MARCAR

BIO\textit{MAR}KERS & MOLECULAR TUMOUR CLASSIFICATION FOR NON-GENOTOXIC \textit{CAR}CINOGENESIS
What patients need

- 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)?

DNA damage
- Base alteration
- Crosslink
- Abasic site
- Double strand break
- Pyrimidine dimer
- Single strand break

Chromosome damage
- Point mutations

Carcinogenesis
- Multistage process

Cancer

Genotoxicity testing
- Required for IND
- Genetox battery
- Cost: $60K/cmpd
- Time: 1-3 month

Non-genotoxic mechanisms
- Nuclear receptor activation
- Proliferation
- Epigenetics
  - miRNA
  - Methylation

Carcinogenicity testing
- Required for NDA
- 2-year bioassay
- Cost: $3M/cmpd
- Time: 3 years

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

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

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

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

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

Luger et al., (1997)
Nature 389:251-260
Expected outcomes & benefits to patients

- 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
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

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

- **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
Further information

www.IMI-MARCAR.EU

towards novel biomarkers for cancer risk assessment

www.imi.europa.eu