INTERNATIONAL PhD PROGRAMME MAINZ

# EPIGENETICS IN THE CONTEXT OF HEALTH AND MEDICINE

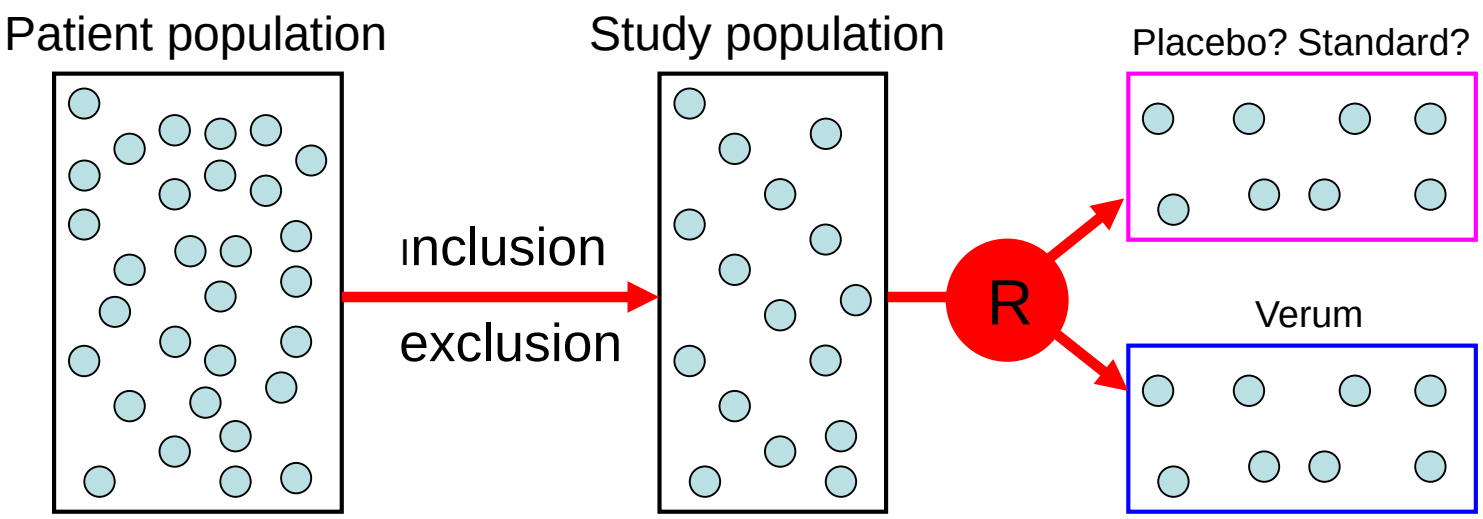
Prof. Leszek Wojnowski

# Learning objectives

INTERNATIONAL PhD PROGRAMME MAINZ

1) What are the main phases of the clinical drug and marker development?
2) Which epigenetic markers are currently used in patient management?
3) Which epigenetic drugs are currently used in the clinics?
*4) What are my interests in epigenetics?*

# Prospective validation of new drugs and treatments

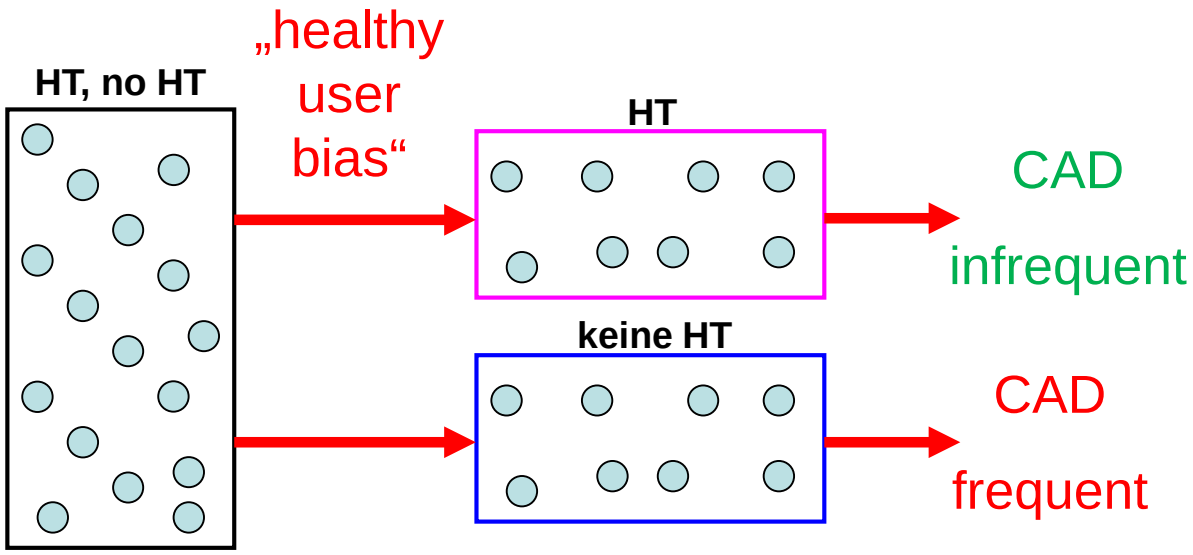



1. **<u>Randomized</u> (non-randomized)**
2. **Prospective (retrospective)**
3. **Controlled (uncontrolled)**
4. **Interventional (observational; all drug trials are interventional)**

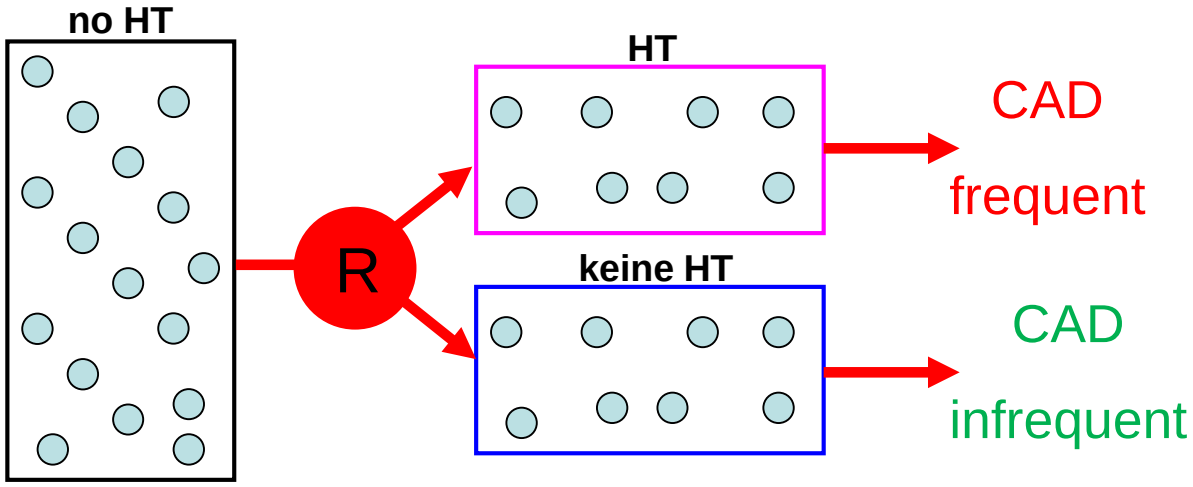
Benefit in*:

- healing
- survival
- life quality
- treatment costs

# Nurses- vs. WHI-Study

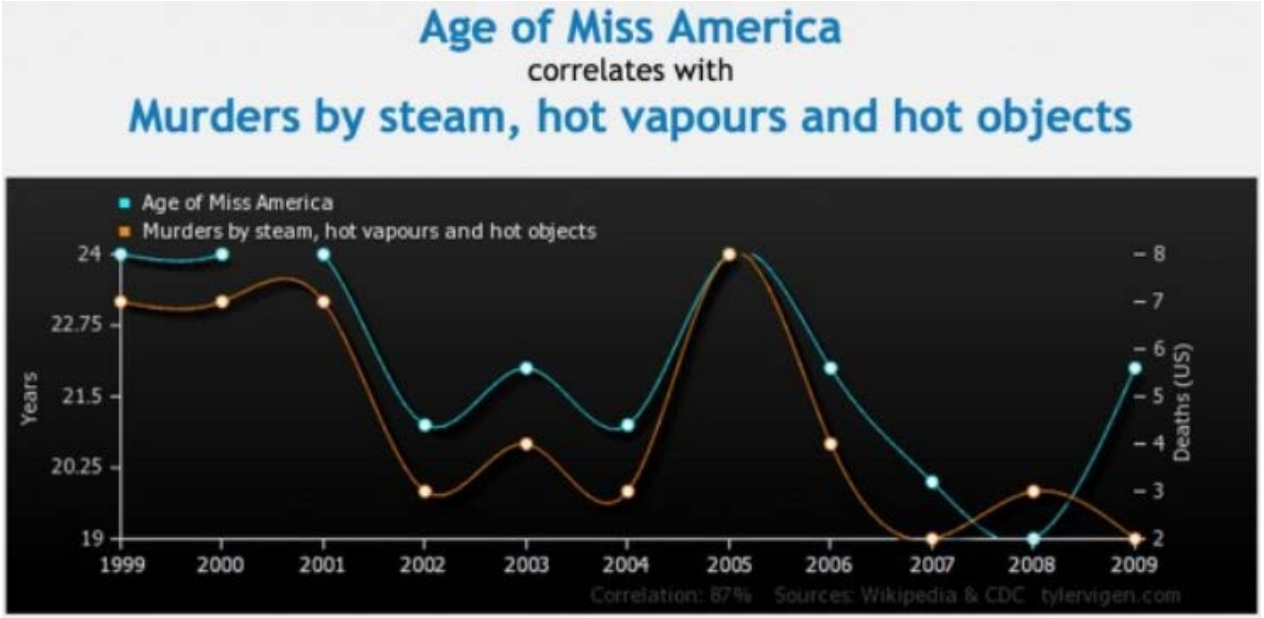



Also: less homicides, suicides, car accidents




Randomisation reduces the risk of biased selection

# What is the primary (preferentially clinical) end-point of the study?



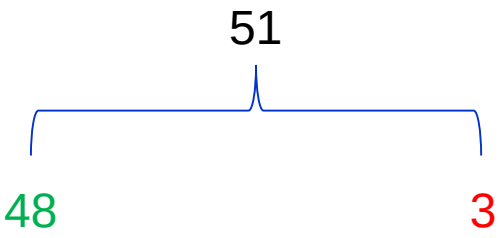

**The risk of false-positive findings increases with the number of statistical tests – „the more you search, the more you will find“.**

**The sequence of tests must be set prior to study onset.**

1. **Primary – most reliable, determines the study design**
2. **Secondary, tertiary… – less reliable**

# *Publication bias

Published antidepressant studies




**48/51 = 94%**

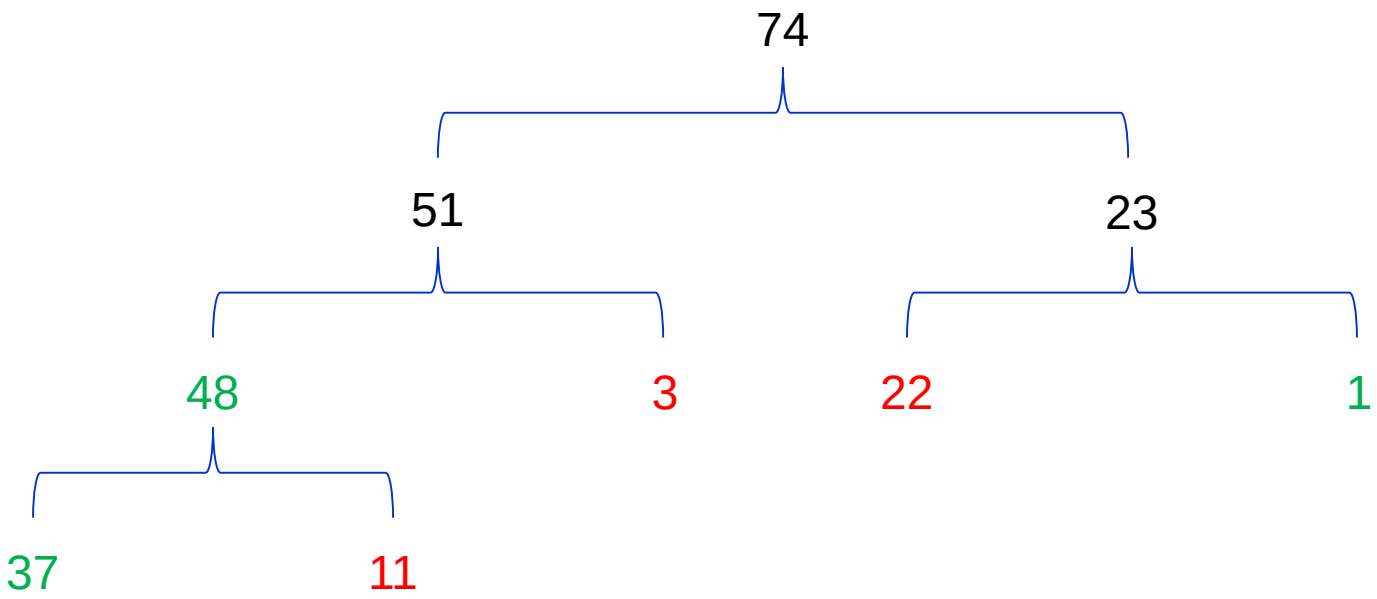
Positive effect

Negative or questionable effect

EH Turner et al. NEJM 358:252-260 (2008)

# Publication bias

Antidepressant studies registered at the FDA



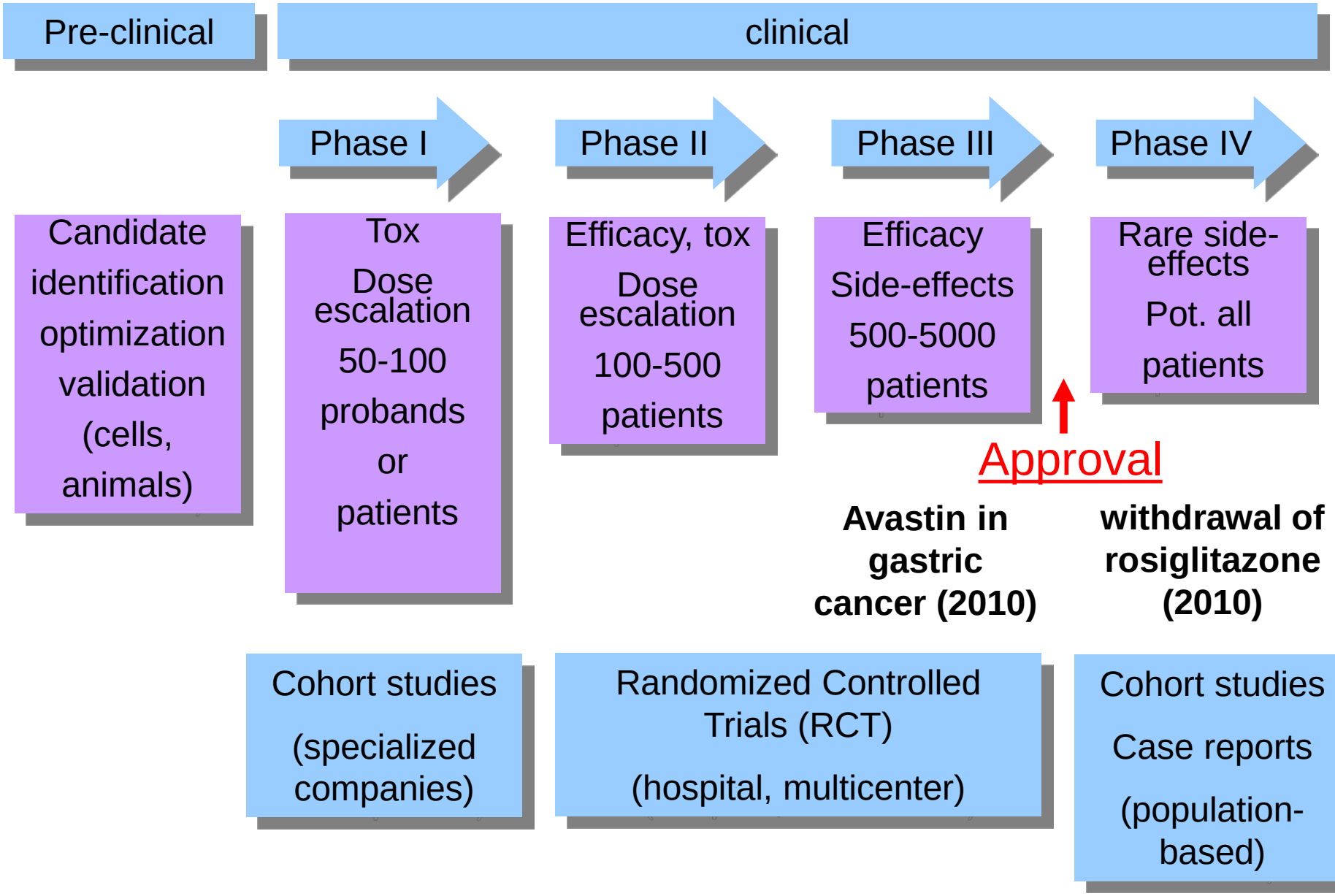

**38/74 = 51%** Positive effect

Negative or questionable effect

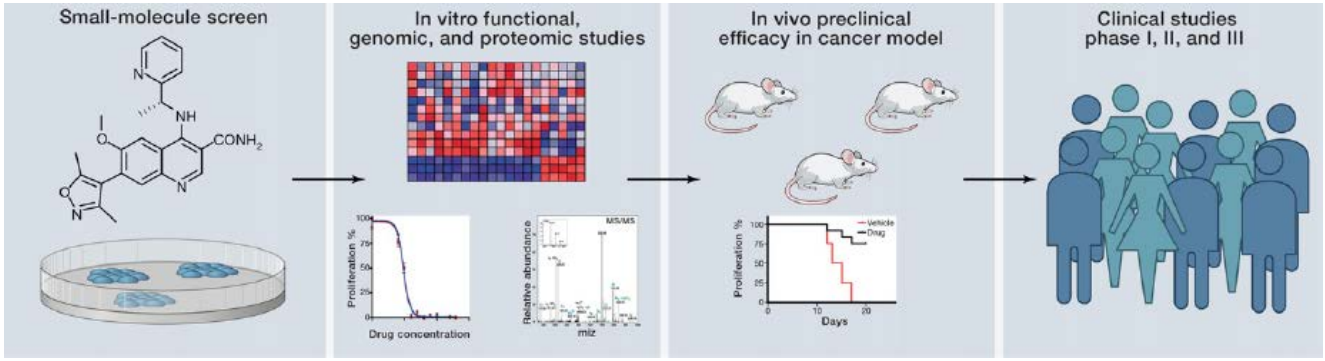
As a result, best journals require prior registration of trials. Nevertheless, industry-sponsored studies are currently less trusted than tax payer-sponsored studies (Kesselheim, NEJM, Sept 20, 2012)

EH Turner et al. NEJM 358:252-260 (2008)

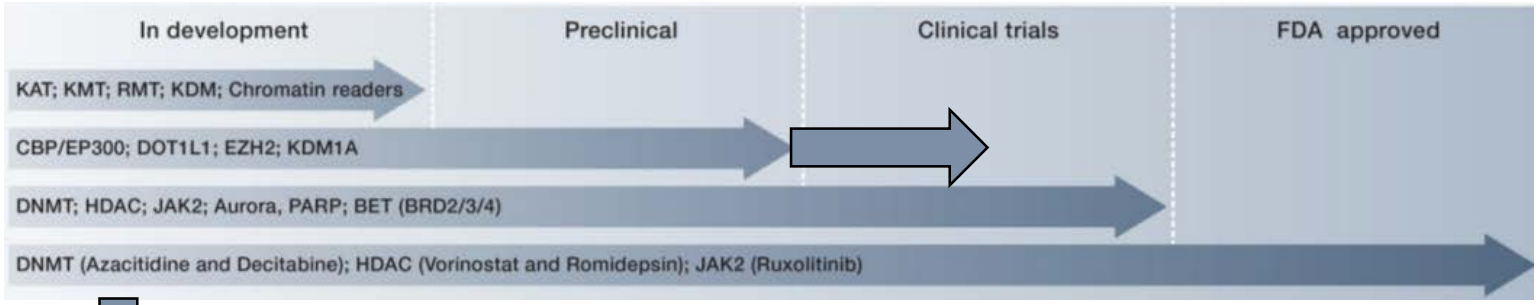
# The life cycle of a drug



# Epigenetic modifiers as cancer drugs




2016

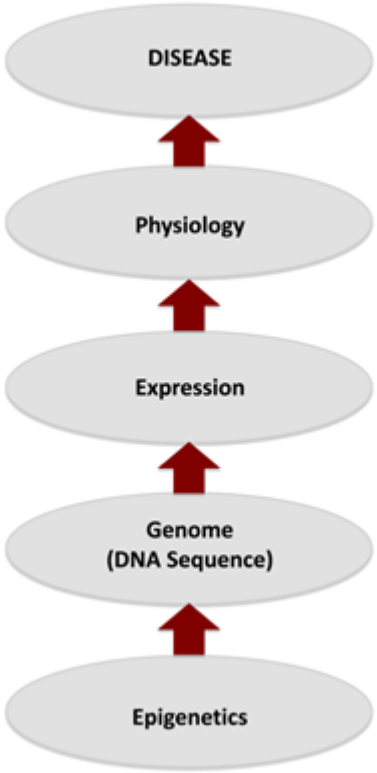



**FDA and EMA approved**:

- DNMT: Azacitidine (myelodysplastic syndrome- FDA and EMA), Decitabine (AML in adults- EMA, myelodysplastic syndrome- FDA)
- HDAC: Belinostat (peripheral T cell lymphoma- FDA), Panobinostat (multiple myeloma- FDA), Romidepsin, Vorinostat (cutaneous T cell lymphoma- FDA)

Dawson and Kouzarides, Cell 2012; Jones PA, Issa JJ and Baylin S, Nat Rev Genet 2016; Ahuja N, Sharma AR and Baylin SB, Annu Rev Med 2016

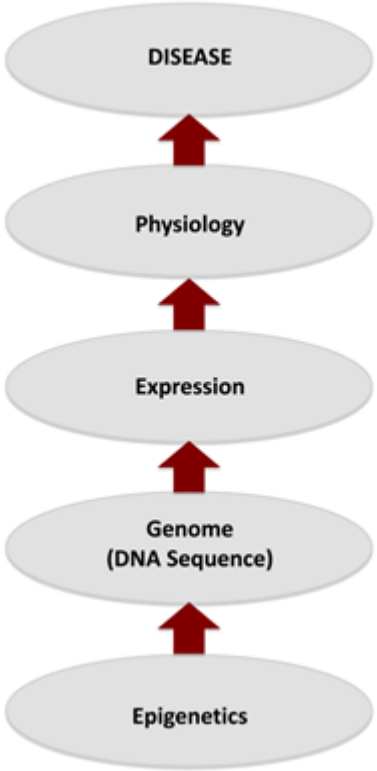
# Expected impact of epigenetics on disease management




Markers
- detection
- diff. diagnosis
- classification
- prognosis
- therapy

New drugs

# Detection of colorectal cancer – Septin9 methylation




Markers*

- detection
- diff. diagnosis
- classification
- prognosis
- therapy


New drugs

In October 2009, the Septin9 test was approved as a CE-marked test in Europe.

12.12.2013 Epigenomics AG Welcomes Reimbursement for Septin9 Testing by French Insurance Provider

27.11.2013 Epigenomics AG Announces FDA Advisory Committee Meeting to Review Epi proColon®

# US approval history

02.06.2014
FDA Issues Response Letter for Epigenomics' Colorectal Cancer Screening Blood Test Epi proColon® Requesting Further Data Pre-Approval

(…) need for additional data demonstrating that the blood-based Epi proColon® test will increase compliance to CRC screening in the intended use population, i.e. in those patients who today do not undergo CRC screening by guideline recommended methods such as colonoscopy or FIT.

13.04.2016 Epigenomics receives FDA approval for Epi proColon®

16.06.2016 Epigenomics' Epi proColon® Included in Newly Issued USPSTF Guidelines for Colorectal Cancer Screening


Gut, 2014, 63: 317-25
Sensitivity 48%; 35% in Stage I
"(…) the utility of the test for population screening for CRC will require improved sensitivity for detection of early cancers and advanced adenomas."

**Table 1. Comparison of Key Features of Screening Strategies.***

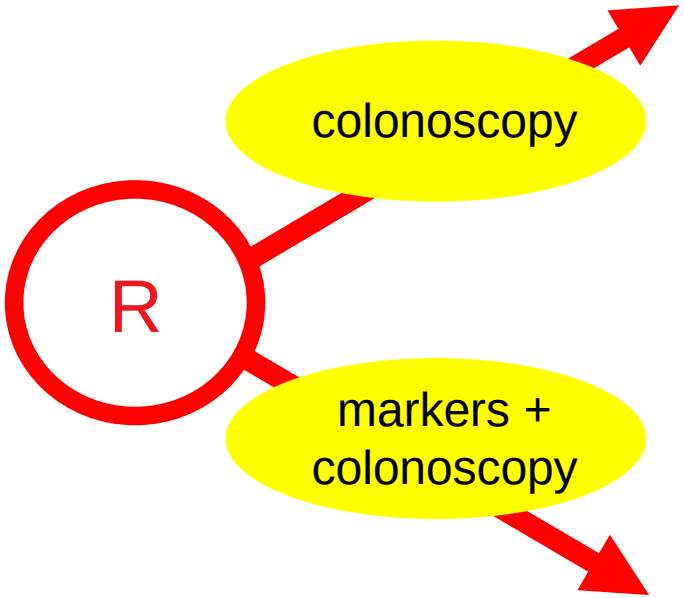
| Strategy and Effect on Cancer Mortality† | Quality of Evidence | Interval | Cost-Effectiveness‡ | Convenience and Requirements | Detection of Precancerous Neoplasia |
|---|---|---|---|---|---|
| Guaiac FOBT and FIT: 32% lower mortality | Multiple RCTs have shown a mortality benefit (reduction in mortality) for guaiac FOBT[2-7]; although FIT is more accurate than guaiac FOBT, RCTs evaluating FIT are lacking | Annual | May be more effective and less expensive than no screening; total costs lower than no screening, because of the high expense of late-stage cancer treatment with biologic agents | Performed at home | Does not reliably detect precancerous neoplasia |
| Flexible sigmoidoscopy: 27% lower mortality | RCTs have shown a mortality benefit[8,9] | Every 5 yr | Cost-effective as compared with no screening and other strategies | Limited bowel preparation as compared with colonoscopy | Can detect precancerous neoplasia |
| Flexible sigmoidoscopy plus FIT: 38% lower mortality | A single RCT showed that flexible sigmoidoscopy plus FIT reduces cancer mortality more than sigmoidoscopy alone[10] | Annual (FIT) and every 10 yr (sigmoidoscopy) | Cost-effective as compared with no screening and other strategies | Strategy that combines endoscopic and stool testing | Can detect precancerous neoplasia |
| FIT-DNA: unknown effect on mortality | Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer and precancerous polyps by FIT-DNA as compared with colonoscopy[11] | Every 1 or 3 yr | Less effective and more costly than FOBT, FIT, or colonoscopy | Performed at home | Does not reliably detect precancerous neoplasia |
| Colonoscopy: 68% lower mortality | A prospective cohort study showed a mortality benefit[12] | Every 10 yr | Cost-effective as compared with no screening and other strategies | Requires full bowel preparation; usually requires sedation and an escort | Can detect precancerous neoplasia |
| CT colonography: unknown effect on mortality | Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by CT colonography as compared with colonoscopy[13] | Every 5 yr | Less effective and more costly than FOBT, FIT, or colonoscopy | No sedation required but requires bowel preparation | Can detect precancerous neoplasia |
| Circulating methylated *SEPT9* DNA: unknown effect on mortality | Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by circulating methylated *SEPT9* DNA as compared with colonoscopy[14] | Unknown | Unknown | A blood test may be associated with greater adherence than that with other screening tests | Does not reliably detect precancerous neoplasia |

* CT denotes computed tomography, FIT fecal immunochemical test, FIT-DNA fecal immunochemical test combined with stool DNA test, FOBT fecal occult blood test, and RCT randomized, controlled trial.

† The effect on mortality represents a comparison of the strategy with either no screening or other strategies.

‡ Cost-effectiveness was determined as the cost per quality-adjusted life-year gained.

# Prospective validation of colorectal cancer detection




Benefit in*:

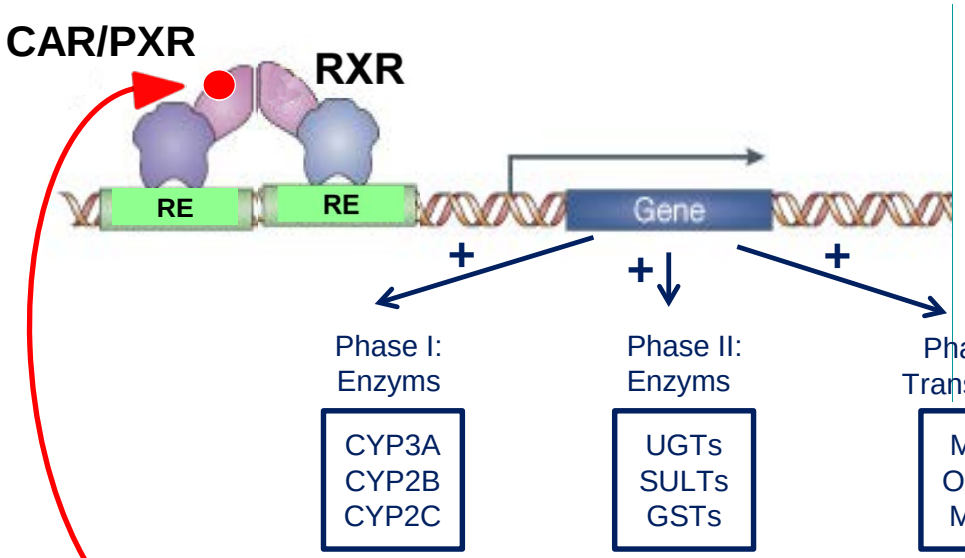
- survival
- life quality
- treatment costs

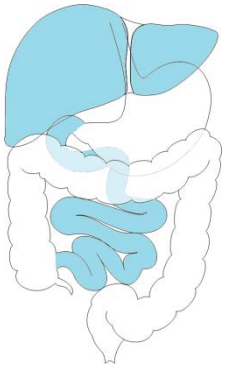
# CAR- and PXR-mediated defence against xenobiotics

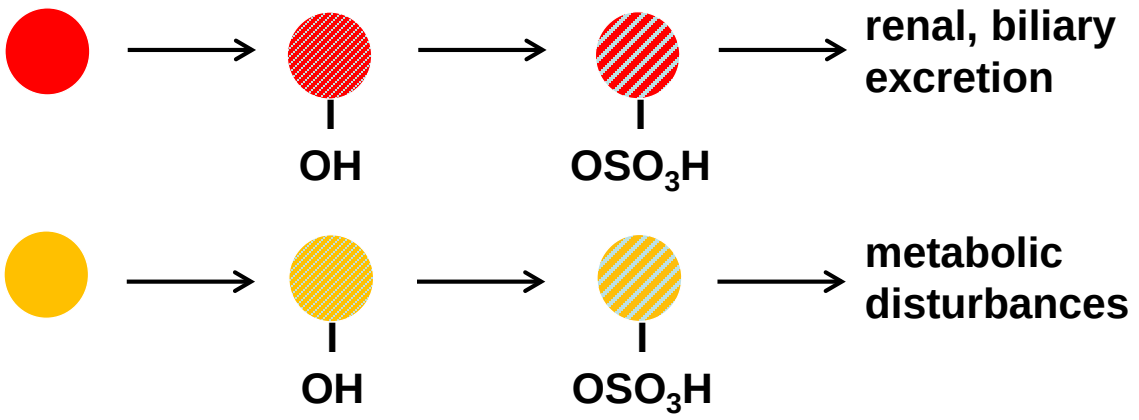
**Drugs:**
Glucocorticoids,
Antibiotics,
Antimycotics,
Statins,
Antiretrovirals,
Barbiturates,
etc.

**Environmental:**
Bisphenol A,
DEHP,
Pesticides, etc.

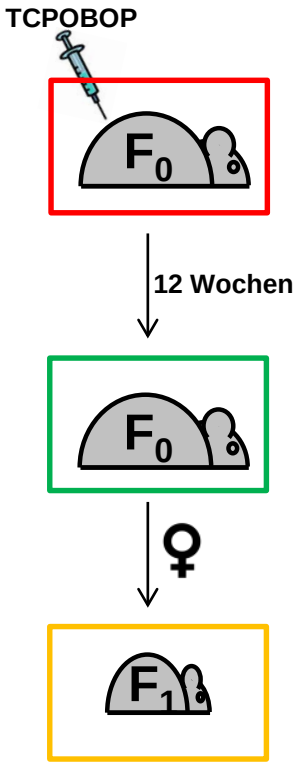
**Endobiotics:**
Steroids,
Bile acids,
Lipids

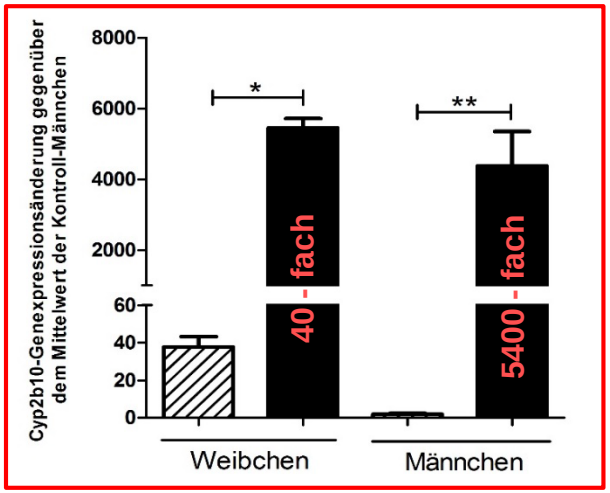


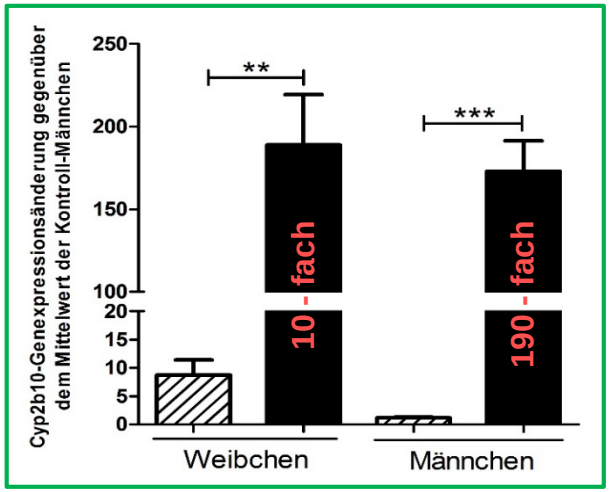



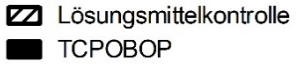


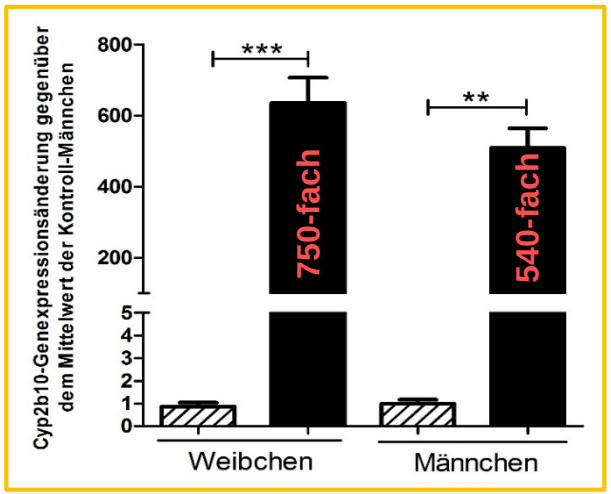
# Transmission of induction to F1

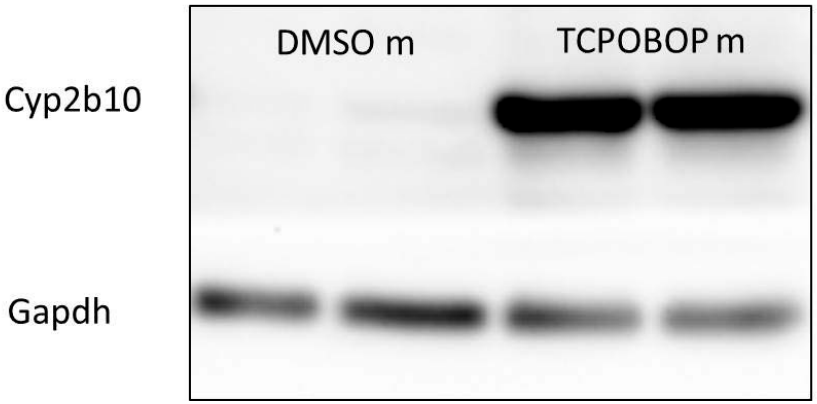


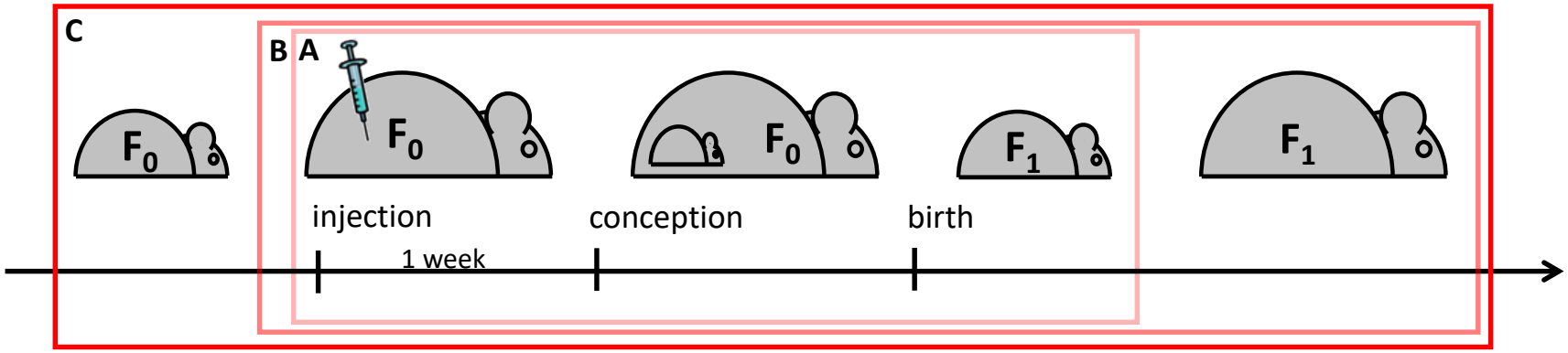



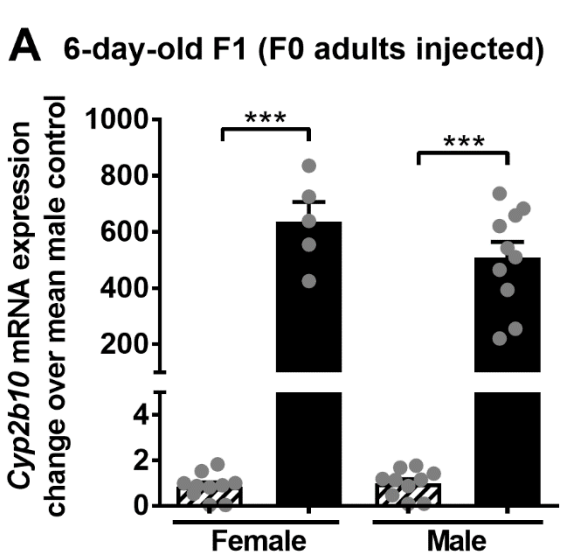



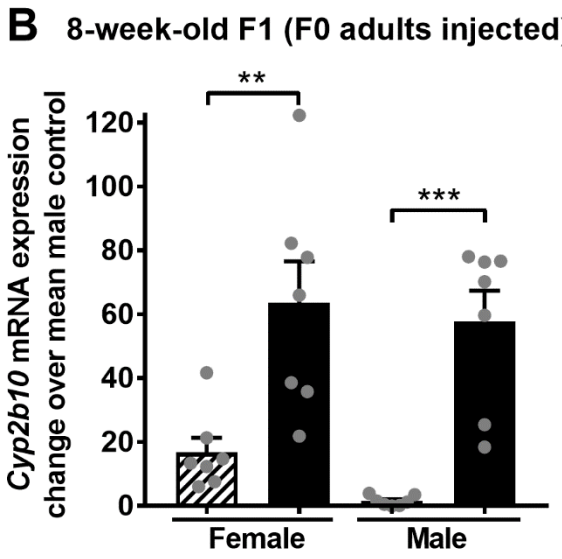



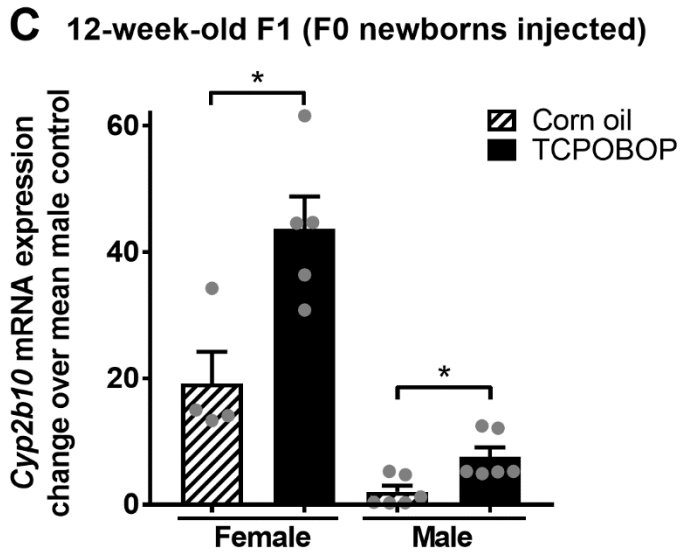

Ergebnisse von Dr. Marianne Mathäs

# Cross-generational *Cyp2b10* induction mediated by the mCAR ligand TCPOBOP



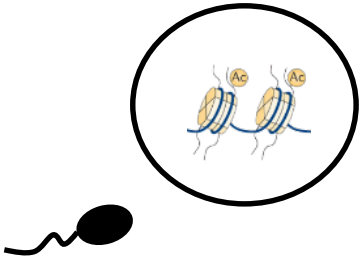



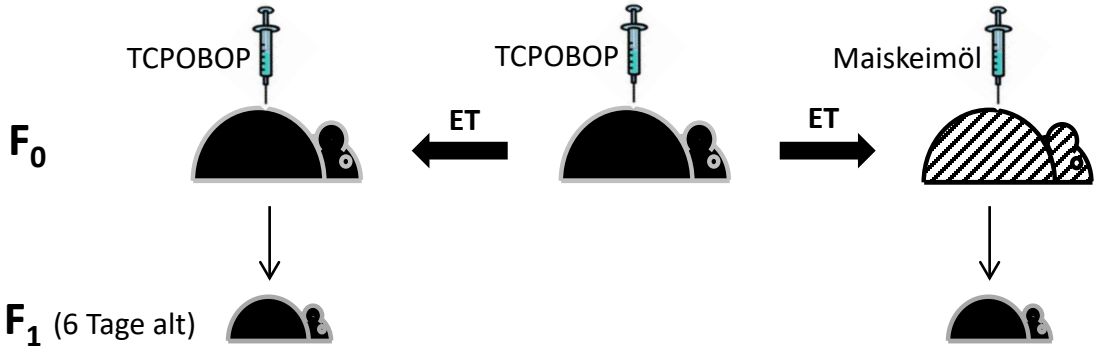



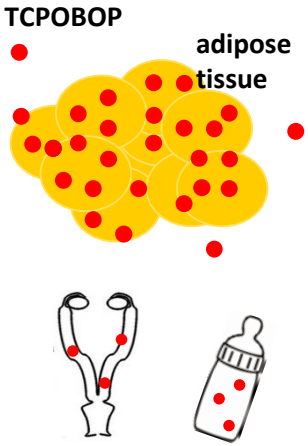
# Mechanism of cross-generational transfer

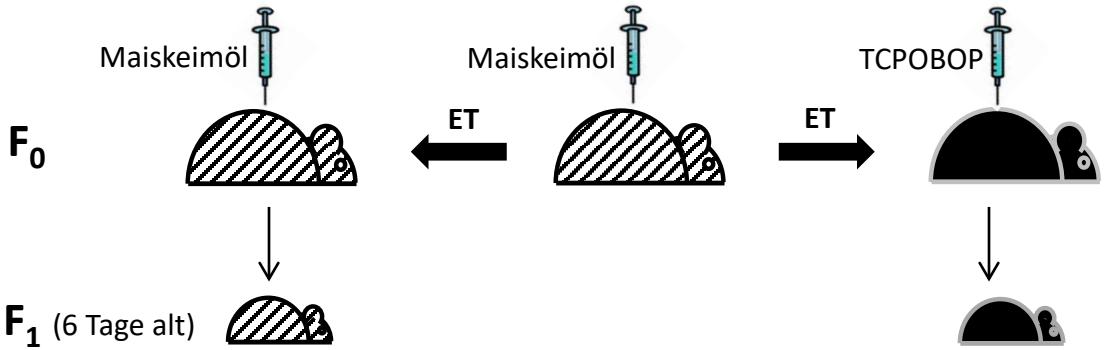
## A. preconceptional exposition



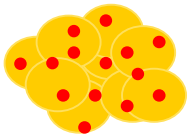



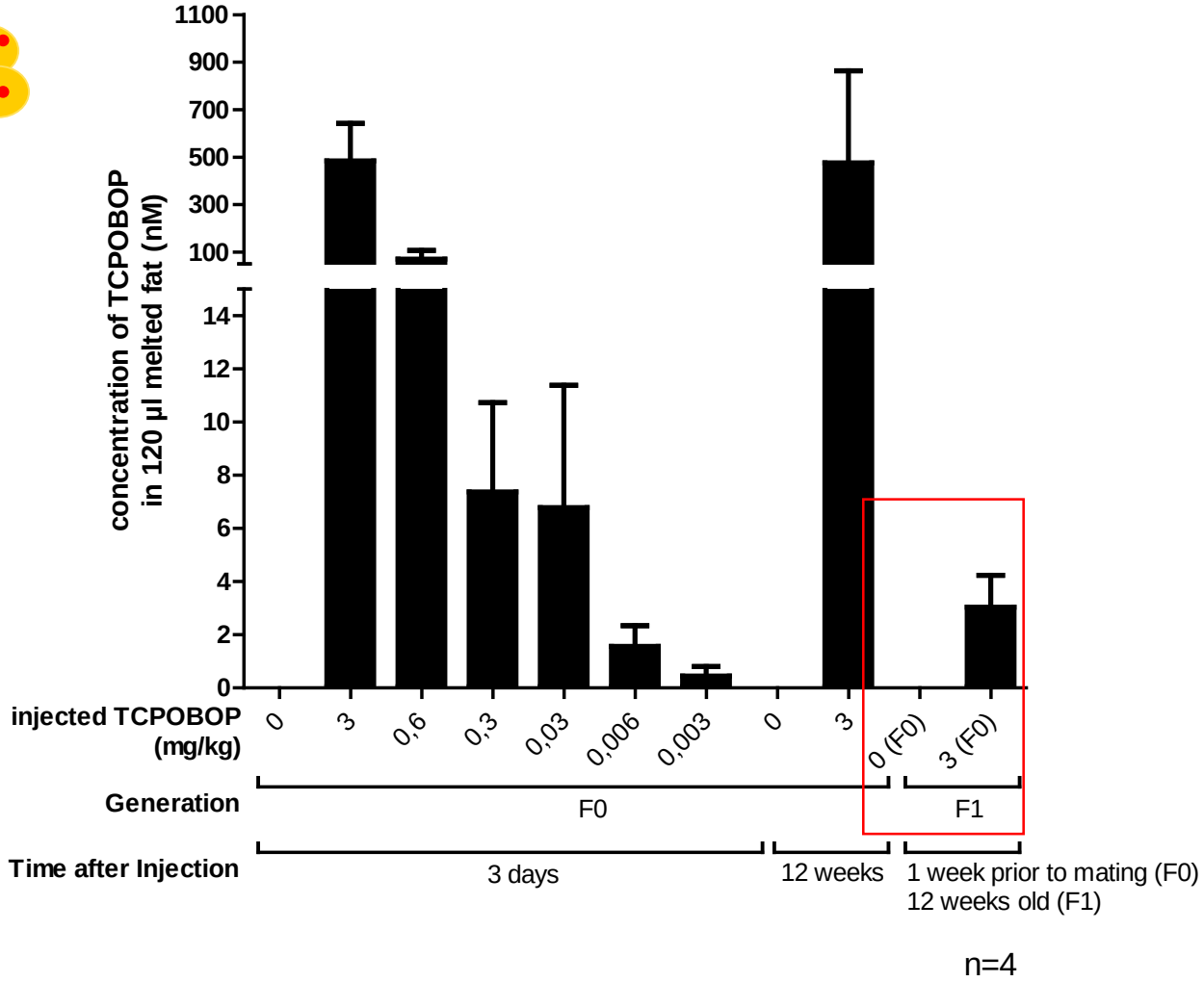

## B. postconceptional / intrauterine exposition



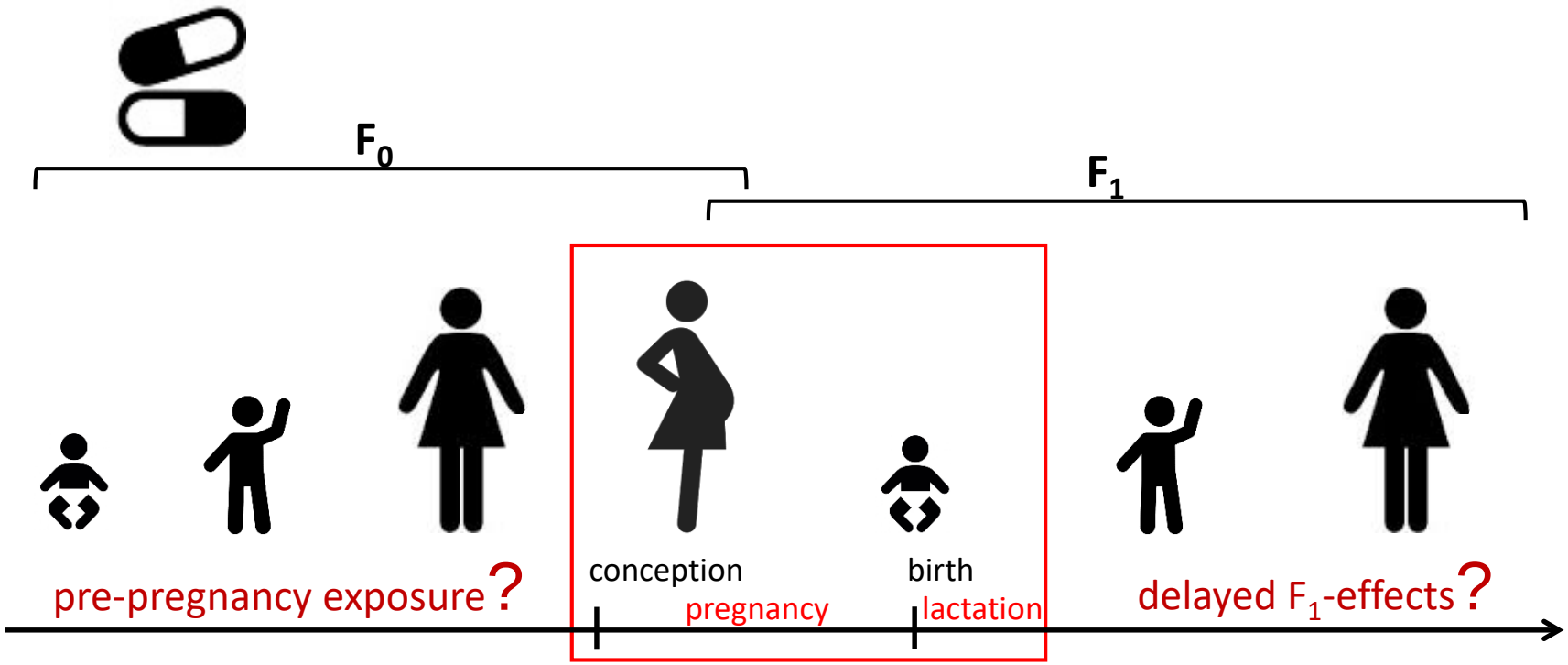
# TCPOBOP is detectable in the adipose tissue of the adult F1 generation






HPLC/MS measurements were conducted in cooperation with the Institute of Molecular Biology by Dr. Michael Musheev

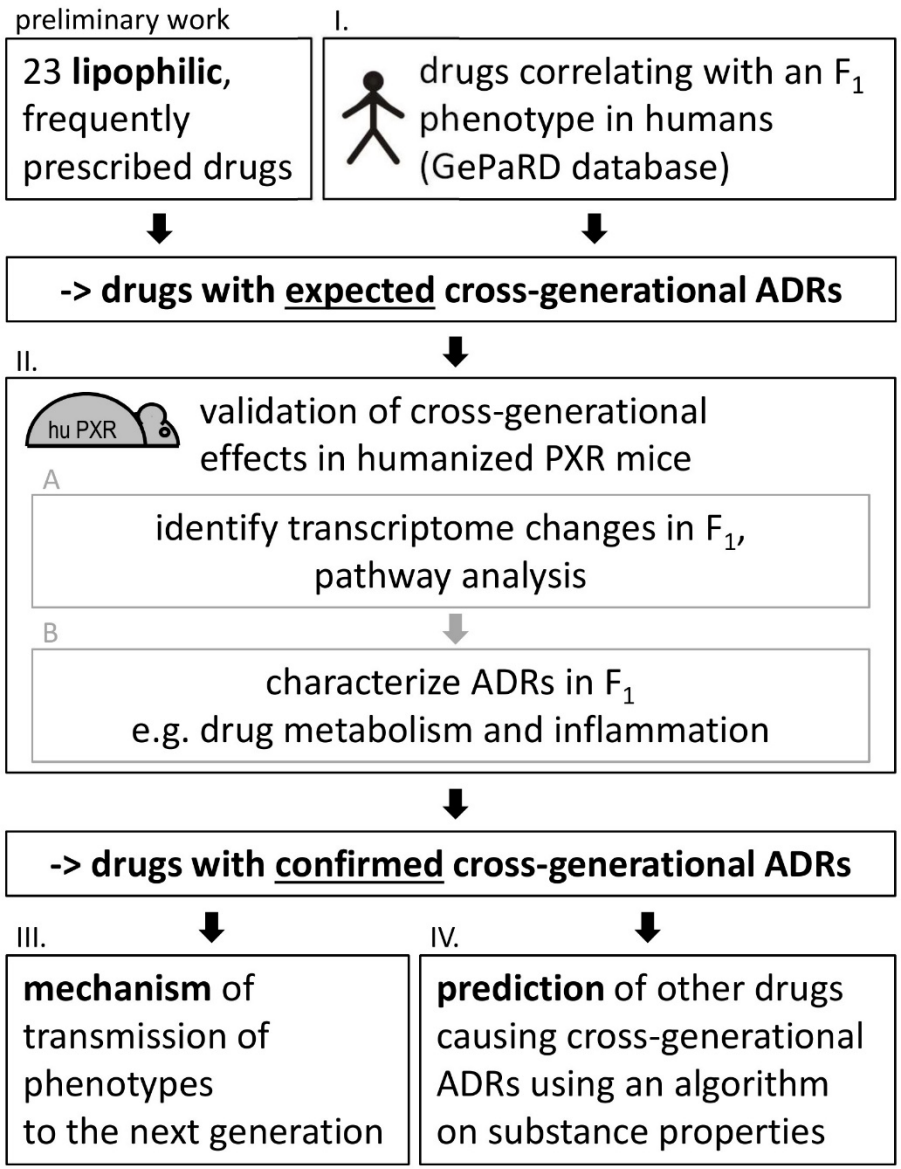
# Sicherheit von Arzneimitteln




termination 6-24month prior to pregnancy
cytostatics, radioiodine,
retinoids, vitamin K antagonists,
amiodarone, leflunomide
methotrexate

- Maternal drug exposure is considered during pregnancy and lactation
- Teratogenic effects right after birth get reported

# Outlook


preliminary work
23 **lipophilic**, frequently prescribed drugs
I.
drugs correlating with an $F_1$ phenotype in humans (GePaRD database)
-> drugs with expected cross-generational ADRs
II.
hu PXR
validation of cross-generational effects in humanized PXR mice
A
identify transcriptome changes in $F_1$, pathway analysis
B
characterize ADRs in $F_1$ e.g. drug metabolism and inflammation
-> drugs with confirmed cross-generational ADRs
III.
**mechanism** of transmission of phenotypes to the next generation
IV.
**prediction** of other drugs causing cross-generational ADRs using an algorithm on substance properties