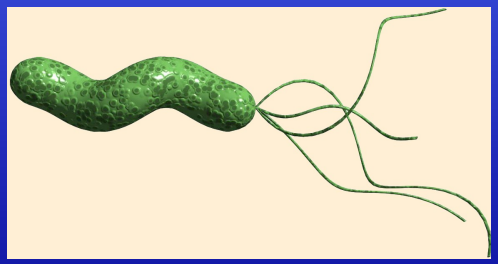
Cancer / Chemicals and complex mixtures

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Cancer / Microbial diseases

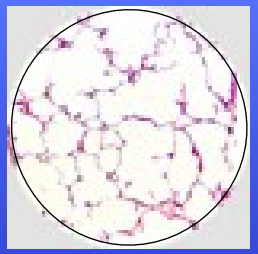




Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

COPD



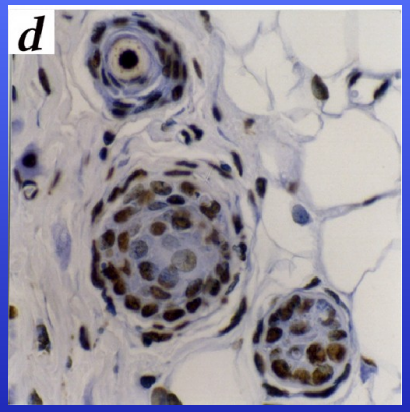
(A. Izzotti et al., FASEB J. 17, 1127-29, 2003)

(R. Balansky et al., Carcinogenesis 30, 1398-401, 2009)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Alopecia

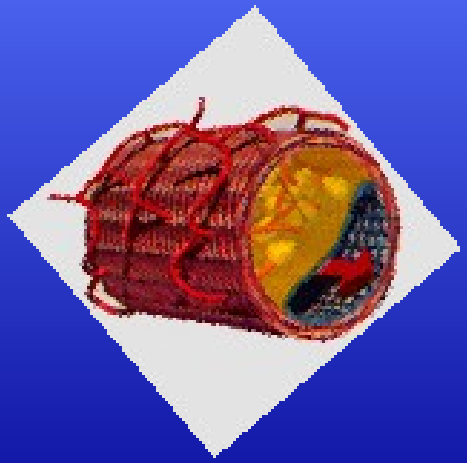


(R. Balansky et al., PNAS USA 103, 7823-28, 2006)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

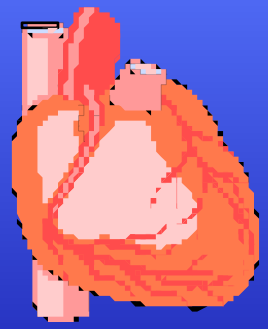
Atherosclerosis



Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Heart diseases

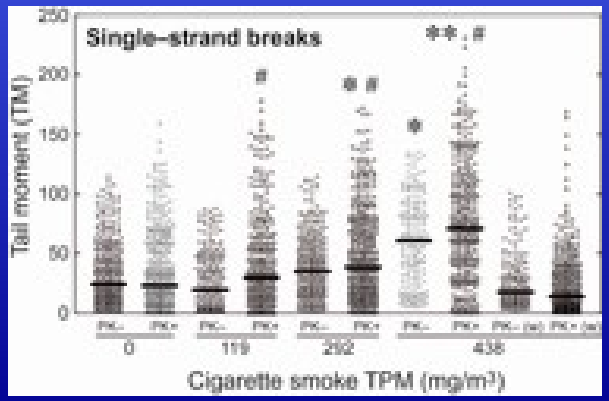


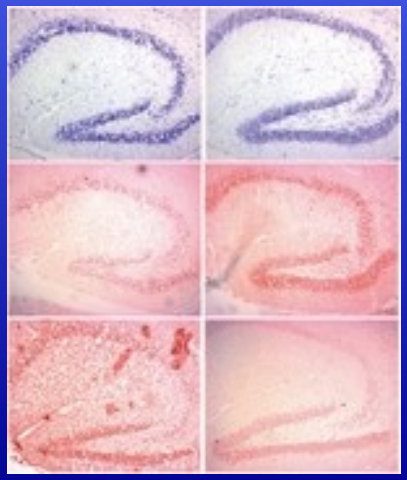
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Neurodegenerative diseases

(S. La Maestra et al., 2010)

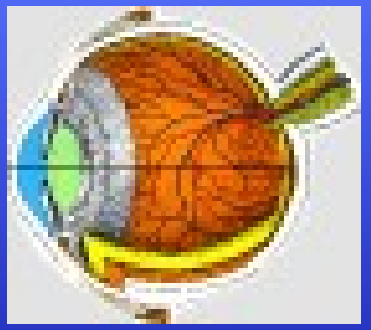




Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Eye diseases



(A. Izzotti et al., Am. J. Med. 114, 638-646, 2003)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Pathological conditions

Rare genetic diseases

(A. Izzotti et al., Neurology 71, 610-2, 2008)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Physiological situations

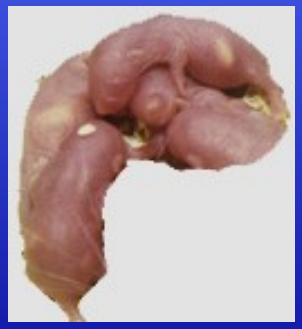
Pregnancy

(A. Izzotti et al., FASEB J. 17, 1127-9, 2003)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Physiological situations

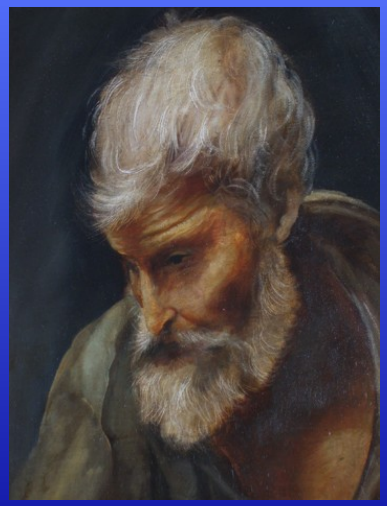
Perinatal period



Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Physiological situations

Aging



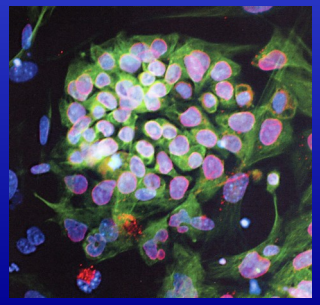
(R. Balansky et al., Cancer Res. 56, 1642-7, 1996)

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Physiological situations

Stem cells

(S. De Flora et al., Int. J. Oncol. 29, 521-529, 2006)

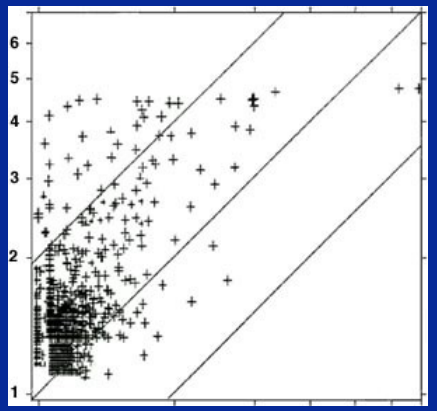
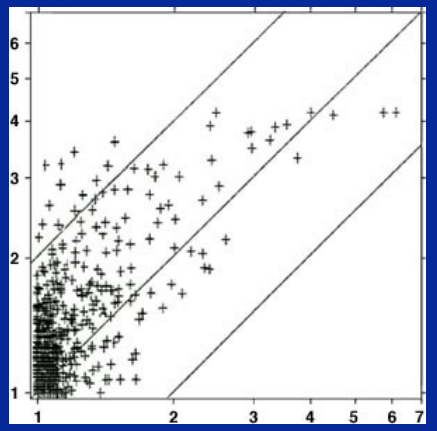


GENOMIC CHANGES IN MOUSE LUNG AT BIRTH

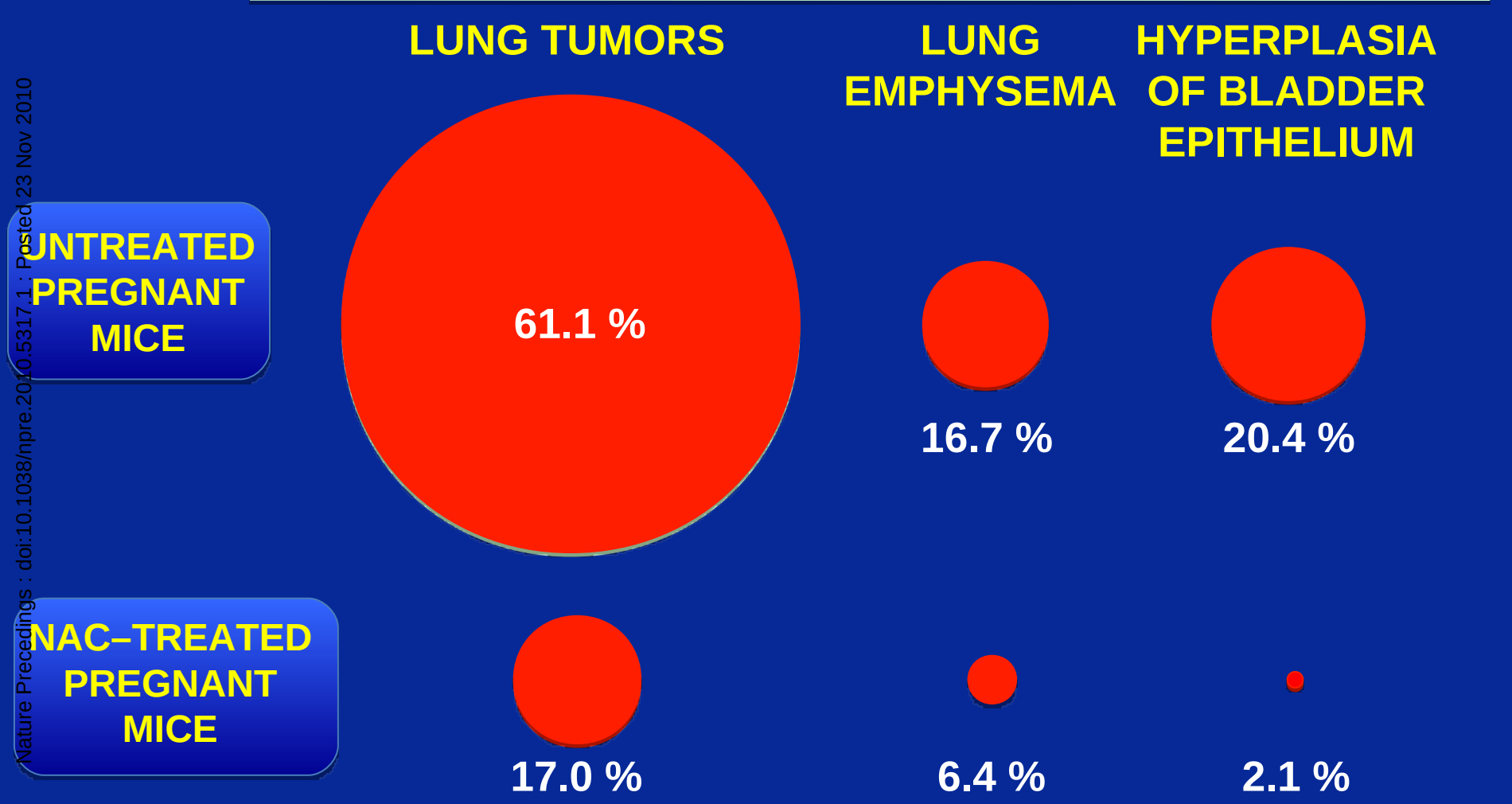
A. Izzotti et al., Mutat. Res. (Rev. Genetic Toxicol.), 544, 441-449, 2003

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Newborn mice / fetuses

	8-oxo-dGuo	DNA adducts	Expression of 746 genes
UNTREATED PREGNANT MICE	1.9 P < 0.05	5.0 P < 0.001	
NAC–TREATED PREGNANT MICE	0.9 NS	2.0 NS	

MICE EXPOSED TO SMOKE AFTER BIRTH



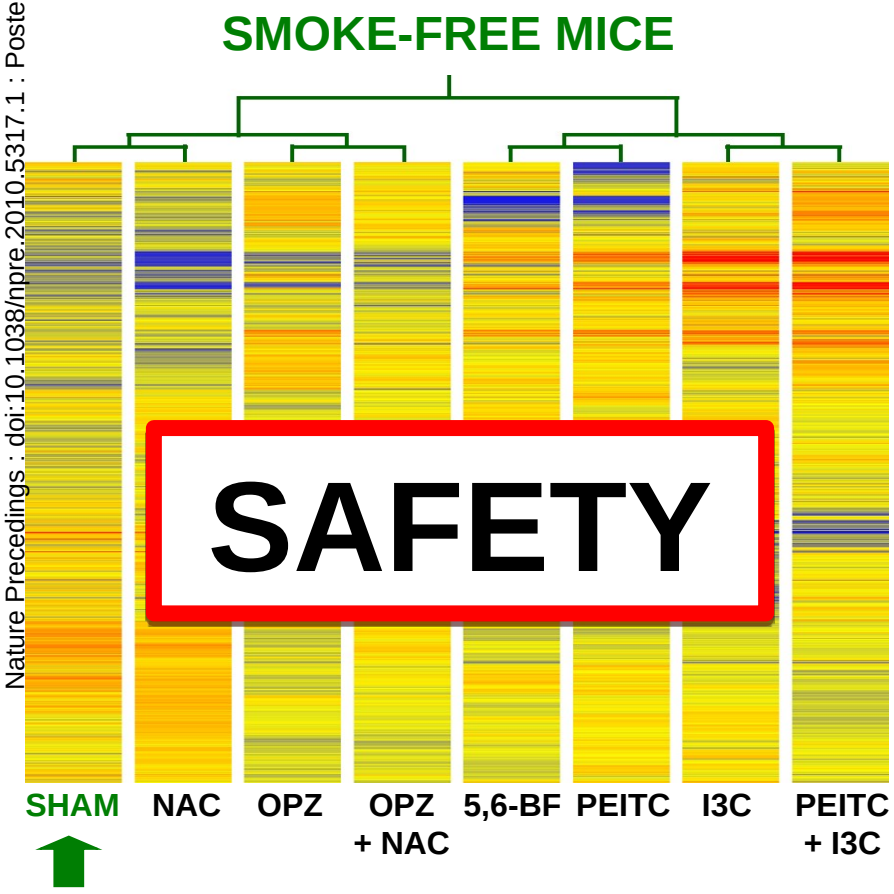
R. Balansky et al., Carcinogenesis 30, 1398-1401, 2009

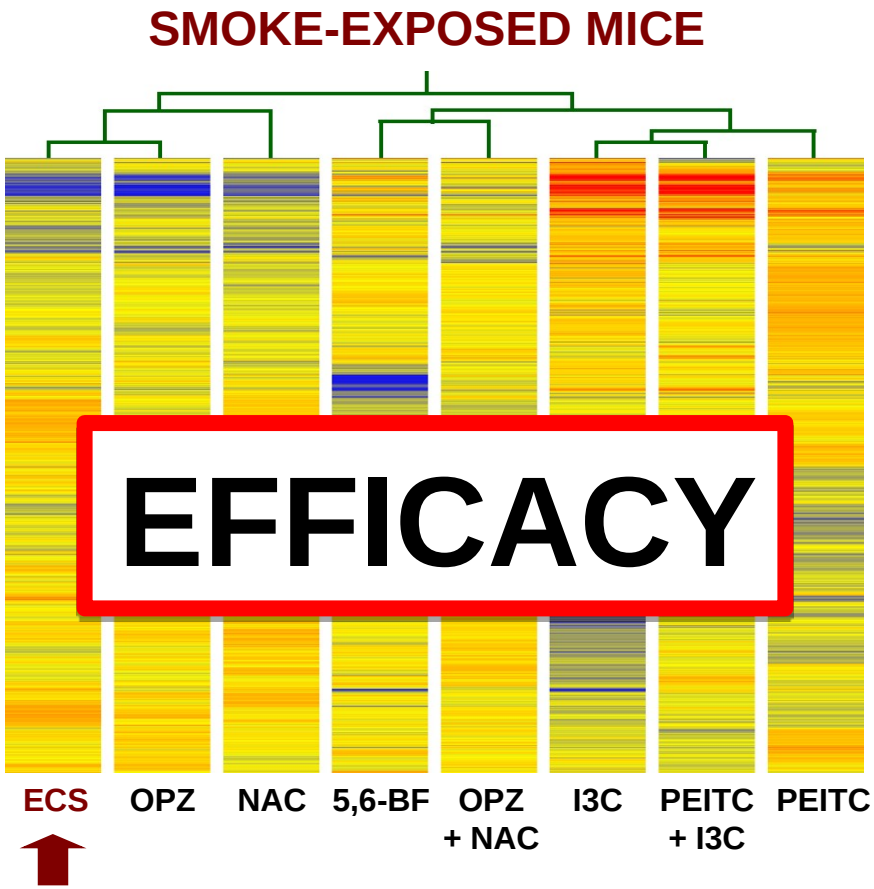
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

EXPRESSION OF 4858 GENES IN MOUSE LUNG

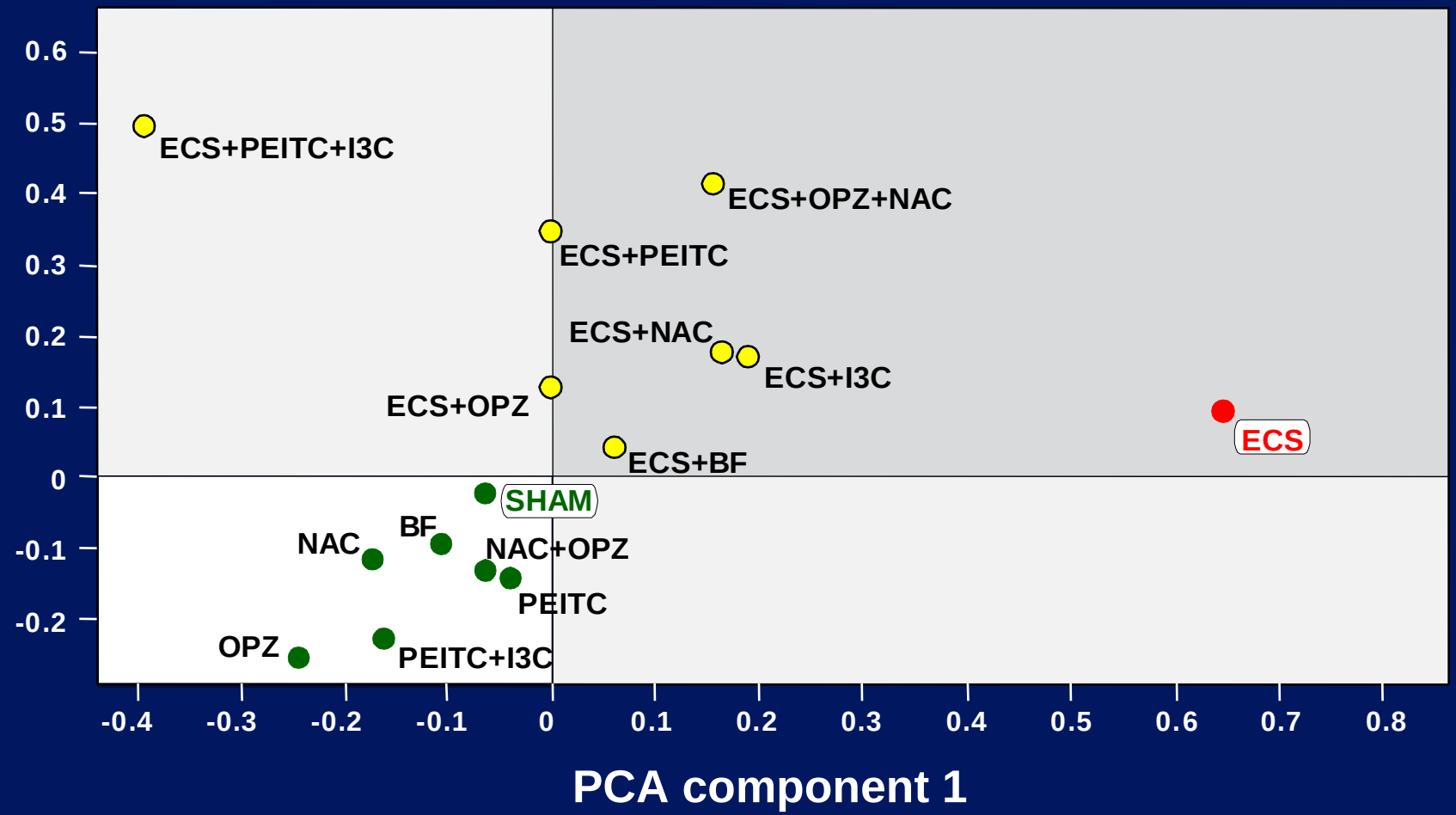
A. Izzotti et al., Mutat. Res. 591, 212–223, 2005





EFFECT OF CIGARETTE SMOKE (ECS) AND CHEMOPREVENTIVE AGENTS ON miRNA EXPRESSION IN RAT LUNG

Nature Precedings : doi : 10.1038/npre.2010.5317.1 : Posted 23 Nov 2010



A. Izzotti et al, Cancer Prev. Res. 3, 62–72, 2010

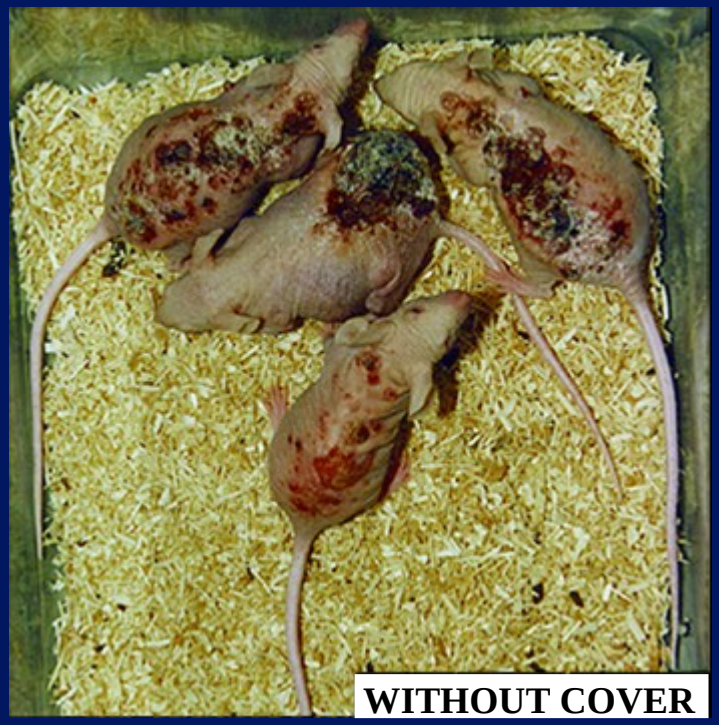
EXPOSURE OF HAIRLESS MICE TO HALOGEN LAMPS

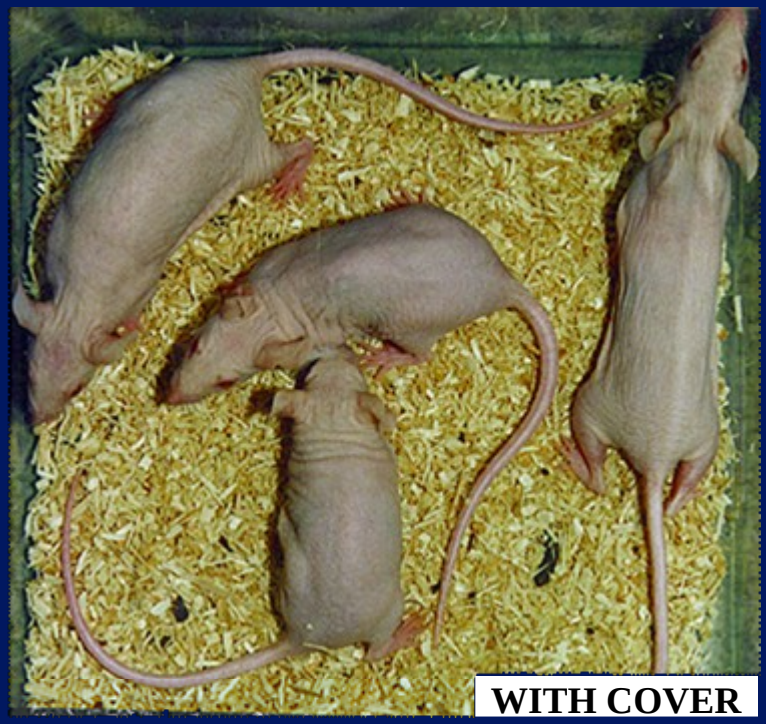
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

SKIN CARCINOGENICITY OF HALOGEN LAMPS

S. De Flora & F. D'Agostini, Nature 356, 569, 1992

F. D'Agostini & S. De Flora, Cancer Res. 54, 5081–5, 1994





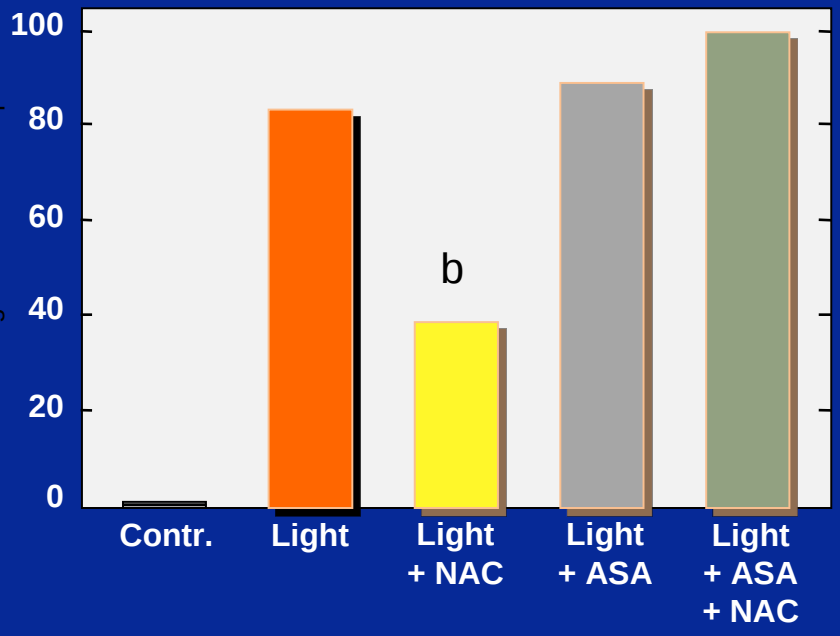
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

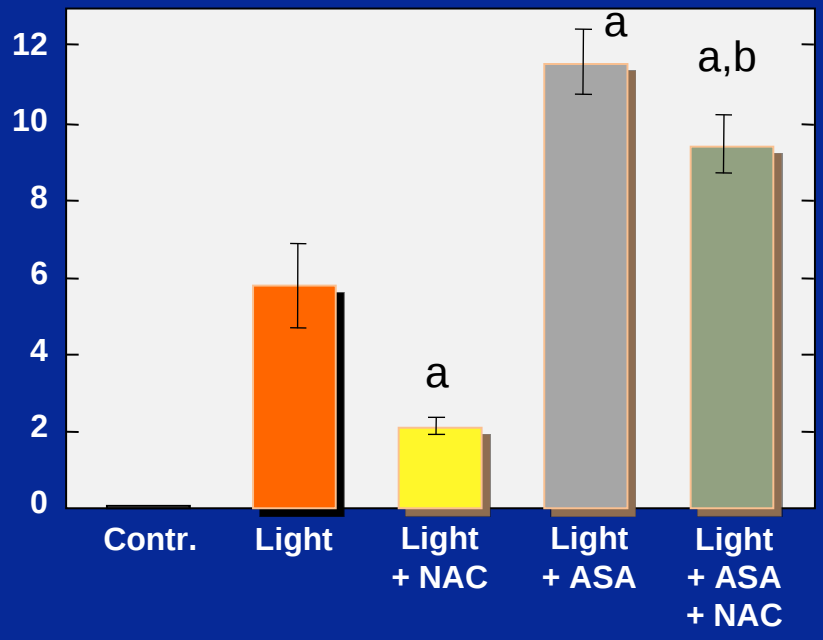
MODULATION OF LIGHT-INDUCED SKIN TUMORS BY *N*–ACETYLCYSTEINE (NAC) AND ASCORBIC ACID (ASA)

F. D'Agostini et al., Carcinogenesis 26, 657–664, 2005

Incidence (%)



Multiplicity (mean ± SE)



[a]*P* <0.001, as compared with Light; [b]*P* <0.001, as compared with Light + AsA

THE PREVENTION OF INFECTION–ASSOCIATED CANCERS

(S. De Flora and P. Bonanni, 2010)

Pathogen	IARC Group	Main asociated cancer
Hepatitis viruses		
HBV	1	Hepatocellular carcinoma
HCV	1	Hepatocellular carcinoma
HDV	3	None
Papillomaviruses		
α HPV type 16	1	Cancers at several sites
α HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	1	Cervical cancer
α HPV type 68	2A	Cervical cancer
α HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97	2B	Cervical cancer
β HPV type 5 and 8	2B	Skin cancer
α HPV type 6 and 11	3	None
Other β and γ HPV types	3	None
Polyomaviruses		
JCV	NA	CNS tumors and colorectal cancer?
MCV	NA	Skin cancer (Merkel cell carcinoma)
SV40	NA	Malignant mesothelioma ?
Herpesviruses		
EBV or HHV4	1	Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma
KSHV or HHV8	1	Kaposi's sarcoma, primary effusion lymphoma

Pathogen	IARC Group	Main asociated cancer
Retroviruses		
HTLV-I	1	Adult T-cell leukemia/lymphoma
HTLV-II	3	None
HIV-I	1	Kaposi's sarcoma, non-Hdgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anus cancer, conjunctive cancer
HIV-II	2B	Kaposi's sarcoma, non-Hodgkin's lymphoma
HERV-K	NA	Human breast cancer
Helicobacter pylori	1	Gastric cancer, MALT
Schistosomes		
S. haematubium	1	Urinary bladder cancer
S. japonicum	2B	Colorectal and liver cancers
S. mansoni	3	None
Liver flukes		
Opistorchis viverrini	1	Cholangiocarcinoma
Opistorchis felineus	3	None
Chlonorchis sinensis	1	Cholangiocarcinoma

Infectious agents cause 17% of all cancers worldwide, 26% in developing world, 8% in developed world

D.M. Parkin, Int.J.Cancer 15, 3030-44, 2005

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

THE PREVENTION OF INFECTION–ASSOCIATED CANCERS

(S. De Flora and P. Bonanni, 2010)

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HCV		
HDV		
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α HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59		
α HPV type 68		
α HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97		
β HPV type 5 and 8	2B	Skin cancer
α HPV type 6 and 11	3	None
Other β and γ HPV types	3	None
Polyomaviruses		
JCV	NA	CNS tumors and colorectal cancer?
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SV40	NA	Malignant mesothelioma ?
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EBV or HHV4	1	Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma
KSHV or HHV8	1	Kaposi's sarcoma, primary effusion lymphoma

4.9% of all cancers
85.5% of all HCCs

5.2% of all cancers
100% of cervix cancers

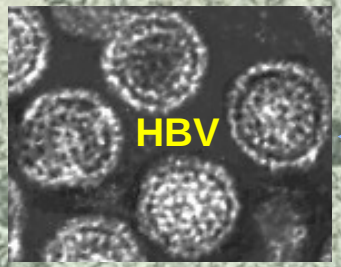
Pathogen	IARC Group	Main asociated cancer
Retroviruses		
HTLV-I	1	Adult T-cell leukemia/lymphoma
HTLV-II	3	None
HIV-I	1	Kaposi's sarcoma, non-Hdgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anus cancer, conjunctive cancer
HIV-II	2B	Kaposi's sarcoma, non-Hodgkin's lymphoma
HERV-K		
Helicobacter pylori		
Schistosomes		
S. haematubium	1	Urinary bladder cancer
S. japonicum	2B	Colorectal and liver cancers
S. mansoni	3	None
Liver flukes		
Opistorchis viverrini	1	Cholangiocarcinoma
Opistorchis felineus	3	None
Chlonorchis sinensis	1	Cholangiocarcinoma

5.5% of all cancers
63.4% of stomach cancers

Infectious agents cause 17% of all cancers worldwide, 26% in developing world, 8% in developed world

D.M. Parkin, Int.J.Cancer 15, 3030-44, 2005

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010



Prevention of HBV infection

PRIMARY PREVENTION OF HEPATOCELLULAR CARCINOMA

Regulations

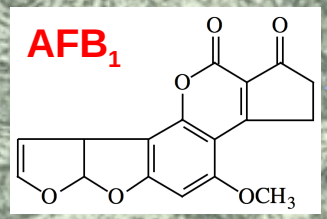
Avoidance of exposure

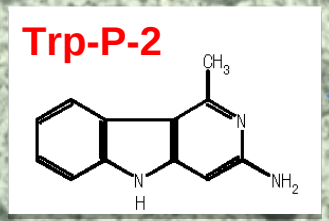
Health education

Chemoprevention

Diet

Drugs





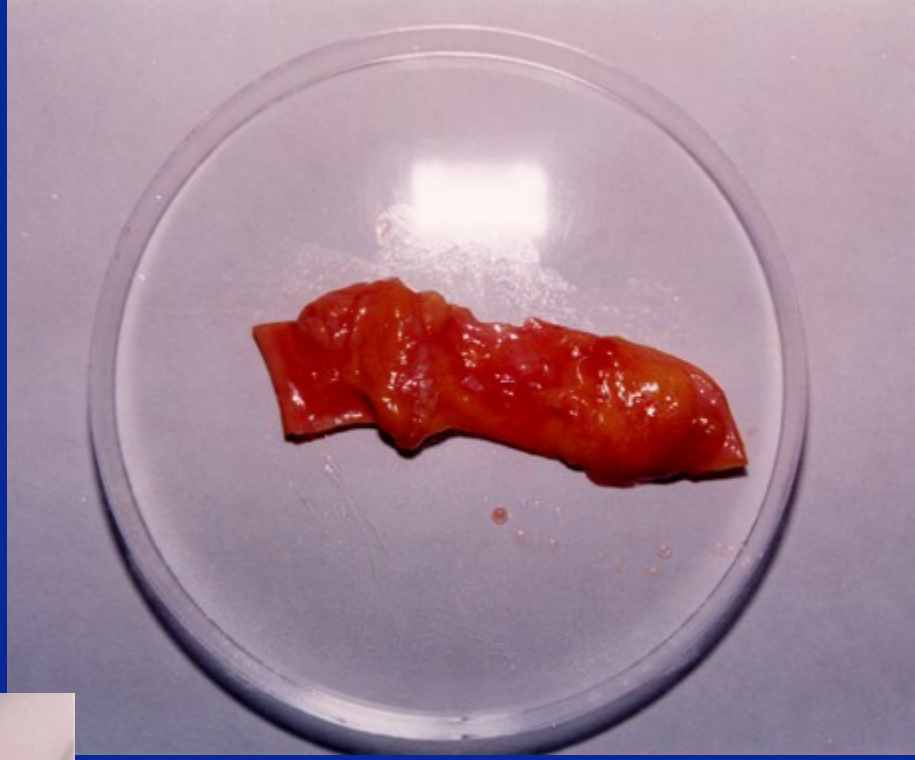
S. De Flora et al, Cancer Res. 47, 4052–8, 1987; Carcinogenesis 10, 1099–1106, 1989

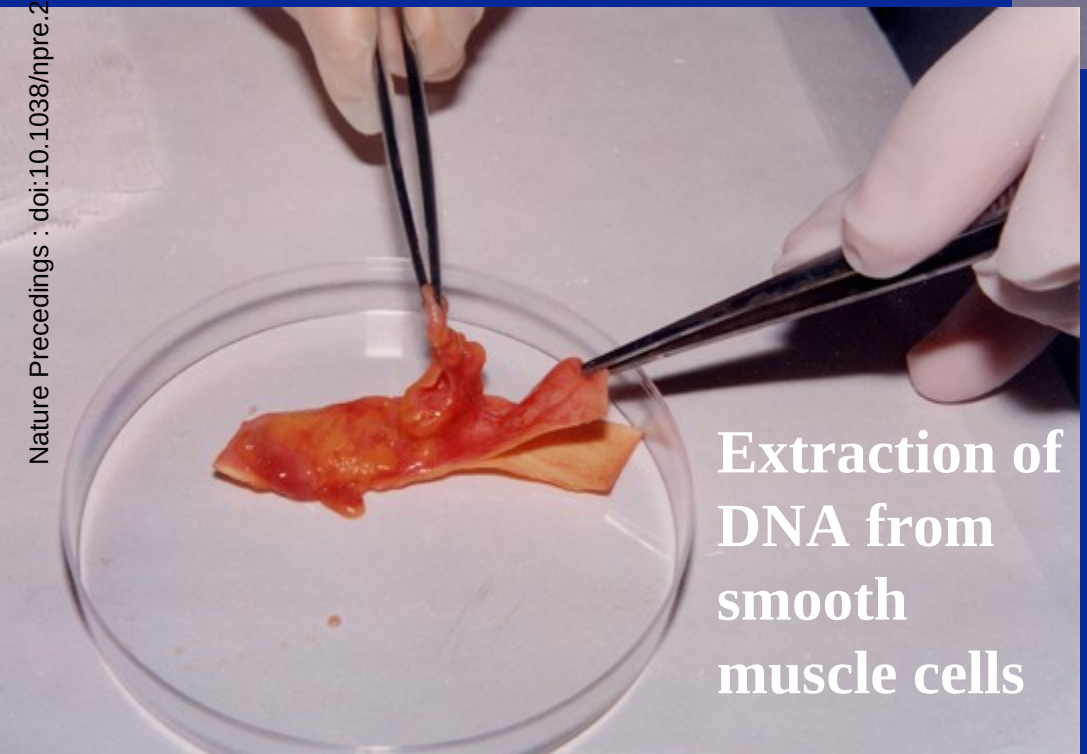
A.Izzotti et al, Chem.-Biol. Int. 97, 273–285, 1995

A. Camoirano et al, Cancer Epid. Biol. Biom. 10, 775–783, 2001

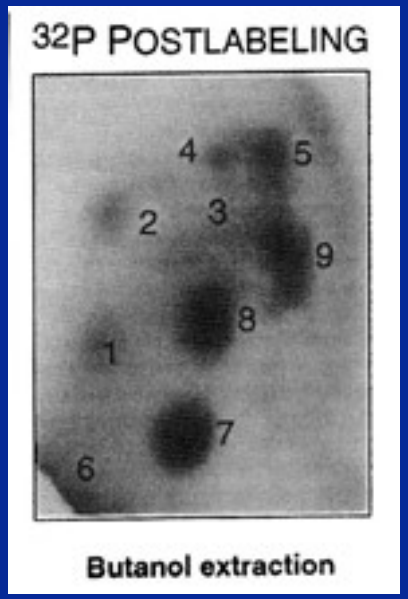
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

HUMAN ABDOMINAL AORTA WITH ATHEROSCLEROTIC LESIONS





Extraction of DNA from smooth muscle cells

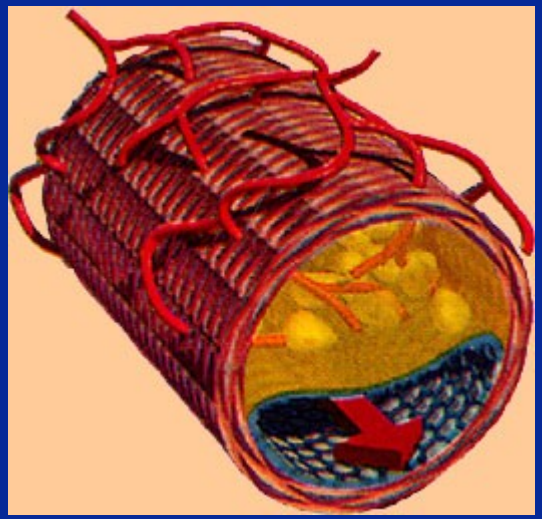


MOLECULAR EPIDEMIOLOGY OF ATHEROSCLEROSIS

S. De Flora et al., FASEB J. 11: 1021-1031, 1997

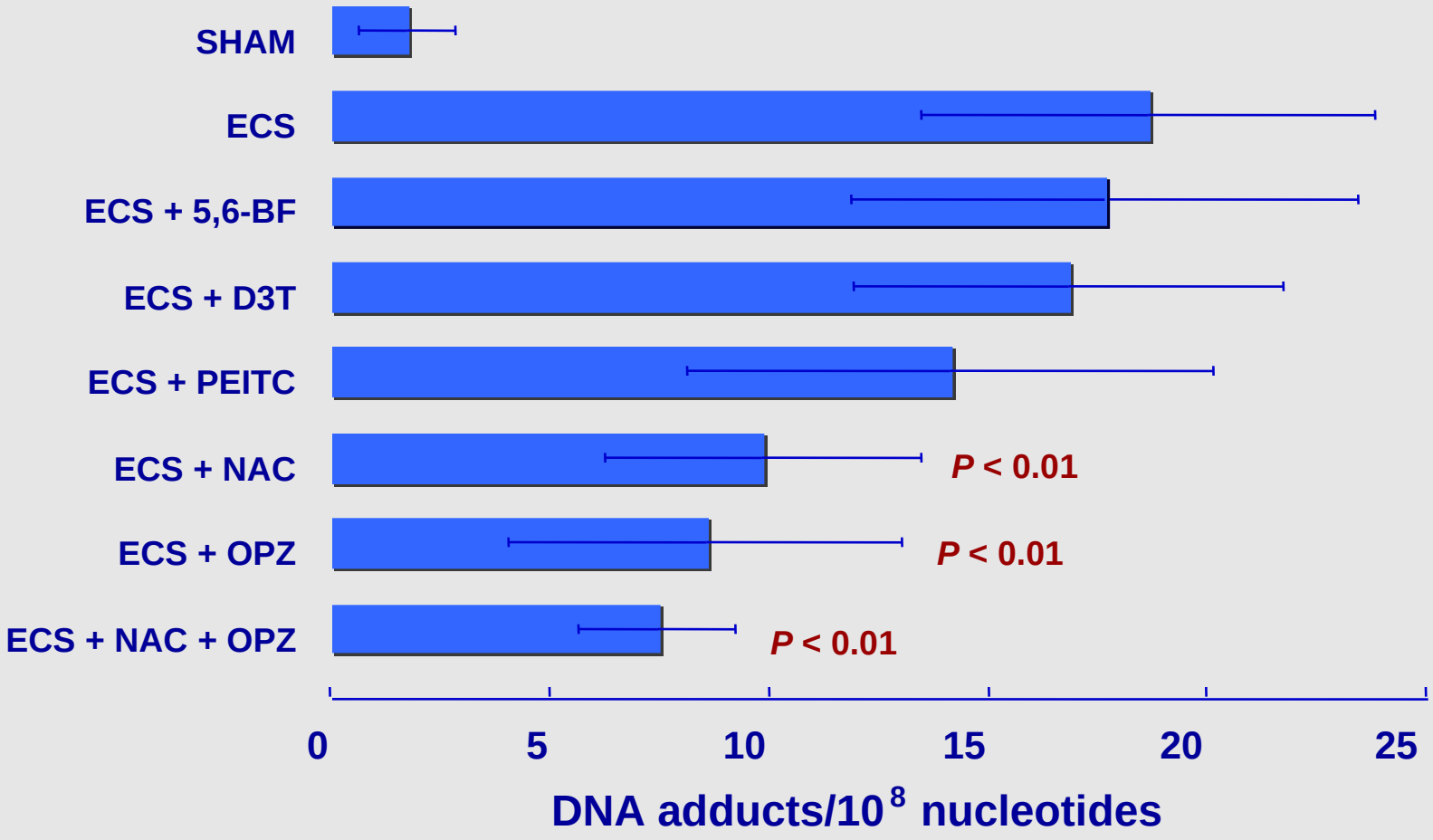
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

The levels of ^{32}P postlabelled DNA adducts in the aorta from 85 atherosclerotic patients were significantly correlated with:



- -Age of patients
- -Number of cigarettes smoked currently
- -High blood pressure
- -Blood triglycerides
- -Blood cholesterol (total/HDL)
- -SFS-positive DNA adducts
- -Oxidative DNA damage (8-OH-dG)

MODULATION OF DNA ADDUCTS BY DIETARY AGENTS IN THE AORTA OF SMOKE-EXPOSED RATS

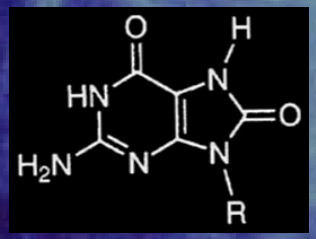


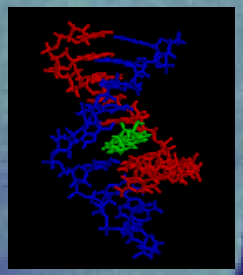
A. Izzotti et al., Mutat. Res. 494, 97-106, 2001

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

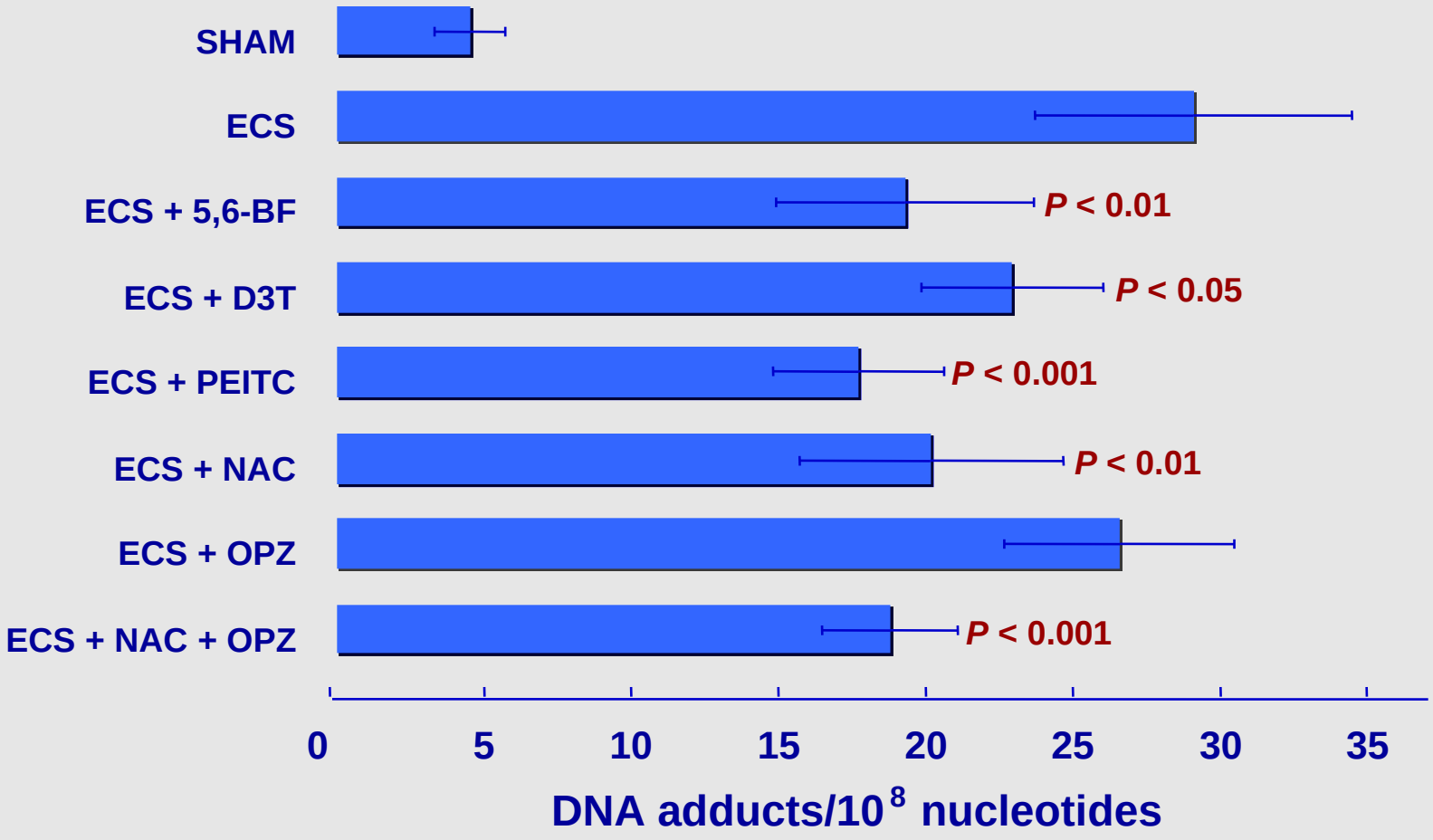
Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

8–oxo–dG **DNA ADDUCTS**





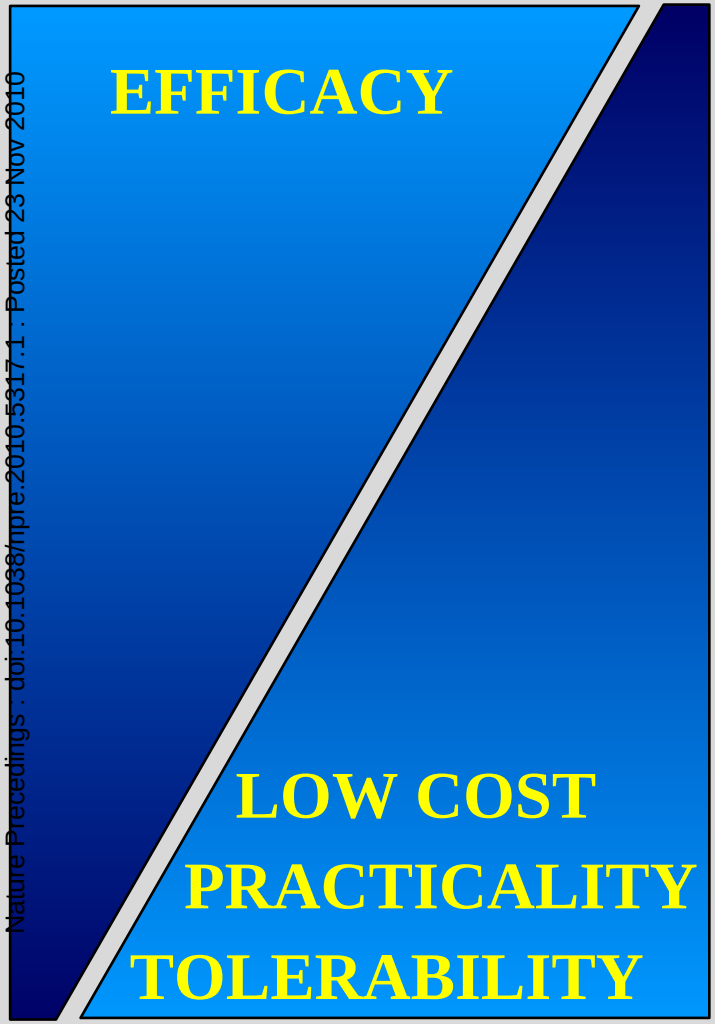
MODULATION OF DNA ADDUCTS BY DIETARY AGENTS IN THE HEART OF SMOKE-EXPOSED RATS



S. De Flora and A. Izzotti, Mutat. Res., 2009

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

Nature Precedings : doi:10.1038/npre.2010.5317.1 : Posted 23 Nov 2010

REQUIREMENTS	INTERVENTION (Targets)
	THERAPY (Cancer patients)
	TERTIARY PREVENTION (Treated cancer patients)
	EARLY INTERVENTION (Cancer patients in preclinical or early stage)
	PREVENTION OF PROGRESSION (Individuals affected by precancerous lesions)
	TARGETED CHEMOPREVENTION (High risk individuals)
	PUBLIC HEALTH INTERVENTION (Healthy subjects in the population)

S. De Flora et al., IARC Sci. Publ. No. 139, 1996, pp. 291-301

PHASE II CHEMOPREVENTION TRIAL WITH NAC IN DUTCH SMOKERS

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		DNA adducts/ 10^8 nucleotides in BAL cells	8–oxo–dGuo/ 10^5 nucleotides in BAL cells	Micronuclei in mouth cells (‰)
Placebo	T_0	6.0 ± 0.7	4.8 ± 0.5	1.2 ± 0.3
	T_6	5.9 ± 0.7	3.2 ± 0.8	1.0 ± 0.2
NAC	T_0	6.0 ± 0.9	4.9 ± 0.7	1.3 ± 0.3
	T_6	4.3 ± 0.8	1.8 ± 0.3	0.9 ± 0.3

Statistically significant as compared to T_0

F.J. van Schooten et al., Cancer Epidem. Biomarkers Prev. 11, 167-175, 2002

PHARMACOGENOMICS / NUTRIGENOMICS OF CHEMOPREVENTIVE AGENTS

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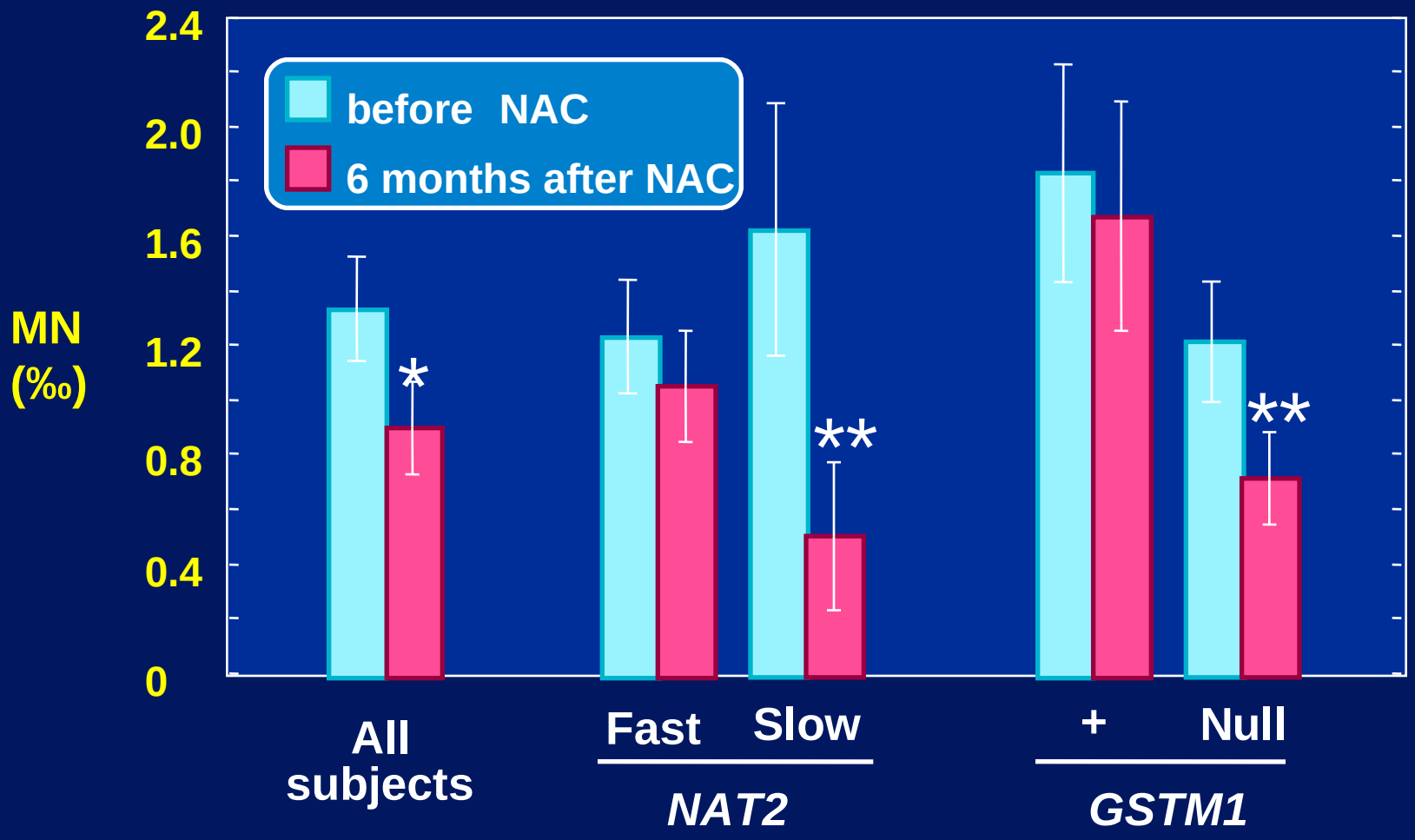

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