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

MECHANISMS OF INHIBITION OF CIGARETTE SMOKE GENOTOXICITY AND CARCINOGENICITY

R. Balansky[1,2], F. D'Agostini[2], A. Izzotti[2], P. Kalpakam[3], V.E. Steele[4], S. De Flora[2]

[1] National Center of Oncology, Sofia, Bulgaria

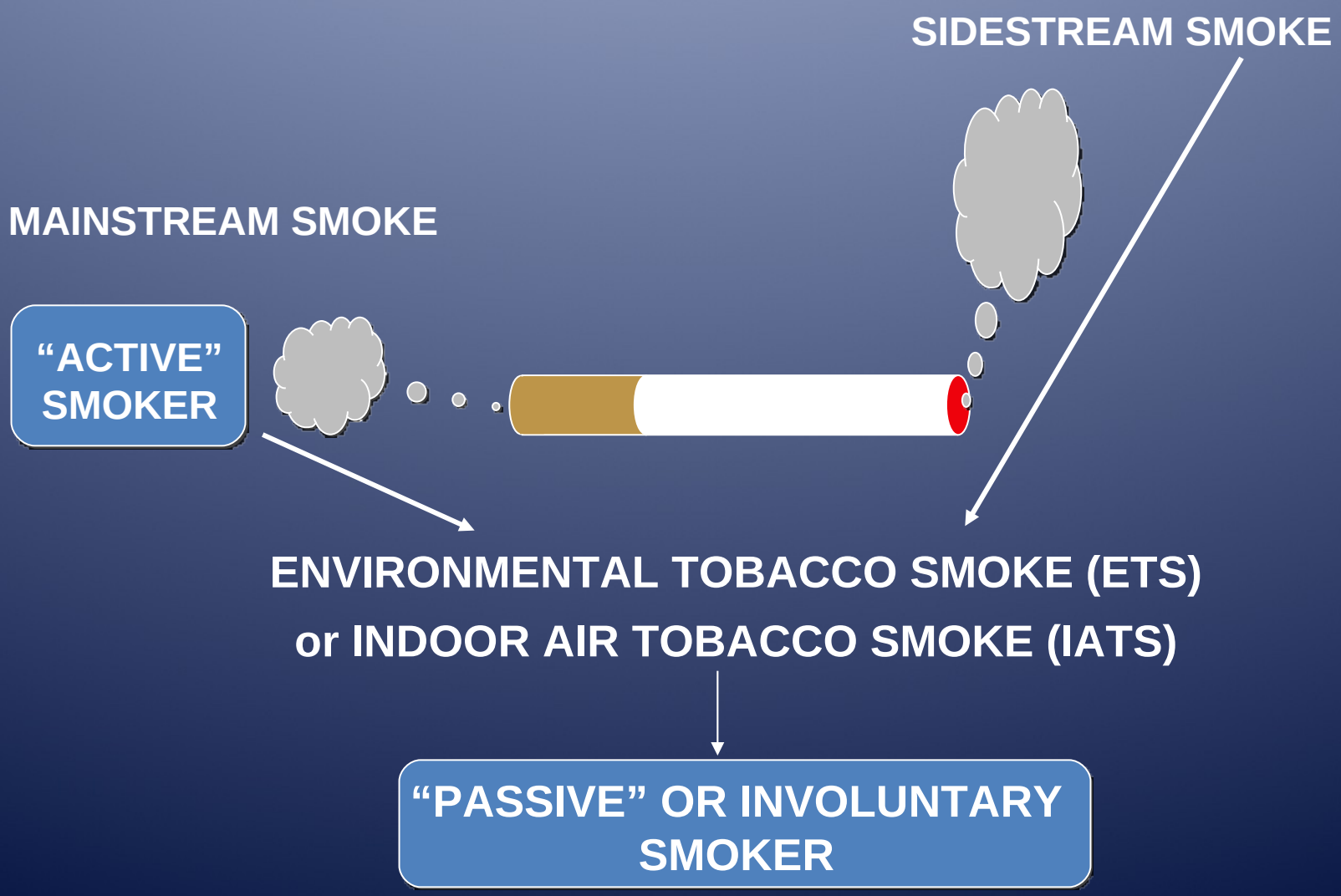
[2] Department of Health Sciences, University of Genoa, Italy

[3] National Institute of Nutrition, Hyderabad, India

[4] National Cancer Institute, Rockville, MD, USA


TOBACCO KUTZ
NICOTIANA
TOBACUM

ACTIVE SMOKE AND PASSIVE SMOKE



CIGARETTE SMOKING AND CANCER

Evidence for causal association

Lung (90%)

Urinary tract (bladder, ureter, and renal pelvis)
Oral cavity
Nasal cavity and paranasal sinuses
Naso-, oro-, and hypopharynx
Larynx
Oesophagus
Stomach
Liver
Pancreas
Uterine cervix
Bone marrow (myeloid leukemia)

Inconclusive evidence for association

Colon-rectum

Evidence for lack of association

Breast
Endometrium
Prostate ?

IARC Vol. 83, 2004

Tobacco Smoke and Involuntary Smoking

DEATHS ATTRIBUTABLE TO TOBACCO SMOKE

TOTAL TUMORS	30%
LUNG TUMORS	85%
AERODIGESTIVE TRACT TUMORS	50–70% synergism with alcohol
CARDIOVASCULAR DISEASES	30% synergism with other risk factors
COPD	75%

EU ~ 500,000 deaths / year

USA ~ 500,000 deaths / year

TOBACCO SMOKE AS A COMPLEX MIXTURE

Balansky RM, Blagoeva PM, Mircheva ZI.
Investigation of the mutagenic activity of tobacco smoke.
Mutat. Res. 1987 May;188(1):13-9.

Balansky RM, Blagoeva PM, Mircheva ZI.
The mutagenic and clastogenic activity of tobacco smoke.
Mutat. Res. 1988 Jul;208(3-4):237-41.

Balansky RM, Blagoeva PM.
Tobacco smoke-induced clastogenicity in mouse fetuses and in newborn mice.
Mutat. Res. 1989 May;223(1):1-6.

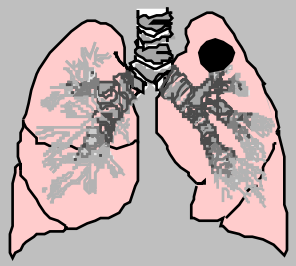
Balansky RM, Blagoeva PM, Mircheva ZI.
Modulation of genotoxic activity of tobacco smoke.
IARC Sci. Publ. 1991;(105):535-7.

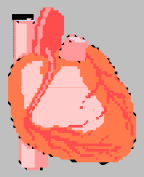
PROTECTIVE FACTORS

Targets for chemoprevention

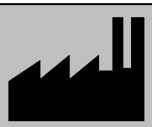
- Addicted current smokers
- Passive smokers
- Ex-smokers
- Other exposures

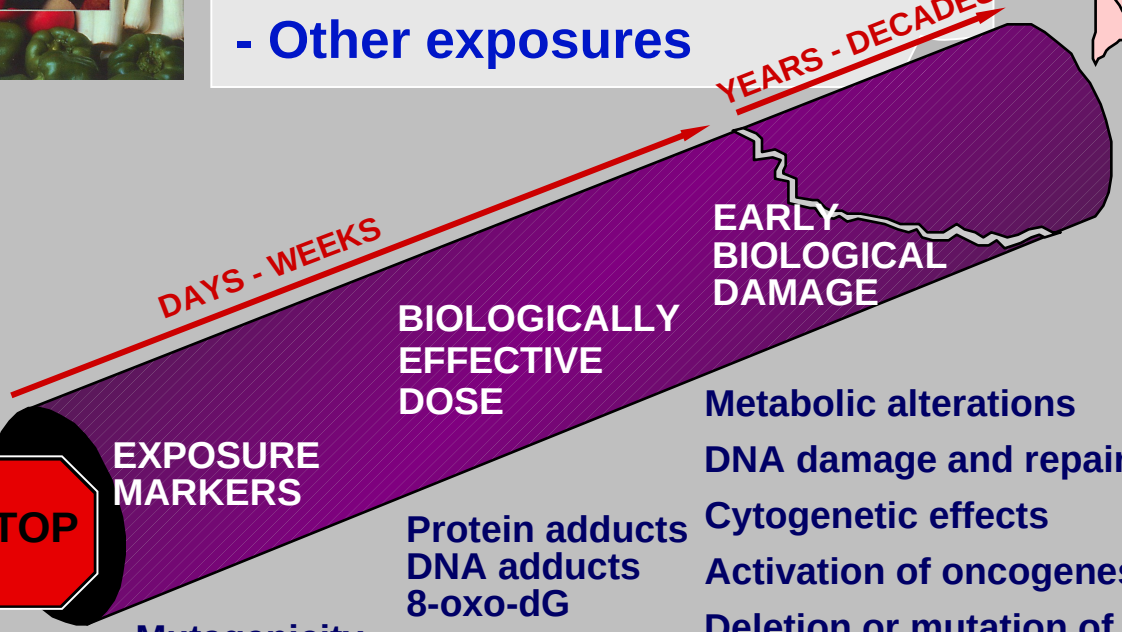
DISEASES





RISK FACTORS





Mutagenicity of escreta

Protein adducts
DNA adducts
8-oxo-dG

Metabolic alterations

DNA damage and repair

Cytogenetic effects

Activation of oncogenes

Deletion or mutation of oncosuppressor genes

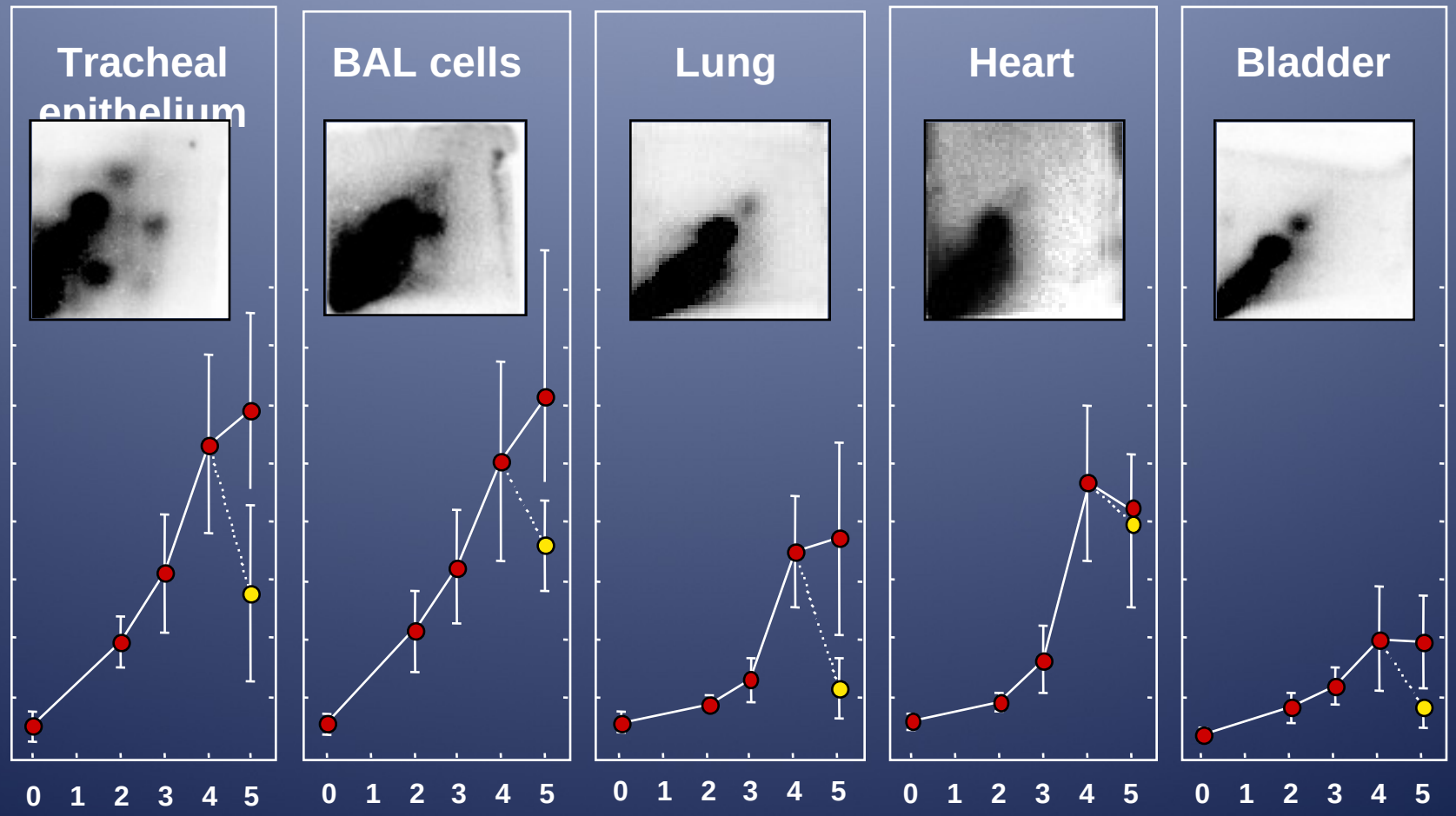
Effects on proliferation, differentiation, apoptosis, etc.

Multigene expression

microRNA profiles

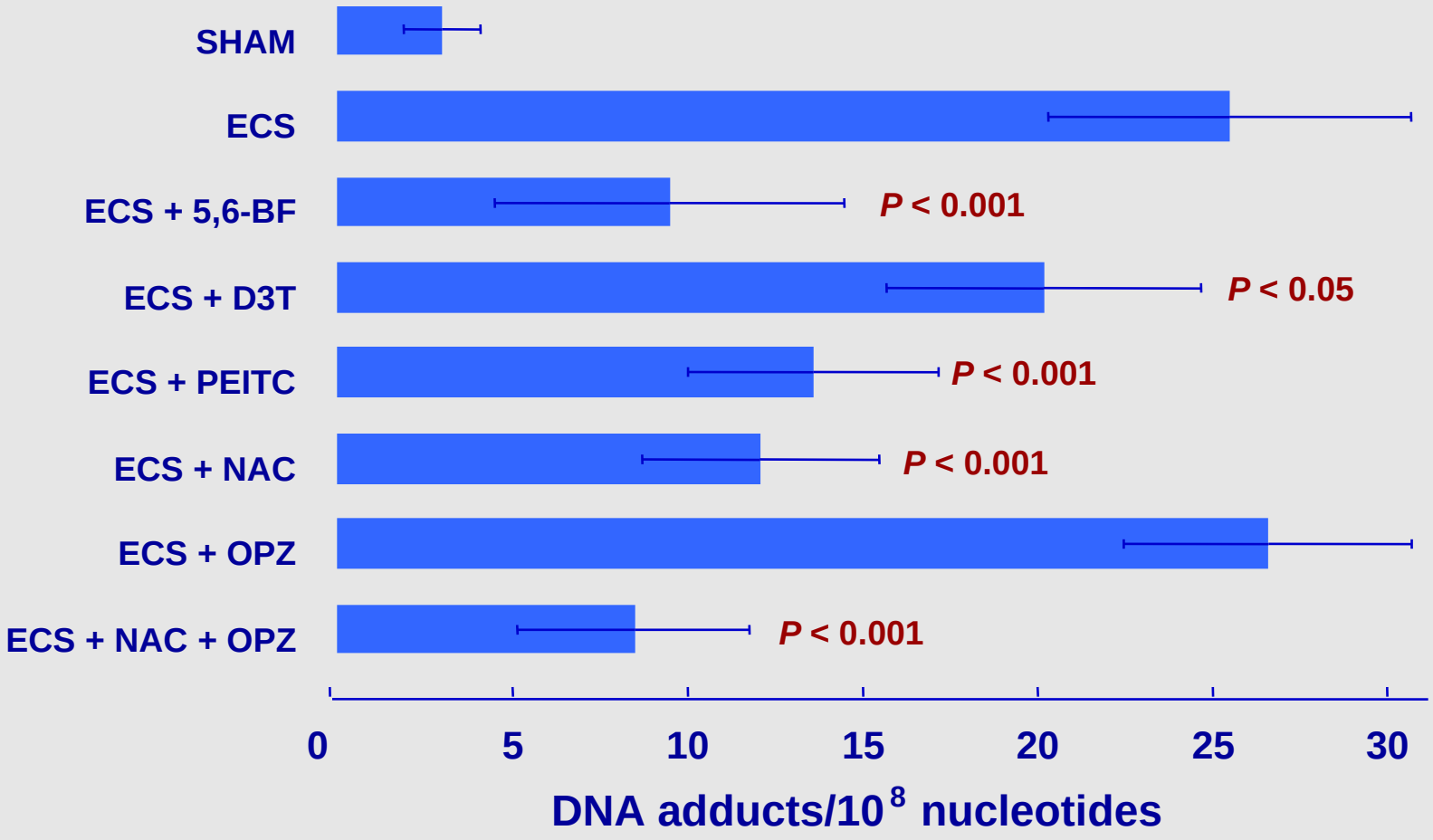
Proteomic profiles

TIME COURSE FORMATION OF DNA ADDUCTS IN RATS EXPOSED TO CIGARETTE SMOKE



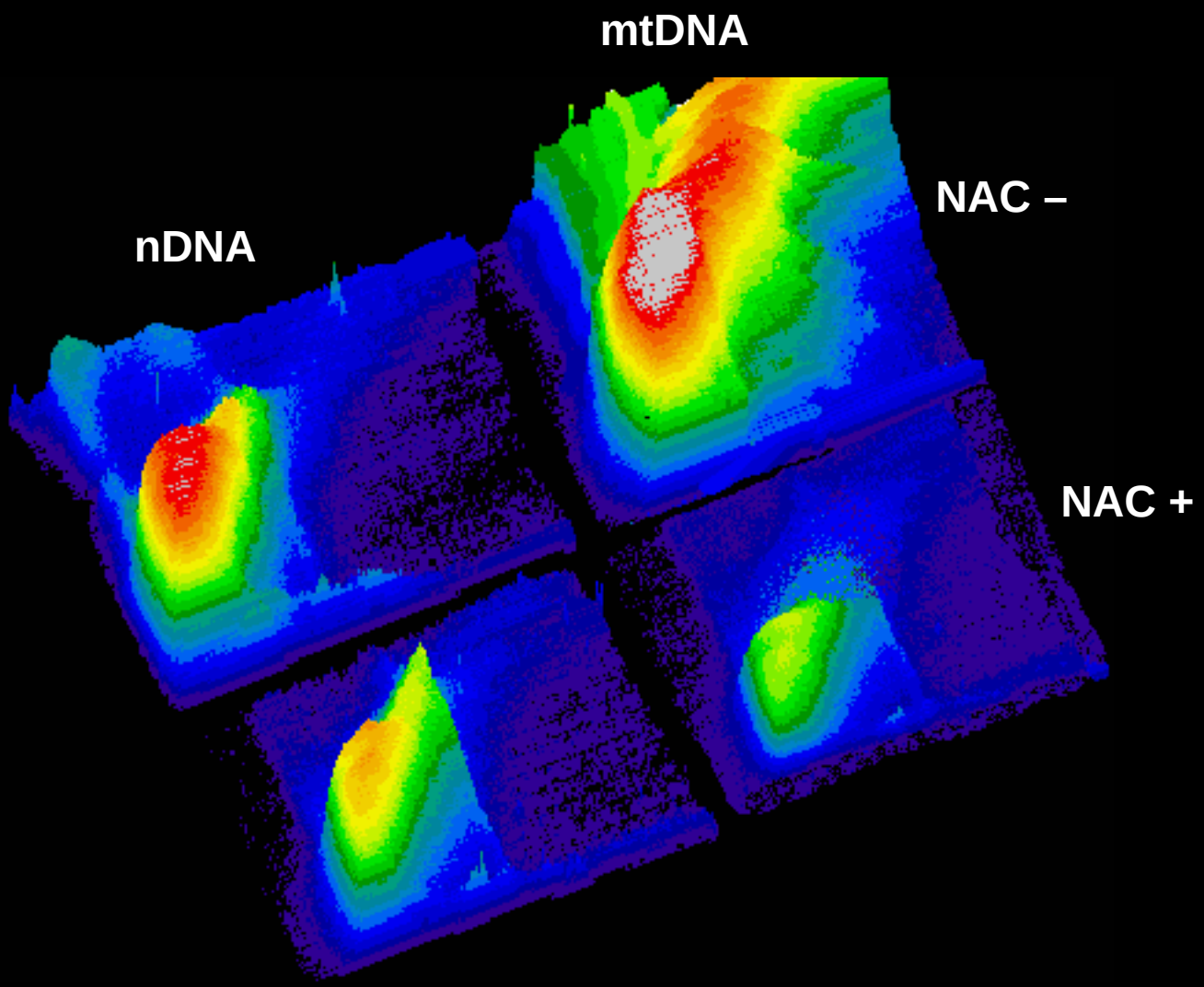
A. Izzotti et al., Carcinogenesis 20, 1499-1505, 1999

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



A. Izzotti et al., Cancer Res., 61, 2472–9, 2001

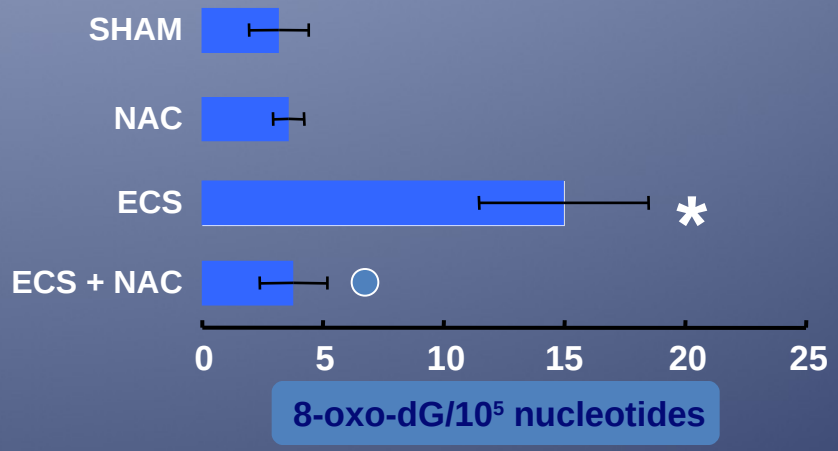
ADDUCTS TO LUNG DNA IN SMOKE–EXPOSED RATS

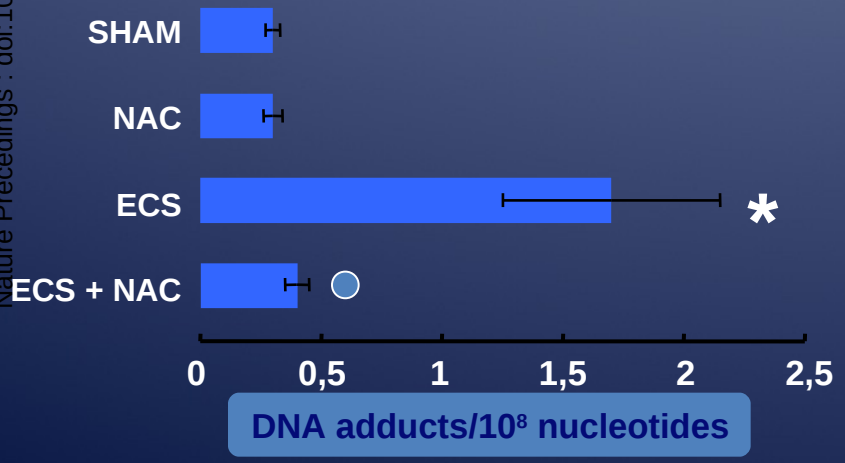


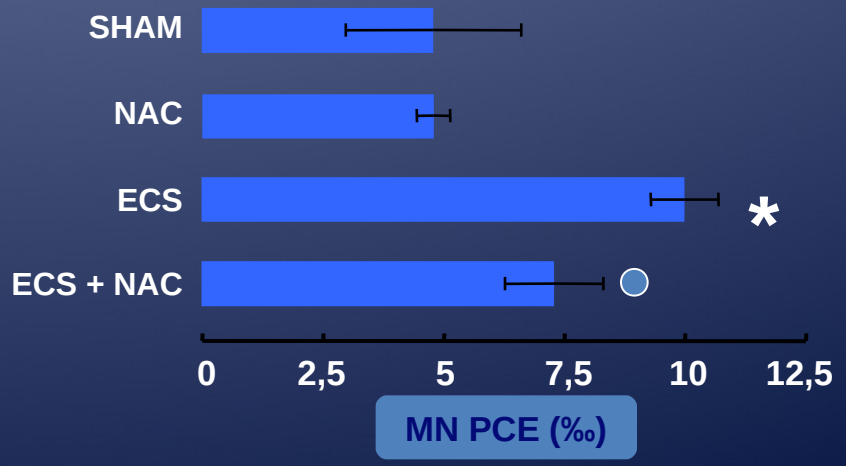
R. Balansky et al., Cancer Res. 56, 1642-1647, 1996

GENOMIC AND TRANSCRIPTIONAL ALTERATIONS IN MOUSE FETUS LIVER

TRANSPLACENTAL CIGARETTE SMOKE



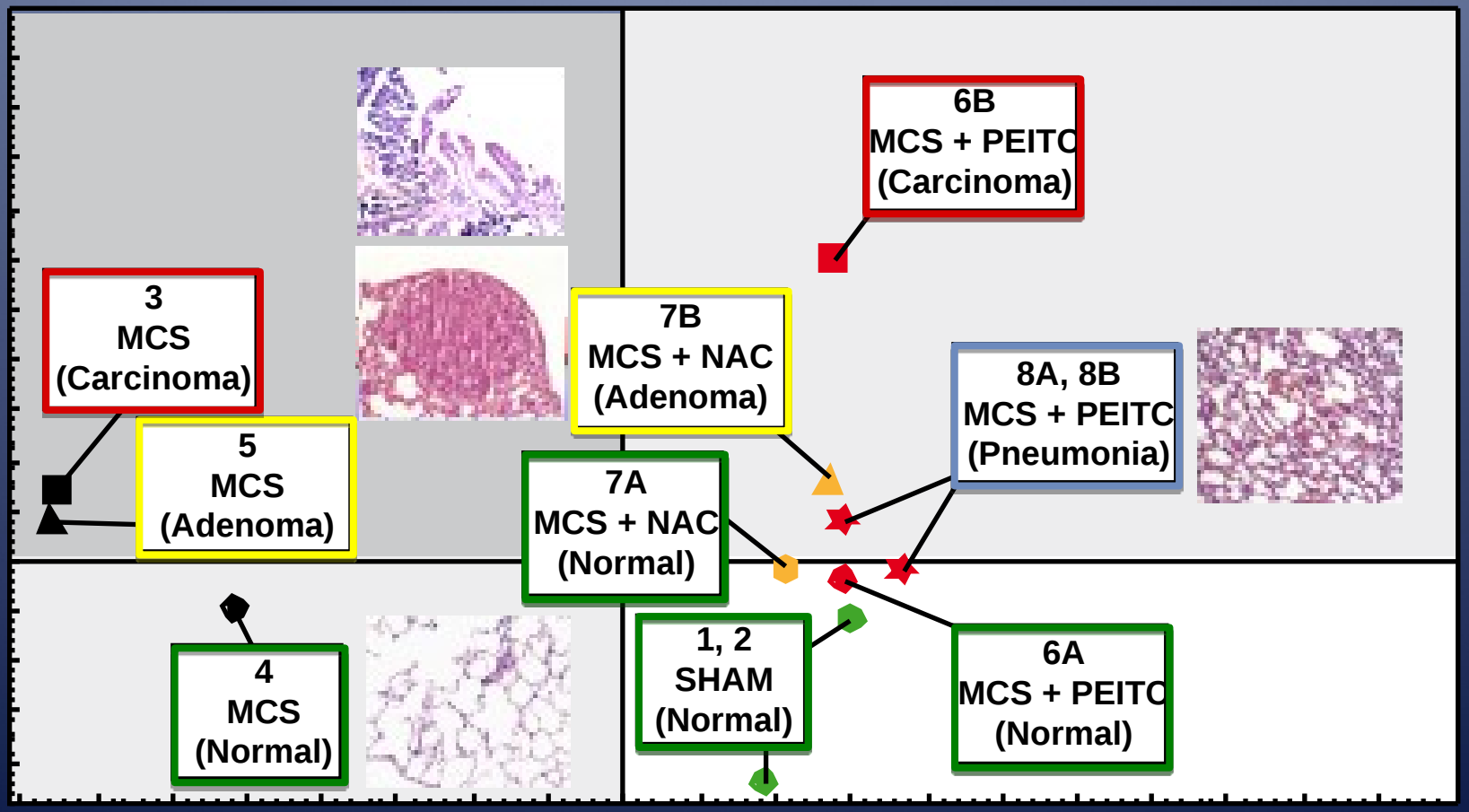




A. Izzotti et al., FASEB J. 17, 126-129, 2003

INTERPLAY BETWEEN HISTOPATHOLOGICAL ALTERATIONS, CIGARETTE SMOKE AND CANCER CHEMOPREVENTIVE AGENTS IN DEFINING microRNA PROFILES IN MOUSE LUNG

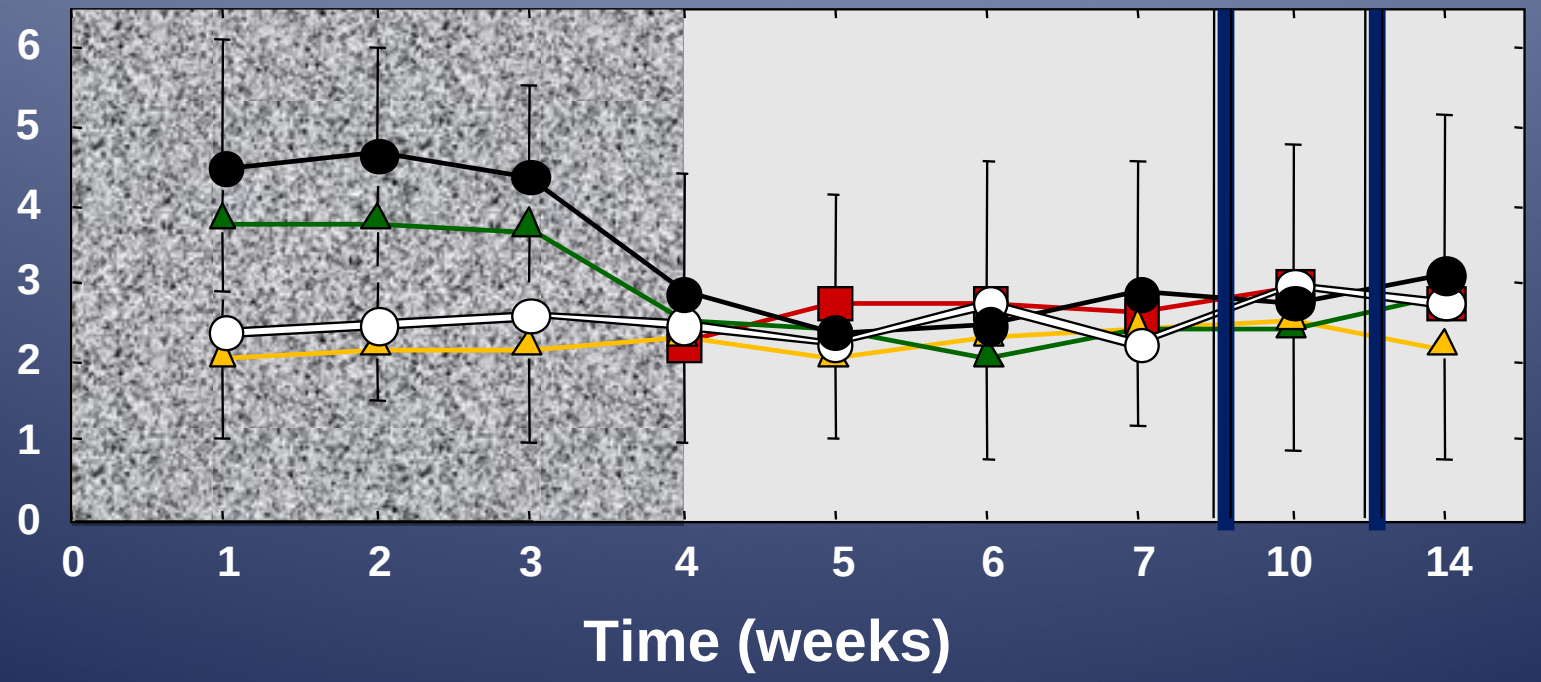
A. Izzotti et al., Mutat. Res., in press



FREQUENCY OF MICRONUCLEI (‰) IN SMOKE-EXPOSED MICE

R. Balansky *et al*., Carcinogenesis 20, 1491-1497, 1999

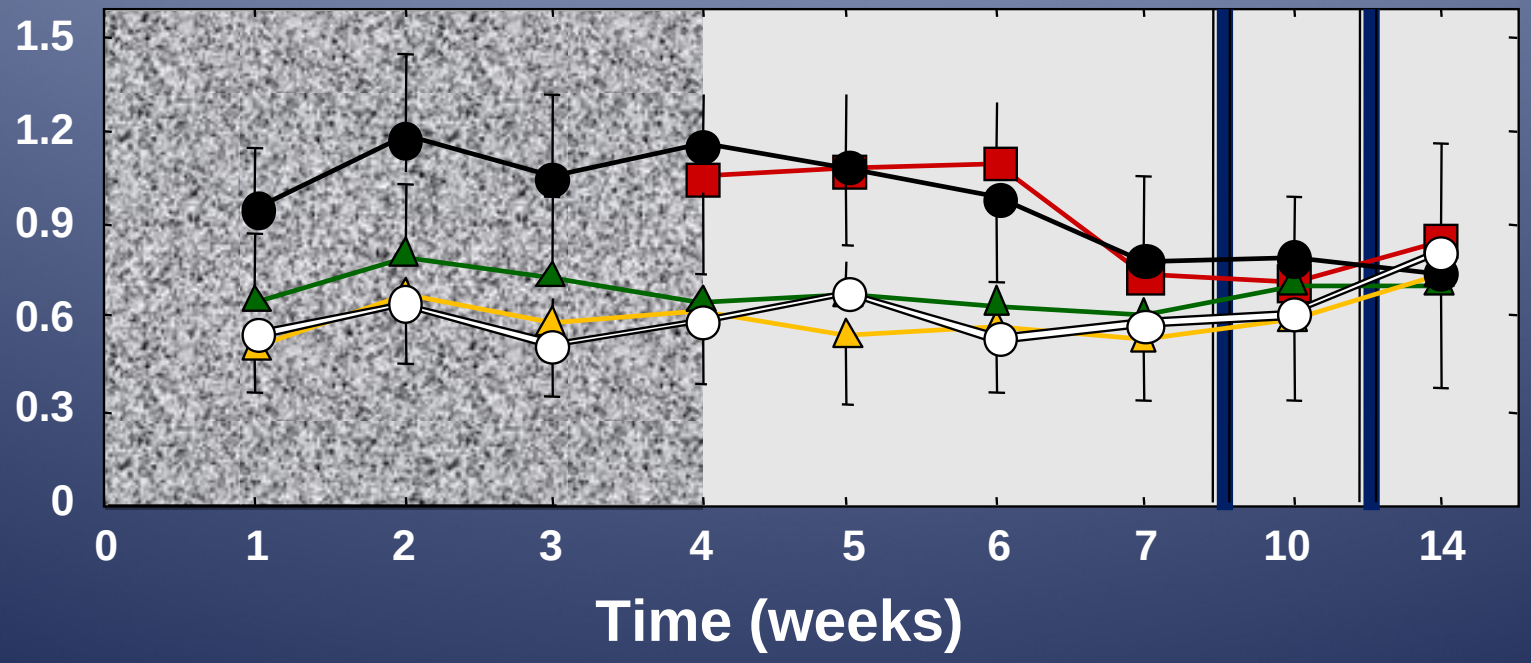
Bone marrow (PCE)



FREQUENCY OF MICRONUCLEI (‰) IN SMOKE-EXPOSED MICE

R. Balansky *et al*., Carcinogenesis 20, 1491-1497, 1999

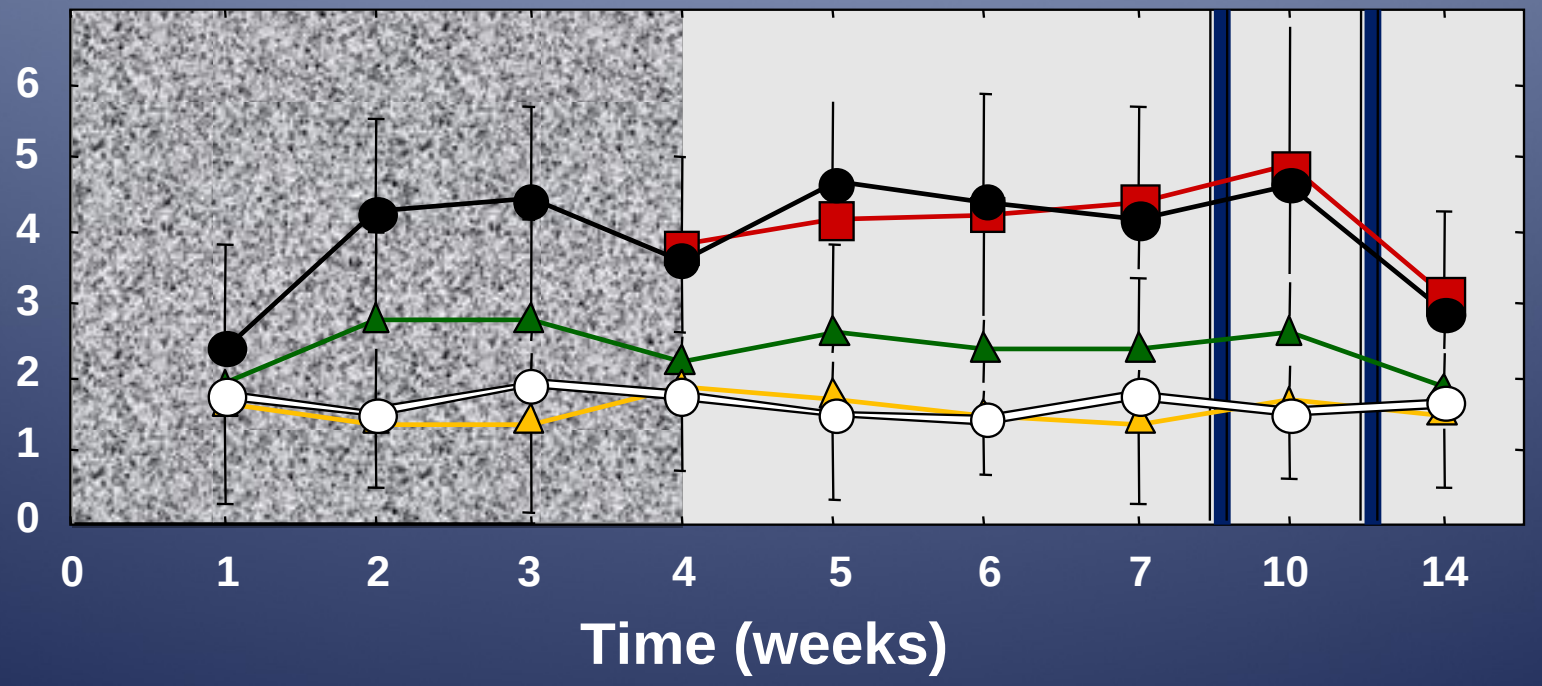
Peripheral blood (NCE)



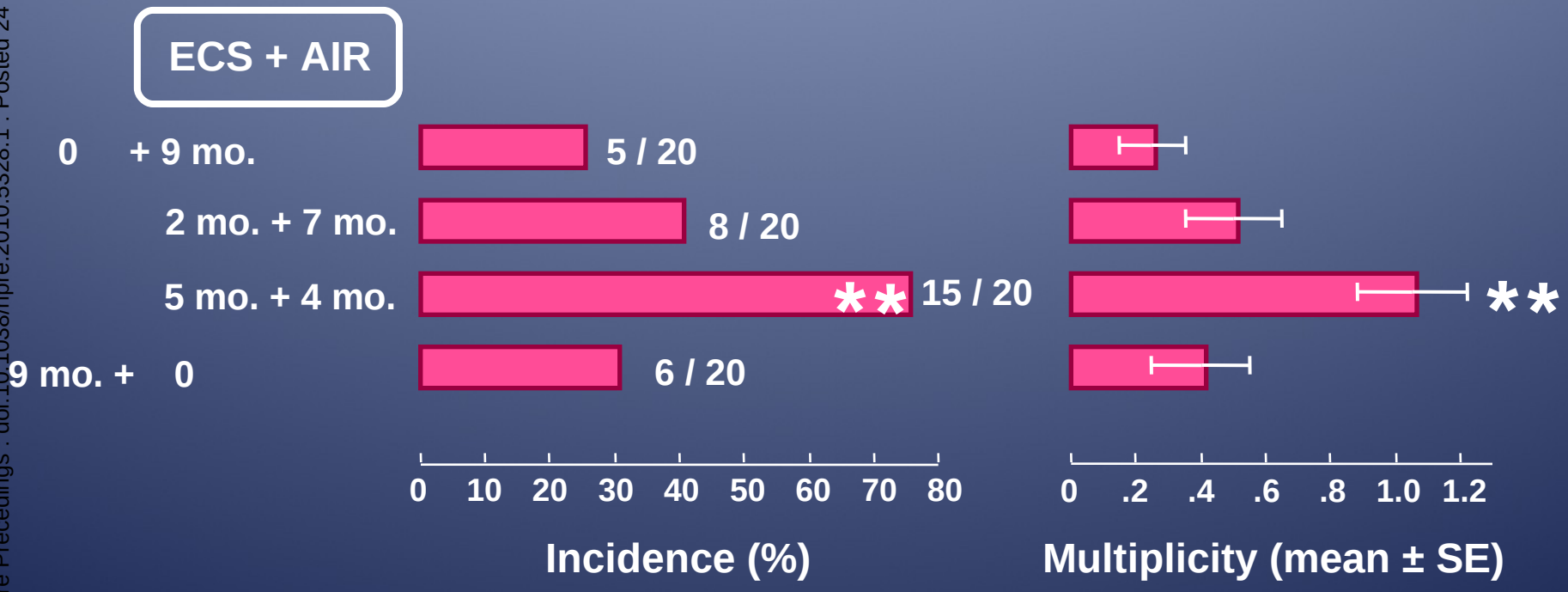
FREQUENCY OF MICRONUCLEI (‰) IN SMOKE-EXPOSED MICE

R. Balansky *et al*., Carcinogenesis 20, 1491-1497, 1999

Respiratory tract (PAM)



LUNG TUMOR YIELD IN A/J MICE EXPOSED TO CIGARETTE SMOKE (ECS)



** *P* < 0.01

F. D'Agostini et al., Int. J. Oncol. 18, 607-615, 2001

EFFECTS OF CIGARETTE SMOKE IN MUTANT MICE

S. De Flora *et al*. Molecular alterations and lung tumors in *P53* mutant mice exposed to cigarette smoke. *Cancer Res.* 63, 793–800, 2003

A. Izzotti *et al*. Gene expression in the lung of *P53* mutant mice exposed to cigarette smoke. *Cancer Res*. 64, 8566–72, 2004

F. D'Agostini *et al*. Early loss of *Fhit* in the respiratory tract of rodents exposed to environmental cigarette smoke. *Cancer Res*. 66, 3936–41, 2006

S. De Flora *et al*. Molecular and cytogenetical alterations induced by environmental cigarette smoke in mice heterozygous for *Fhit*. *Cancer Res*. 67, 1001–6, 2007

INCREASED SUSCEPTIBILITY TO CARCINOGENS AT BIRTH: MECHANISMS

Induction of oxidative DNA damage and formation of bulky DNA adducts

Overexpression of multiple genes

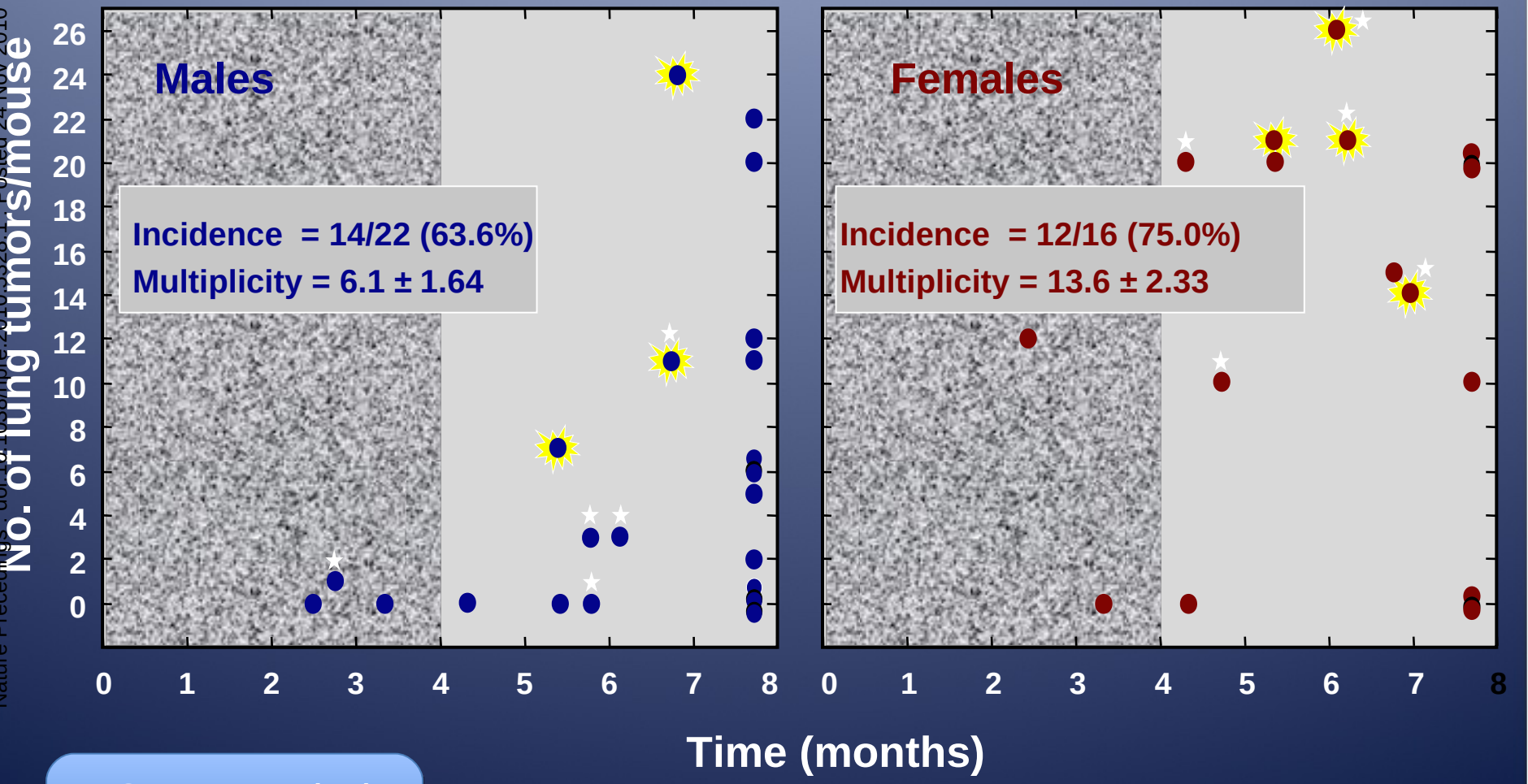
Increased proliferative rate in neonatal organs

Alterations of xenobiotic metabolism

Lower efficiency of certain DNA repair mechanisms

Involvement of stem cells?

INDUCTION OF LUNG TUMORS BY CIGARETTE SMOKE IN MICE EXPOSED EARLY IN LIFE

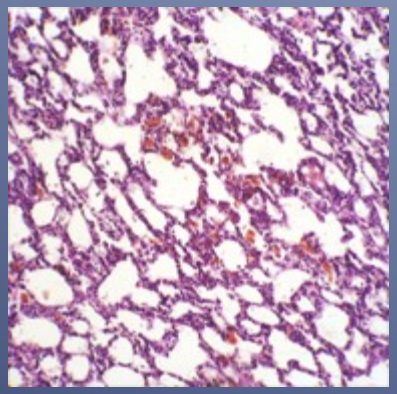


★ Spontaneous deaths

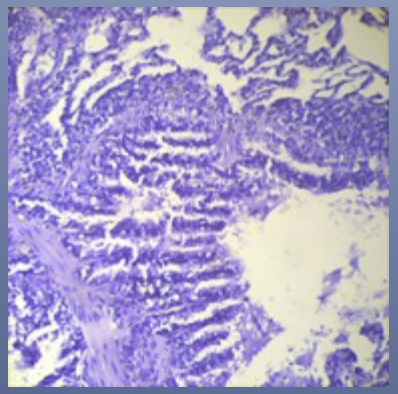
Including one malignant tumor

R. Balansky et al., Carcinogenesis 28, 2236–43, 2007

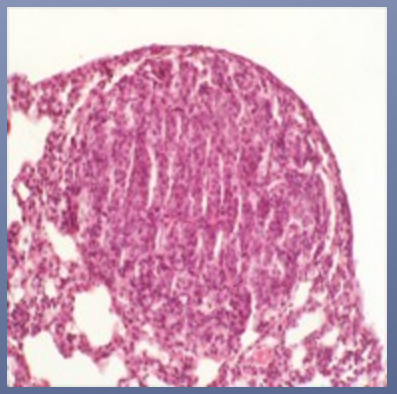
HISTOPATHOLOGICAL ALTERATIONS IN THE LUNG OF MCS–EXPOSED MICE



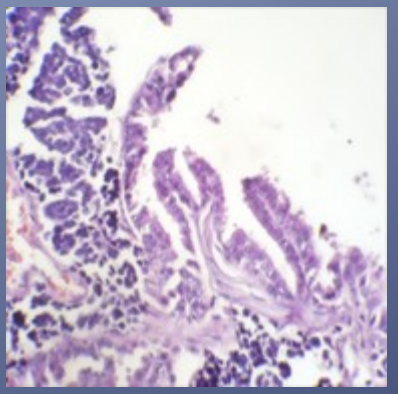
Hyperplasia of alveolar epithelium



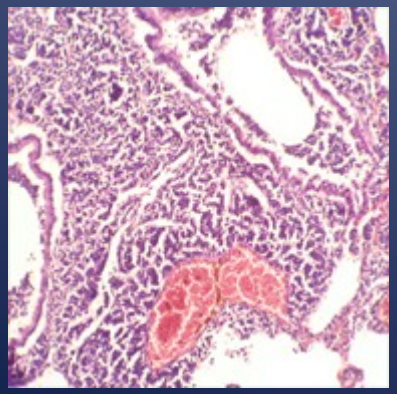
Papillary hyperplasia of bronchial epithelium



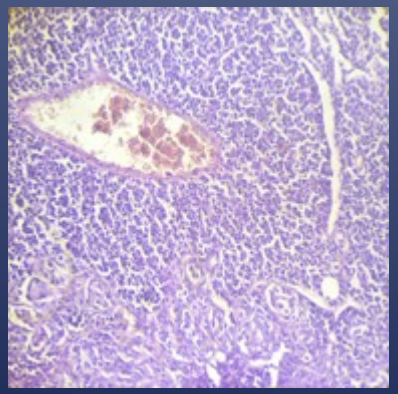
Adenoma



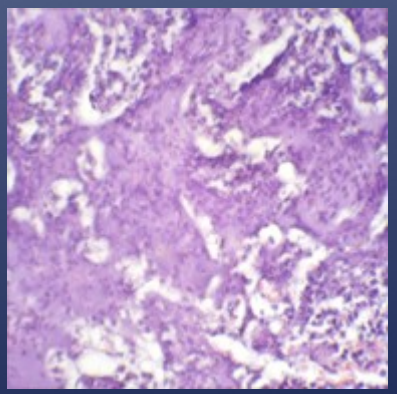
Carcinoma *in situ*



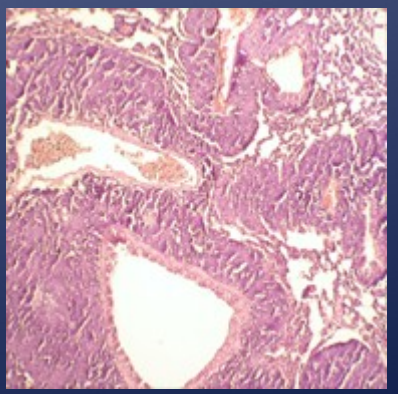
Small cell carcinoma



Tumor containing adenocarcinomatous and small cell areas



Adenosquamous carcinoma

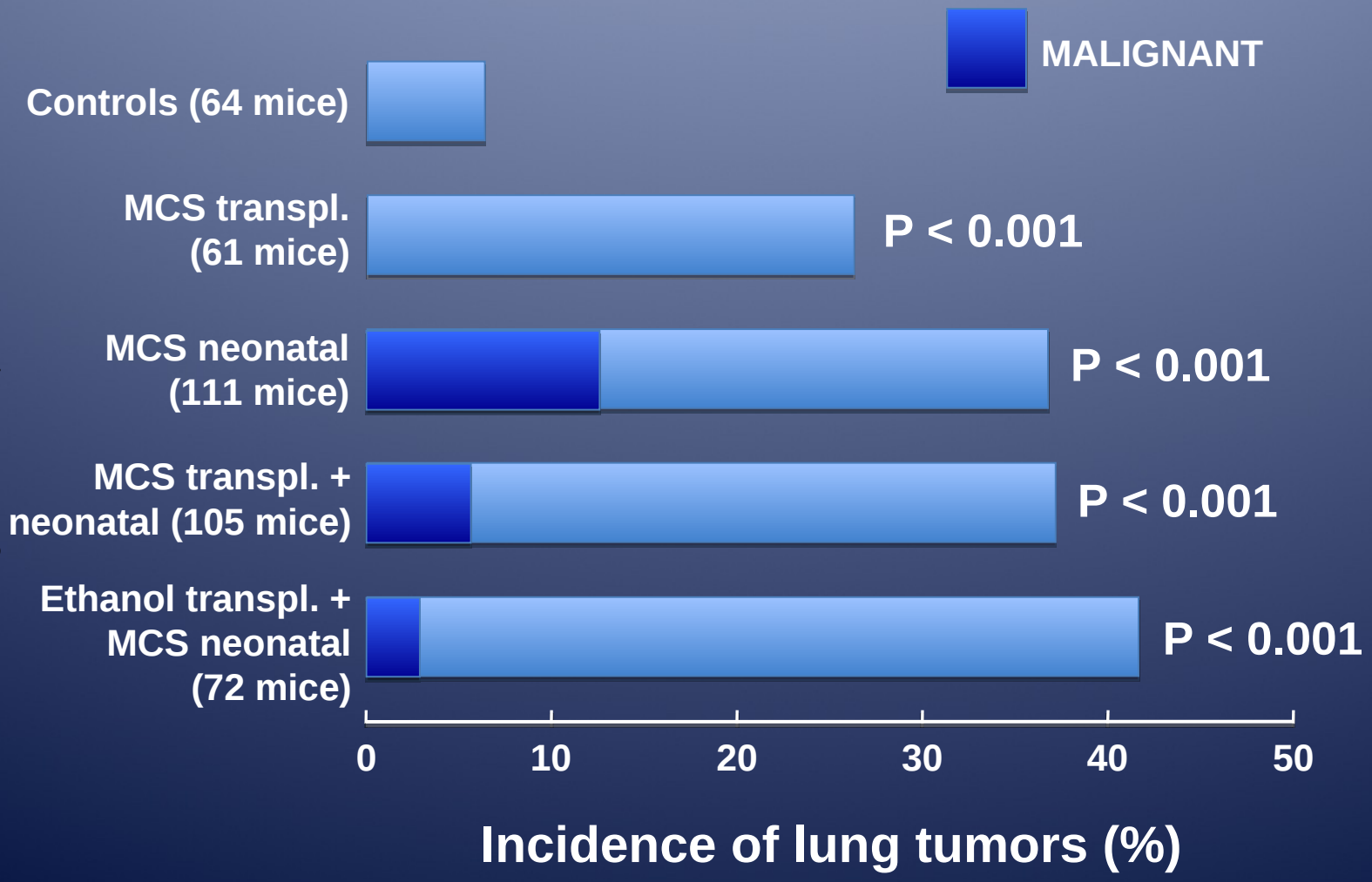


Low differentiated carcinoma

INCIDENCE OF LUNG TUMORS IN MICE EXPOSED TO CIGARETTE SMOKE

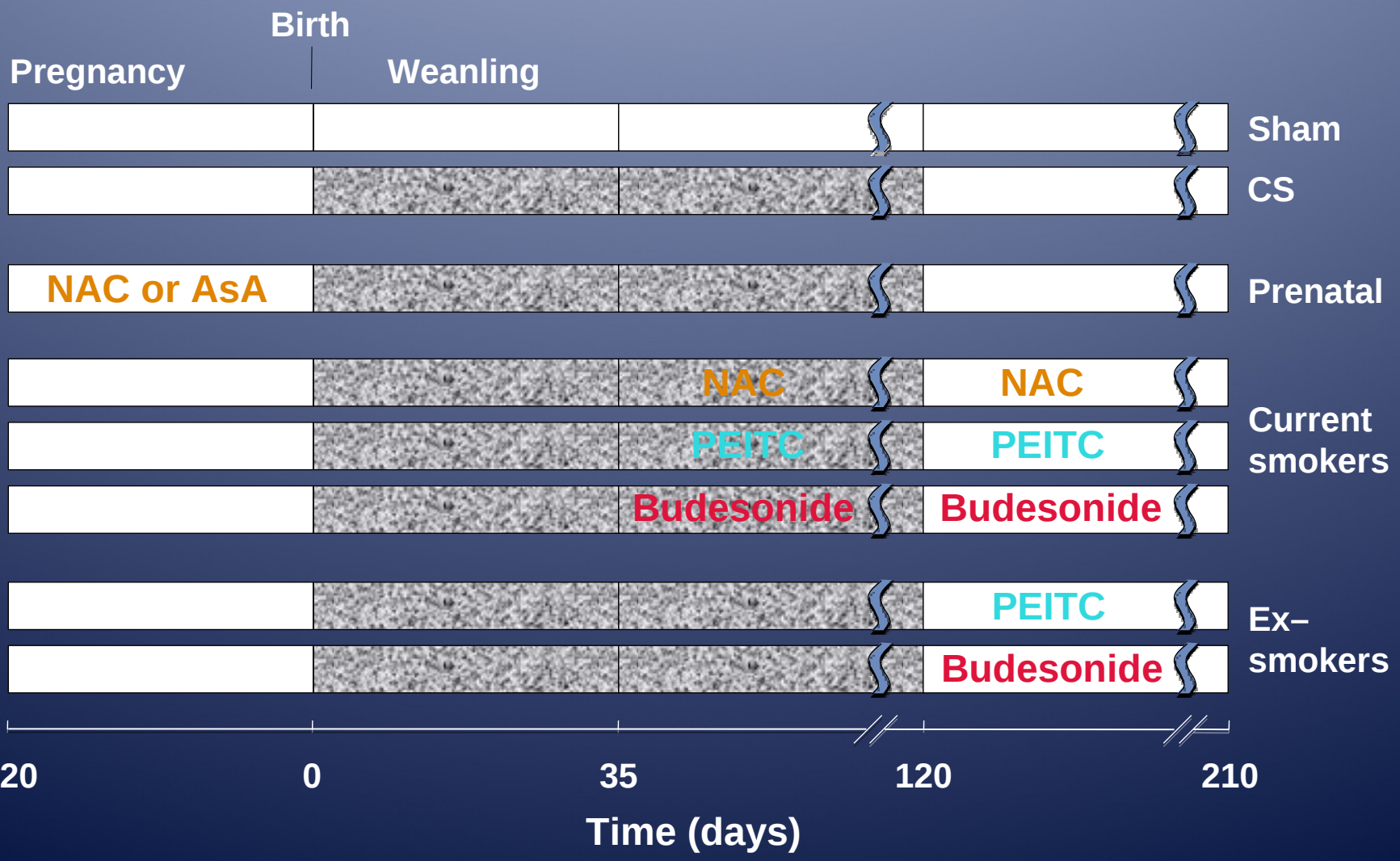
Mouse strain	Exposure period	End of exp.	Sham	Cigarette Smoke		Ref.
			Adenomas	Adenomas*	Malignant t.	
Swiss H	0-4 mo.	7 mo.	0/36	15/38 (39.5%)	7/38 (18.4%)	Balansky et al., 2007
Swiss H	0-4 mo.	7 mo.	1/52 (1.9%)	16/55 (29.1%)	6/55 (10.9%)	Balansky et al., 2009
Swiss H	0-4 mo.	7 mo.	0/34	24/69 (34.8%)	9/69 (13.0%)	Unpublished
Swiss H	0-4 mo.	8 mo.	3/64 (4.7%)	16/111 (14.4%)	2/111 (10.8%)	Unpublished
Swiss H	0-2 mo.	8 mo.	0/36	9/32 (28.1%)	3/32 (9.4%)	Unpublished
Swiss H	3-7 mo.	11 mo.	0/30	2/60 (3.3%)	0/60	Unpublished
Swiss ICR	0-4 mo.	7 mo.	2/57 (3.8%)	25/82 (30.5%)	0/82	Unpublished
DBA/2	0-4 mo.	8 mo.	0/18	3/16 (18.8%)	0/16	Unpublished
C57BL	0-4 mo.	8 mo.	0/19	1/22 (4.5%)	0/22	Unpublished
C57BL	3-7 mo.	11 mo.	0/30	0/27	0/27	Unpublished

CARCINOGENICITY OF MAINSTREAM CIGARETTE SMOKE IN STRAIN H MICE



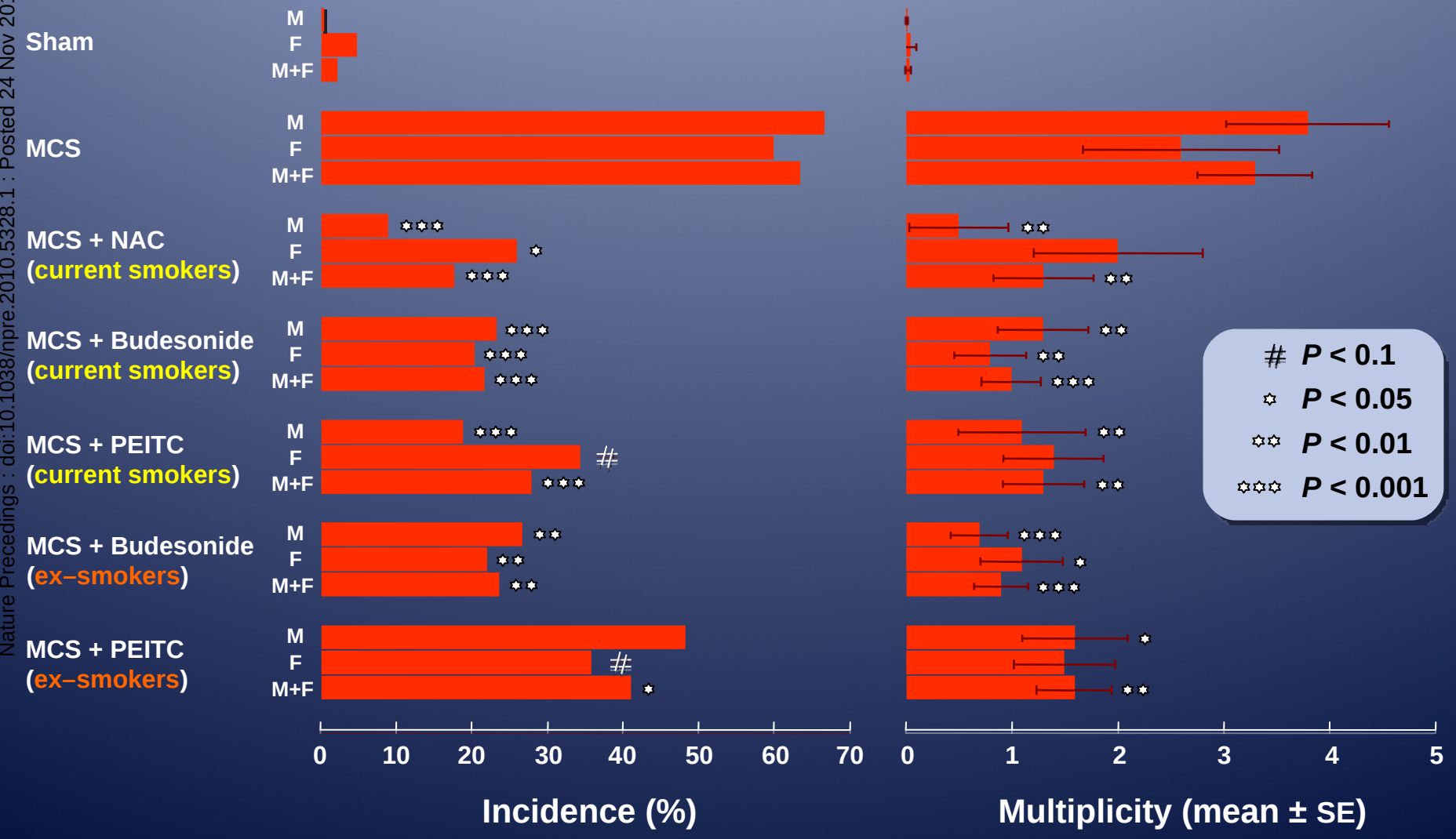
CHEMOPREVENTION OF CIGARETTE SMOKE–INDUCED TUMORS

Experimental design



CHEMOPREVENTION OF CIGARETTE SMOKE–INDUCED TUMORS

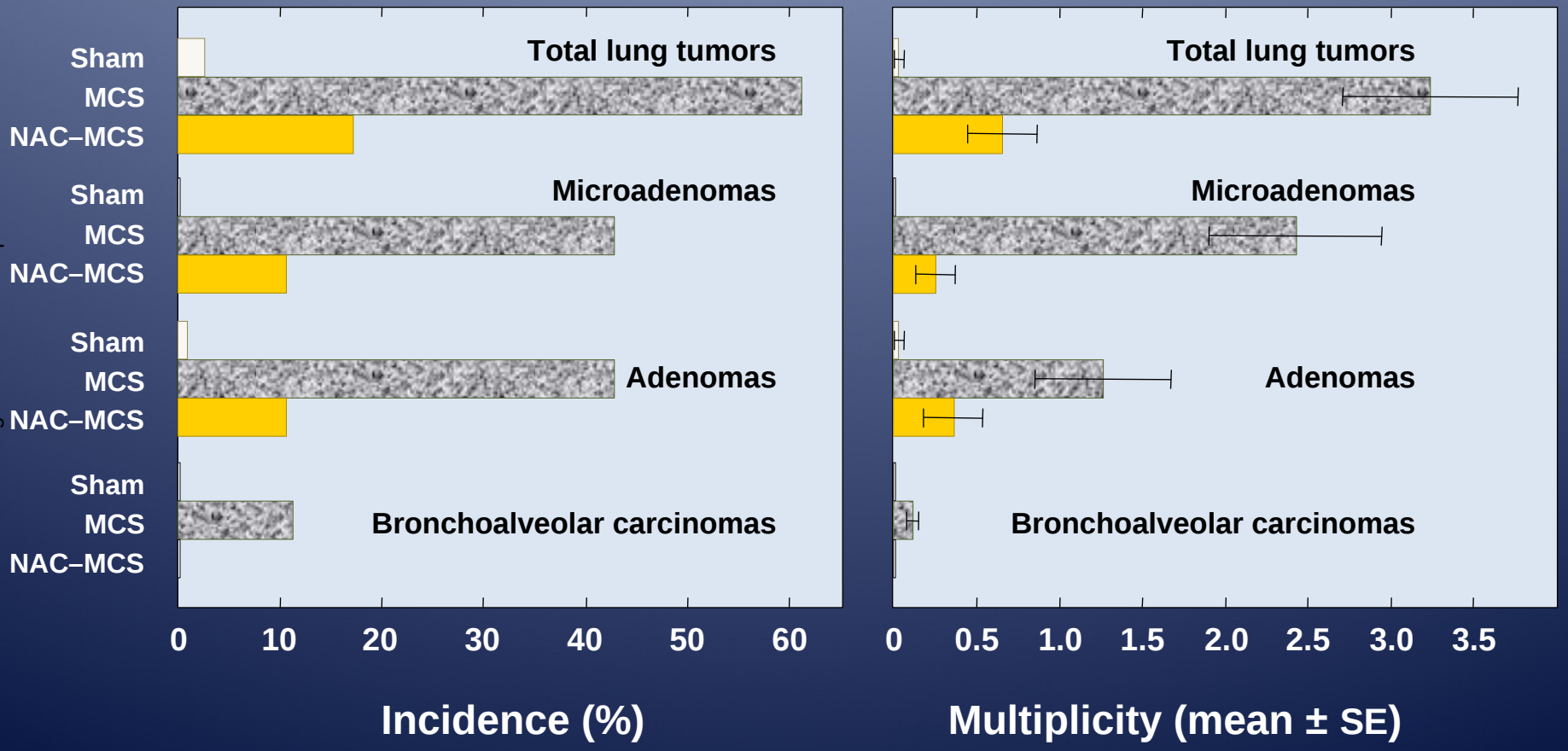
R. Balansky et al., Int. J. Cancer 126, 1046-54, 2010



PRENATAL *N*–ACETYLCYSTEINE (NAC) PREVENTS CIGARETTE SMOKE–INDUCED LUNG TUMORS IN NEONATAL MICE

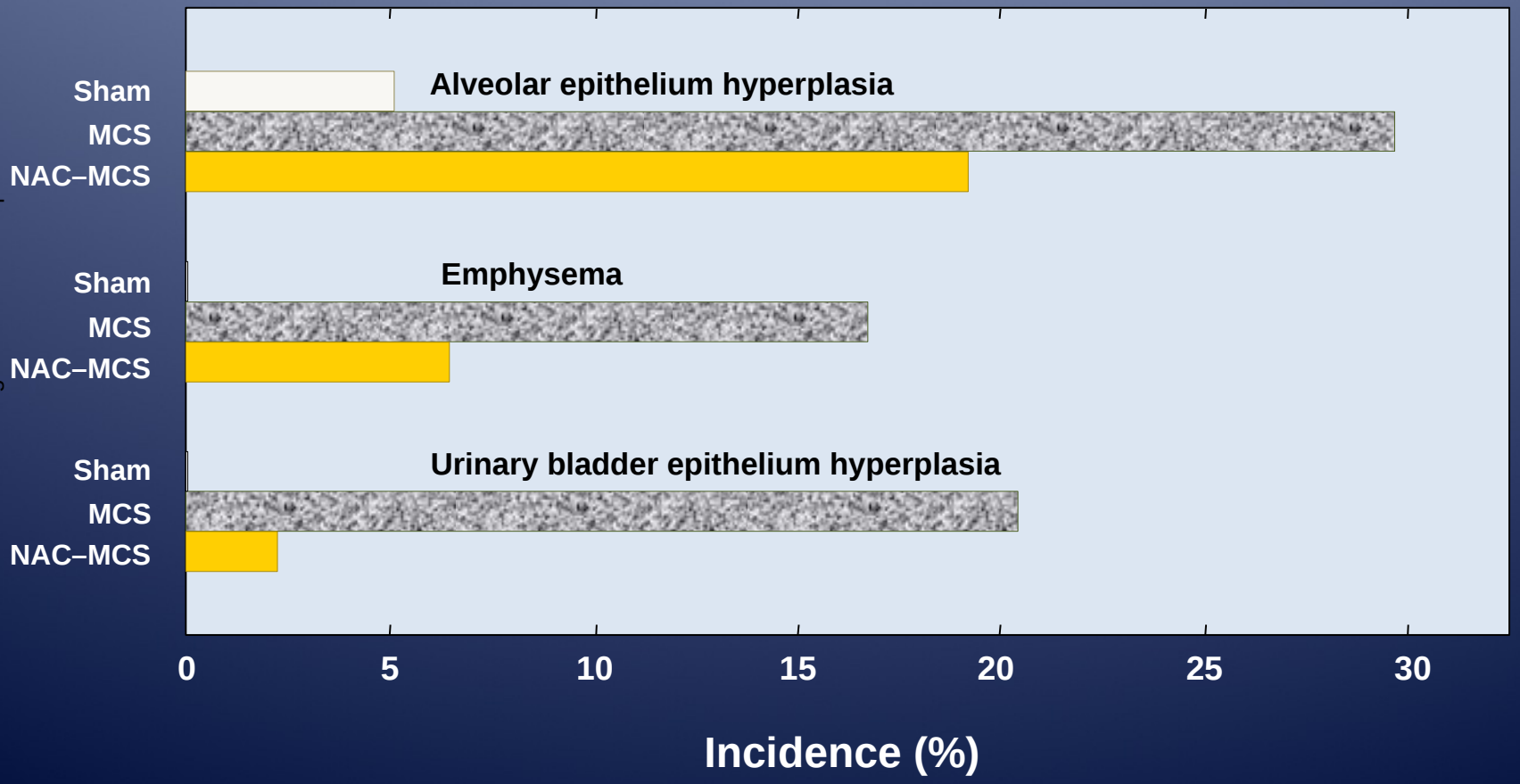
R. Balansky et al., Carcinogenesis 30, 1398–1401, 2009

Nature Precedings : doi:10.1038/npre.2010.5328.1 : Posted 24 Nov 2010

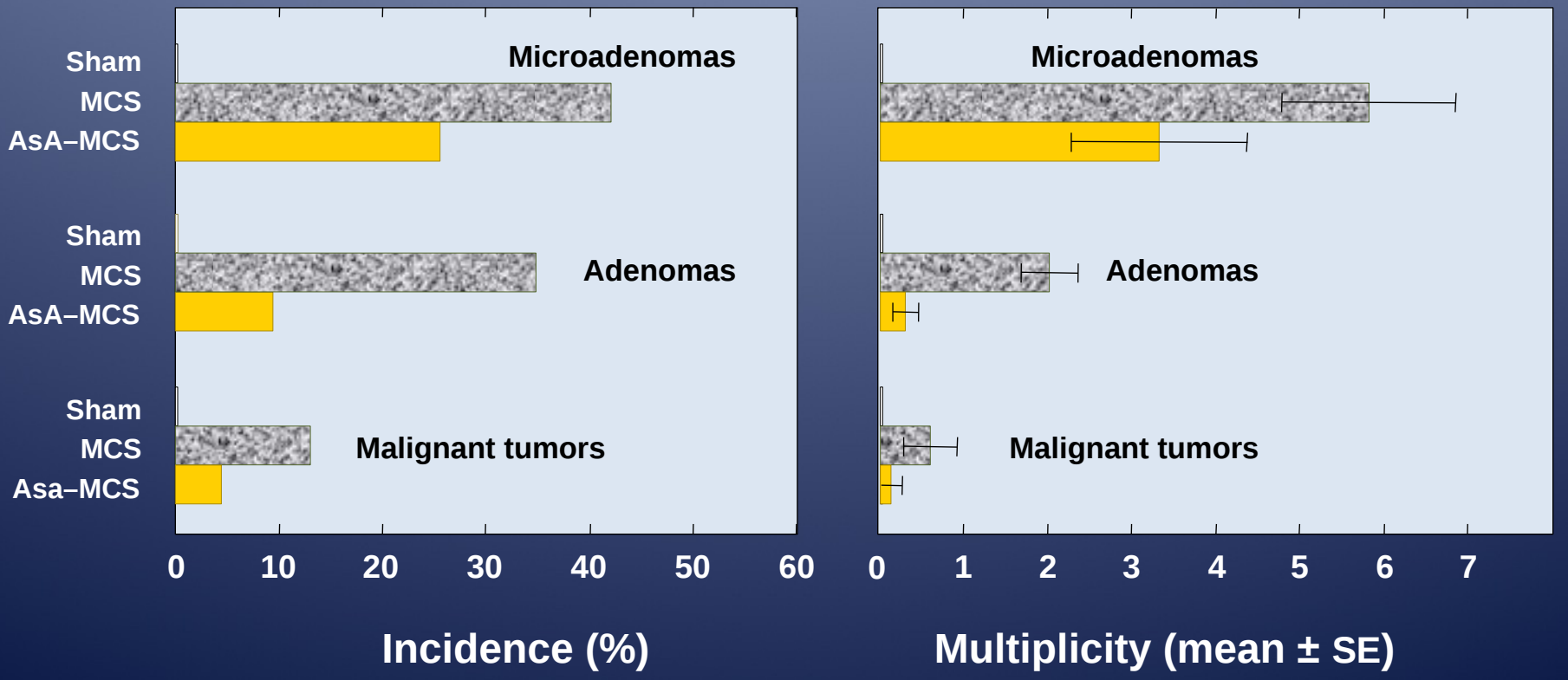


PRENATAL *N*–ACETYLCYSTEINE (NAC) PREVENTS CIGARETTE SMOKE–INDUCED HISTHOPATOLOGICAL ALTERATIONS IN NEONATAL MICE

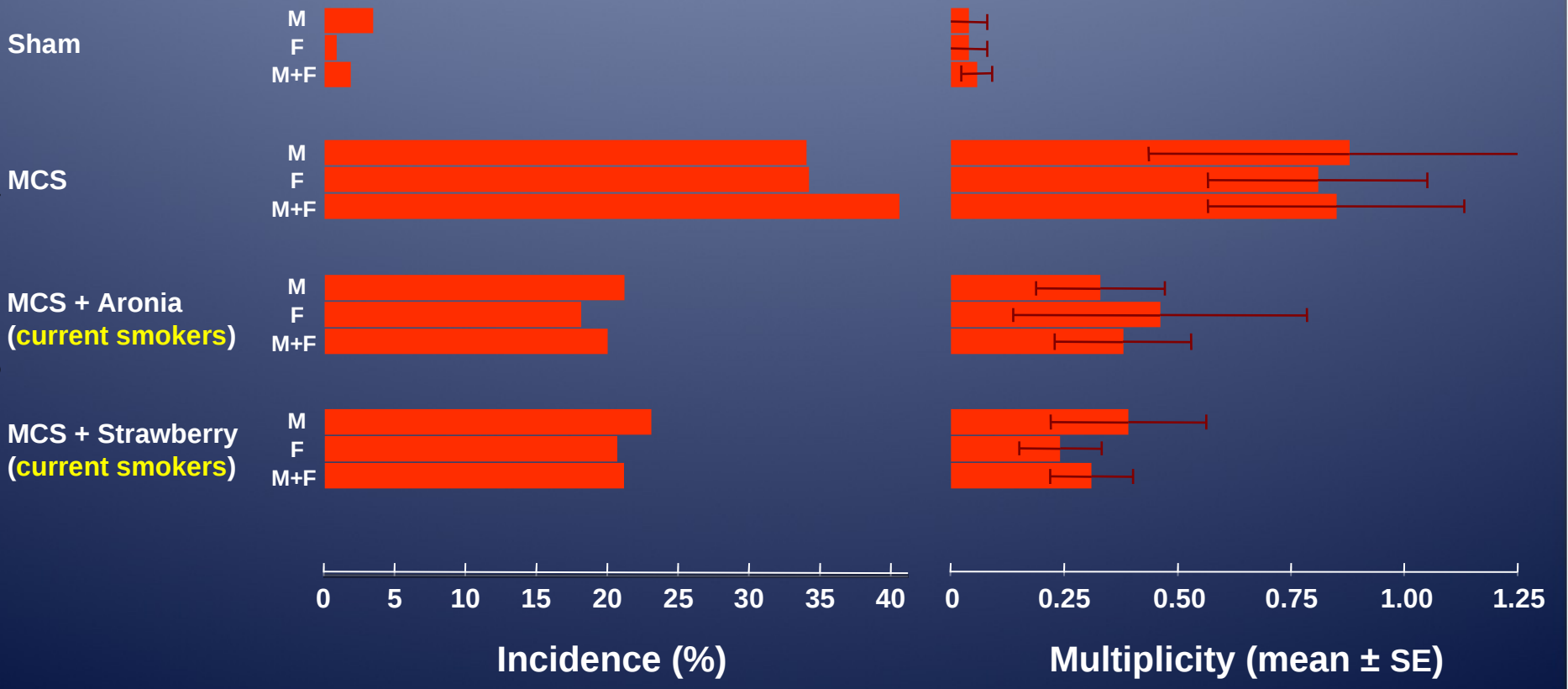
R. Balansky et al., Carcinogenesis 30, 1398–1401, 2009



PRENATAL ASCORBIC ACID (AsA) PREVENTS CIGARETTE SMOKE–INDUCED LUNG TUMORS IN NEONATAL MICE



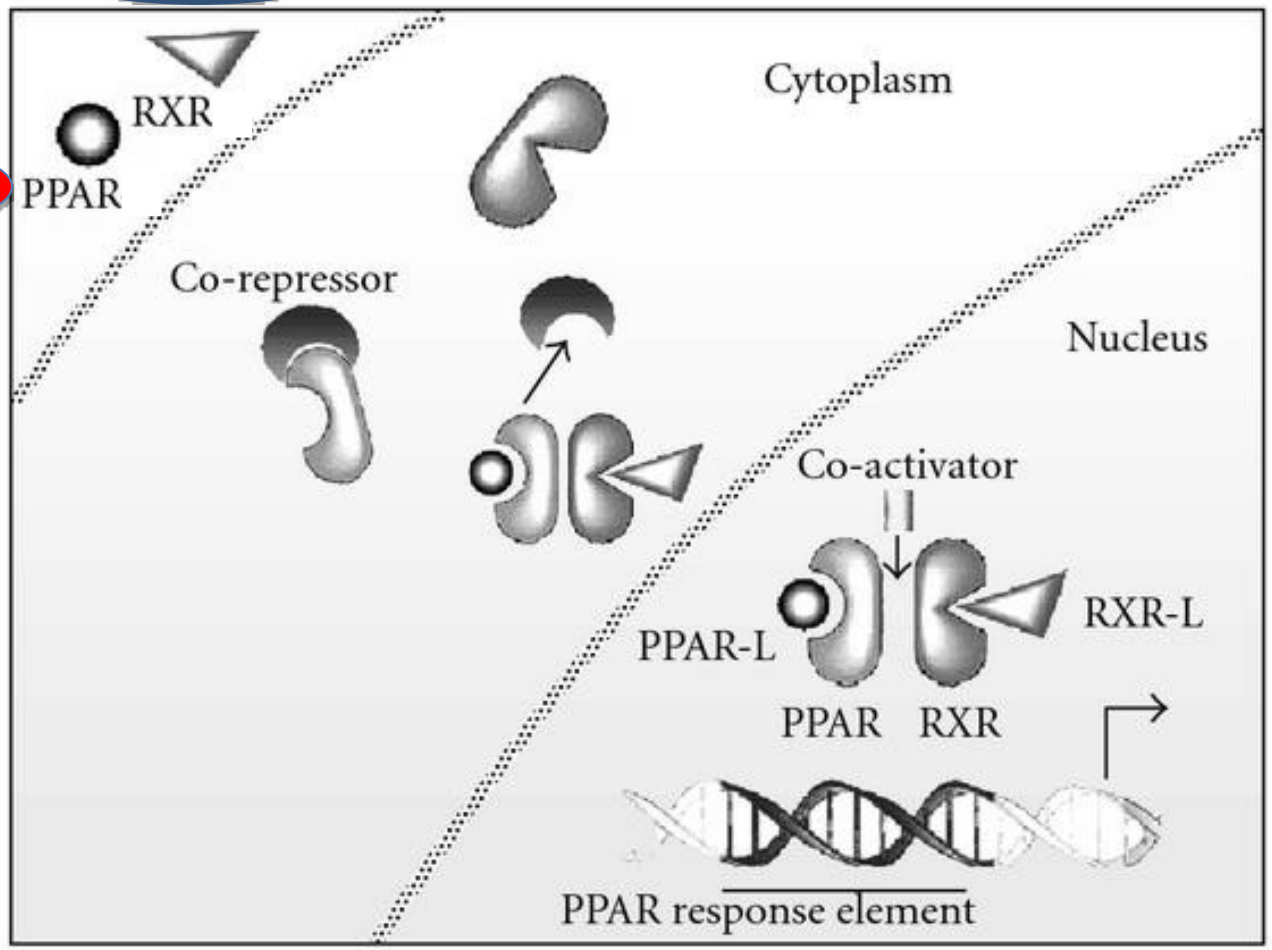
CHEMOPREVENTION OF CIGARETTE SMOKE–INDUCED LUNG ADENOMAS BY NATURAL PRODUCTS



CHEMOPREVENTION OF SMOKE-RELATED ALTERATIONS OF microRNAs AND LUNG TUMORS

BEXAROTENE

PIOGLITAZONE



THANK YOU!!

OBRIGADO!