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towards novel biomarkers
for cancer risk assessment

Innovative Medicines Initiative

MARCAR

BIO**MAR**KERS & MOLECULAR TUMOUR CLASSIFICATION
FOR NON-GENOTOXIC **CAR**CINOGENESIS

efpia

What patients need
What Europe needs

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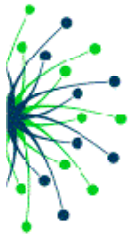
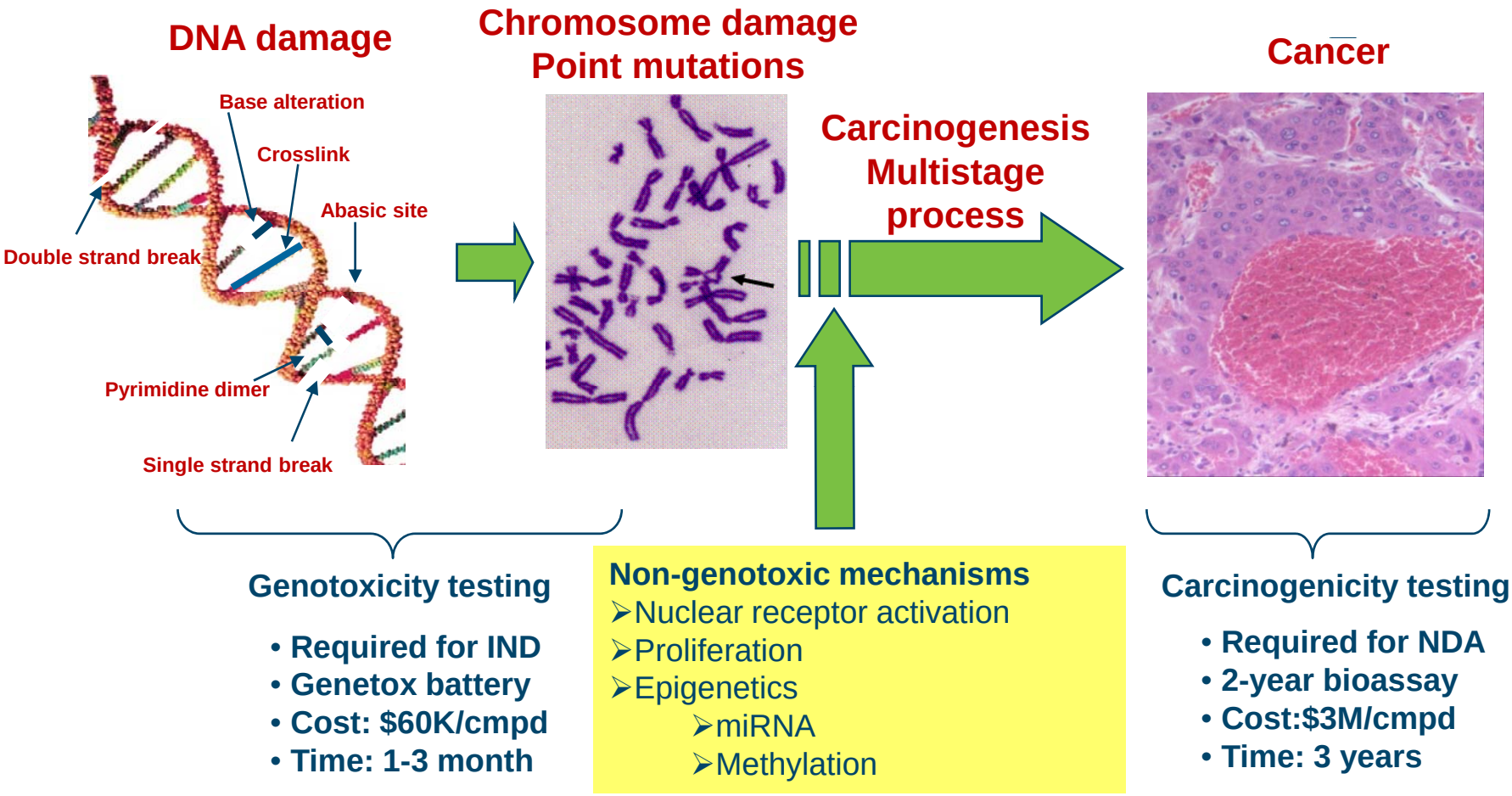
- Improved drug safety
- Increased efficiency of drug development
- Earlier detection of undesired effects of candidate drugs during development

MARCAR focus on **NON-GENOTOXIC CARCINOGENESIS**

- Identify BIOMARKERS:
  - help predict cancer risk more accurately at a very early stage
  - speed up development & increase drug safety for patients



Why focus on Non-Genotoxic Carcinogenesis (NGC)?



Schematic Figure adapted from Ellinger-Ziegelbauer et al., (2009) Toxicol Lett. (Elsevier) 186:36-44 with authors permission

- **No sufficiently accurate or well-validated short-term assays to identify NGC**
- **Need early mechanism-based biomarkers for the design of more predictive tests & improved cancer risk assessment**

What we will do

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MARCAR will search for biological clues (BIOMARKERS) to enable EARLY preclinical DETECTION of drug-induced tumor formation

2 year rodent cancer bioassay supporting clinical development and drug registration

IDENTIFY BIOMARKERS USING INNOVATIVE TECHNOLOGIES AND MECHANISTIC MODELS:

- **EPIGENETICS**; microRNA; BIOINFORMATICS
- MOUSE MODELS CONTAINING HUMAN GENES IMPORTANT FOR NGC
- TRANSLATIONAL *IN VITRO* CELL-BASED MODELS
- NON-INVASIVE IMAGING & REPORTER MODELS

ASSESS PREDICTIVE VALUE OF NOVEL BIOMARKERS & RELEVANCE FOR HUMANS

Emerging importance of epigenetics for cancer biology

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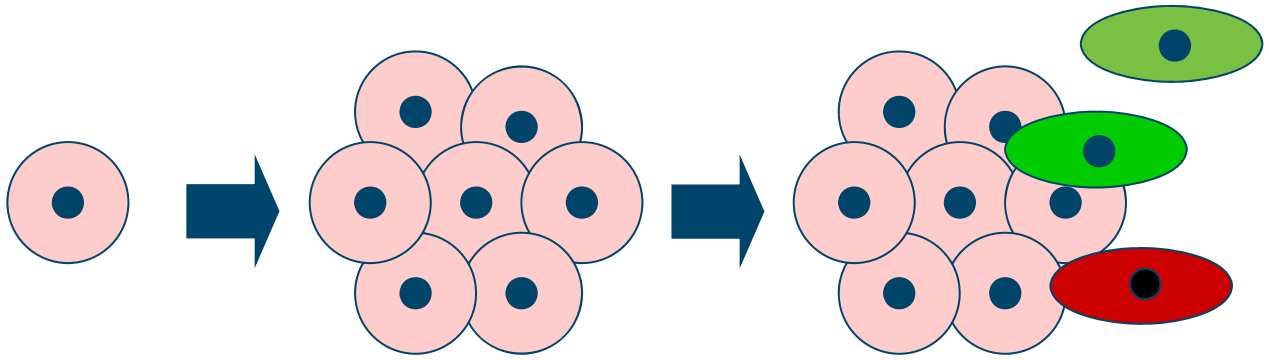
INITIATION PROMOTION PROGRESSION



Clonal expansion

Acquired characteristics
•metastasis, angiogenesis

CLASSICAL	mutation	mutation	mutation
EMERGING VIEW	mutation/ **epimutation**	mutation/ **epimutation**	mutation/ **epimutation**

EPIMUTATIONS:
= Paradigm shift in established models for tumour progression

EPIGENETIC CODES – opportunity to identify novel biomarkers for early cancer detection

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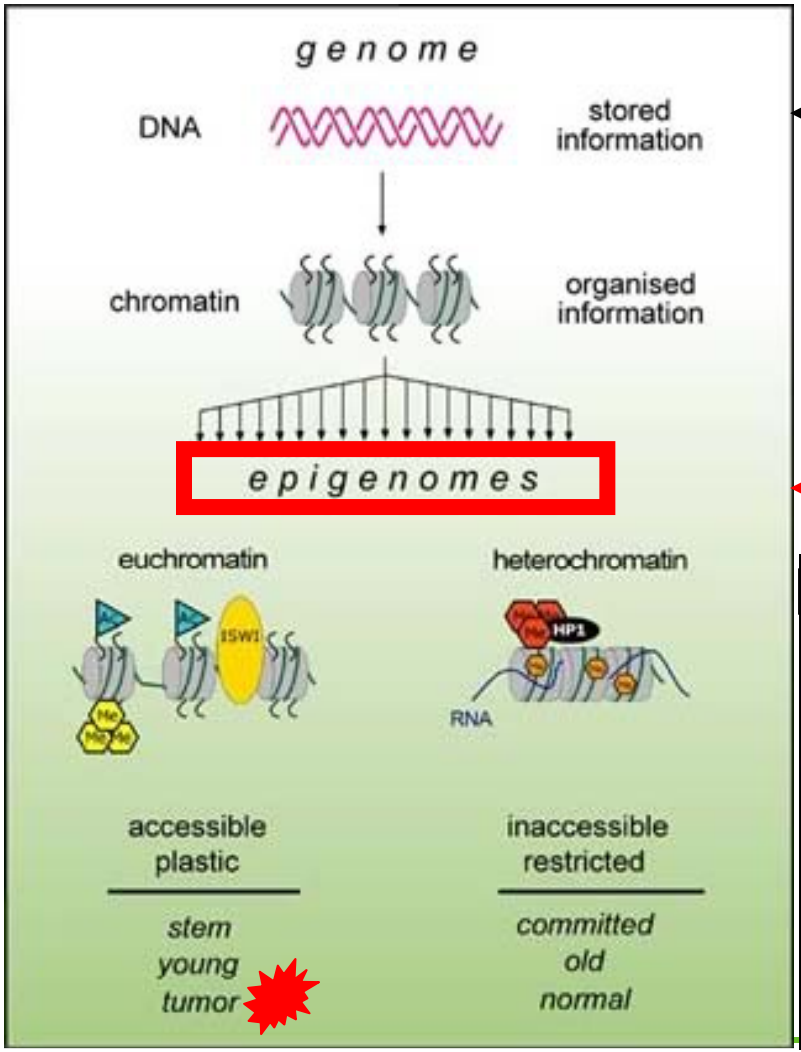
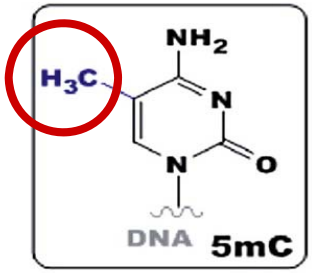


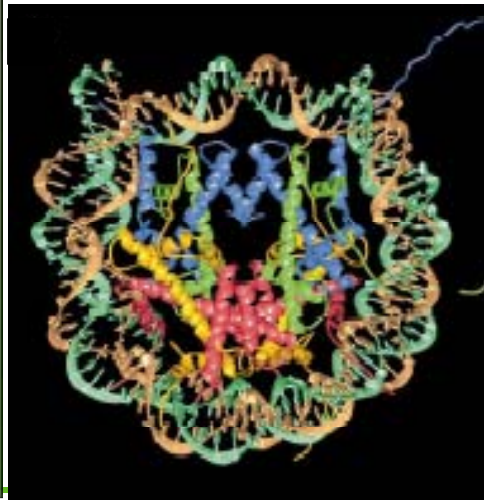
www.epigenome.eu
Epigenome Network of Excellence (NoE)
EU Framework 6 Programme (FP6)

GENETIC CODE (A,C,T,G)

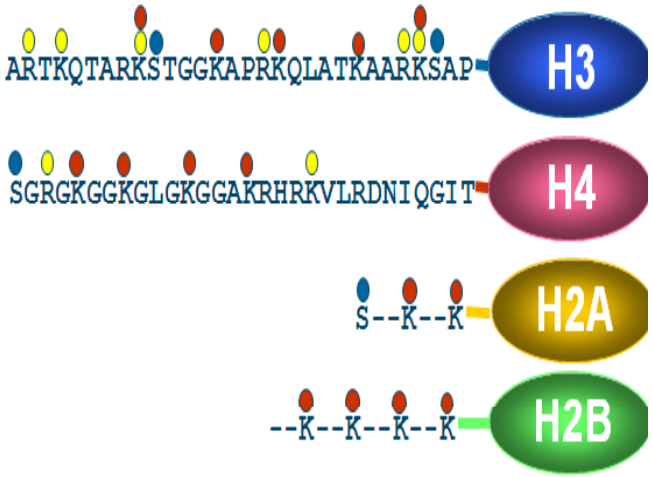


5-methycytosine

EPIGENETIC CODES



Luger et al., (1997)
Nature 389:251-260



Expected outcomes & benefits to patients

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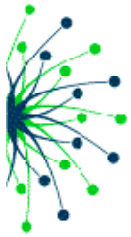
- Improved scientific basis for risk assessment of carcinogenic potential of novel medicines
- Novel early biomarkers for more reliably predicting later cancer development
- Increased efficiency of drug development - fewer delays/attrition during late-phase
- Improved preclinical safety assessment prior to clinical trials & potential translation of early cancer biomarkers to humans



Added value of consortium

- New knowledge + biomarkers can be more rapidly derived by sharing consortium expertise, technologies, models, and archives
  - Extensive collection of archived samples and data from preclinical studies (3Rs)
  - Opportunity for continuous regulatory input (via advisory board) on cancer risk assessment & biomarker qualification
  - Access to unique molecular profiling technologies and mechanistic models

Genotoxic carcinogens	2-Nitrofluorene Dimethylnitrosamine Aflatoxin B1 N-Nitrosomorpholine C.I Direct Black 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone 2-Acetylaminofluorene N-Nitrosopiperidine Methylendianiline
Non-genotoxic carcinogens	Methapyrilene HCl Thioacetamid Diethyl-stilbestrol Wy-14643 Piperonyl-butoxide Methylcarbamate Acetamide Dehydroepiandrosterone Ethionine Acetaminophen Cyproterone acetate Phenobarbital
Non-hepatocarcinogens	Cefuroxime Nifedipine Propranolol Clonidine Prazosin Ibuprofen Allyl alcohol 1,4-Dichlorobenzene

Results/achievements

- New technologies established for monitoring drug-induced perturbation of epigenome and microRNAs in rodent tissues (e.g. INTEGRATED GENOME-WIDE MOLECULAR PROFILING)

- Identification of novel early candidate biomarkers for non-genotoxic carcinogenesis (e.g. NON-CODING RNAs & CANCER SIGNALLING PATHWAYS)

- Novel insight into human relevance of candidate biomarkers using mouse models (e.g. CAR & PXR NUCLEAR RECEPTORS)

Time and money

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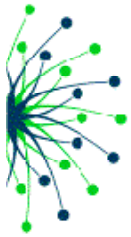
Financing

- IMI funding: € 6.049.578
- EFPIA in kind contribution: € 5.155.604
- Other contributions: € 2.114.051
- Total project cost: € 13.319.233

Timing:

- Starting date: 01.01.2010
- Duration: 60 months



Participants

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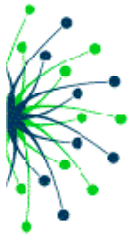
- EFPIA
  - Novartis *(Coordinator)*
  - UCB Pharma SA
  - Bayer Schering Pharma AG
  - Lundbeck
  - Boehringer Ingelheim
- SME
  - CXR Biosciences Ltd., UK
- EMEA & FDA scientists
  - via ad-hoc advisory board
- Academic
  - University of Dundee, UK *(Managing Entity of IMI beneficiaries)*
  - Medizinische Universitat, Vienna, Austria
  - Medical Research Council, Edinburgh, UK
  - Eberhard Karls Universitat, Tubingen, Germany
  - Natural & Medical Sciences Institute, Reutlingen, Germany
  - Institut National de la Sante et de la Recherche, Montpellier, France



CXR biosciences Boehringer Ingelheim Lundbeck NOVARTIS ucb BAYER Bayer

Further information

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www.IMI-MARCAR.EU

www.imi.europa.eu