Centrum pro výzkum toxických látek v prostředí

BIOMARKERS AND TOXICITY MECHANISMS

13 – BIOMARKERS

Omics + final notes

Luděk Bláha, PřF MU, RECETOX
www.recetox.cz

Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

EVROPSKÁ UNIE esf

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

OP Vzdělávání pro konkurenceschopnost

UNIVERSITAS MASARYKIANA BRUNENSIS

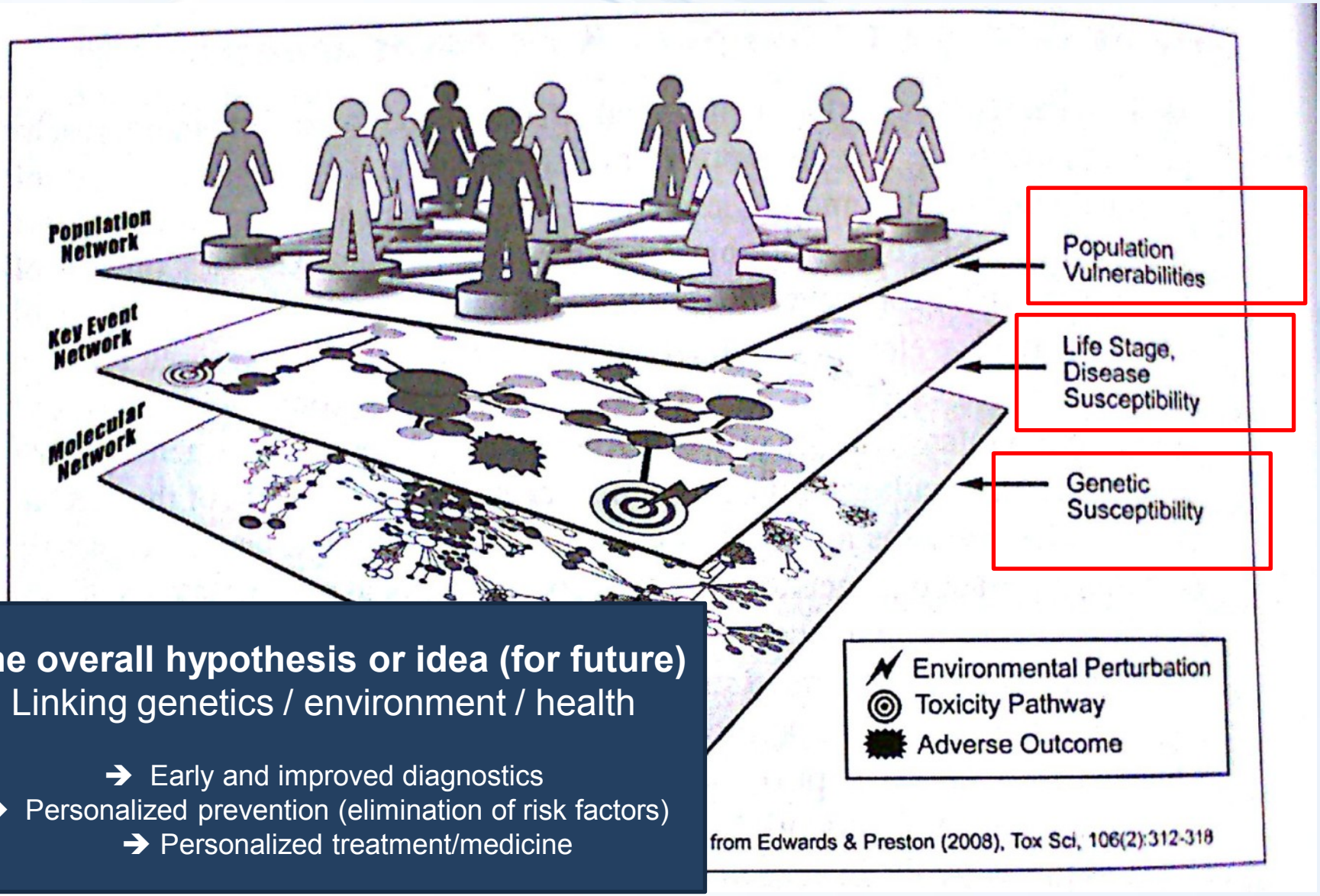
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Topics covered in the final presentation

- Biomarkers at different levels
  - *Omics*
  - *... and beyond*

- Biomarkers in human medicine and drug development
  - Strategy and steps in development
  - Application examples

Systems biology/toxicology/medicine = “omics”



The overall hypothesis or idea (for future)
Linking genetics / environment / health

➔ Early and improved diagnostics
➔ Personalized prevention (elimination of risk factors)
➔ Personalized treatment/medicine

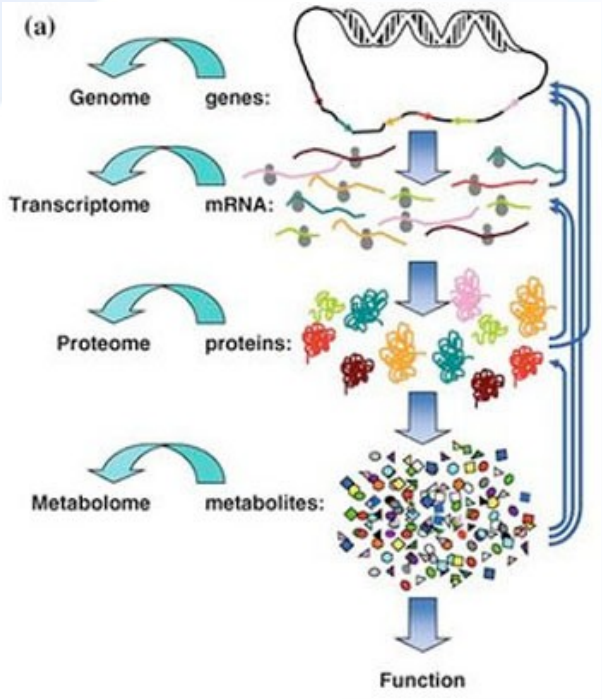
„OMICs“

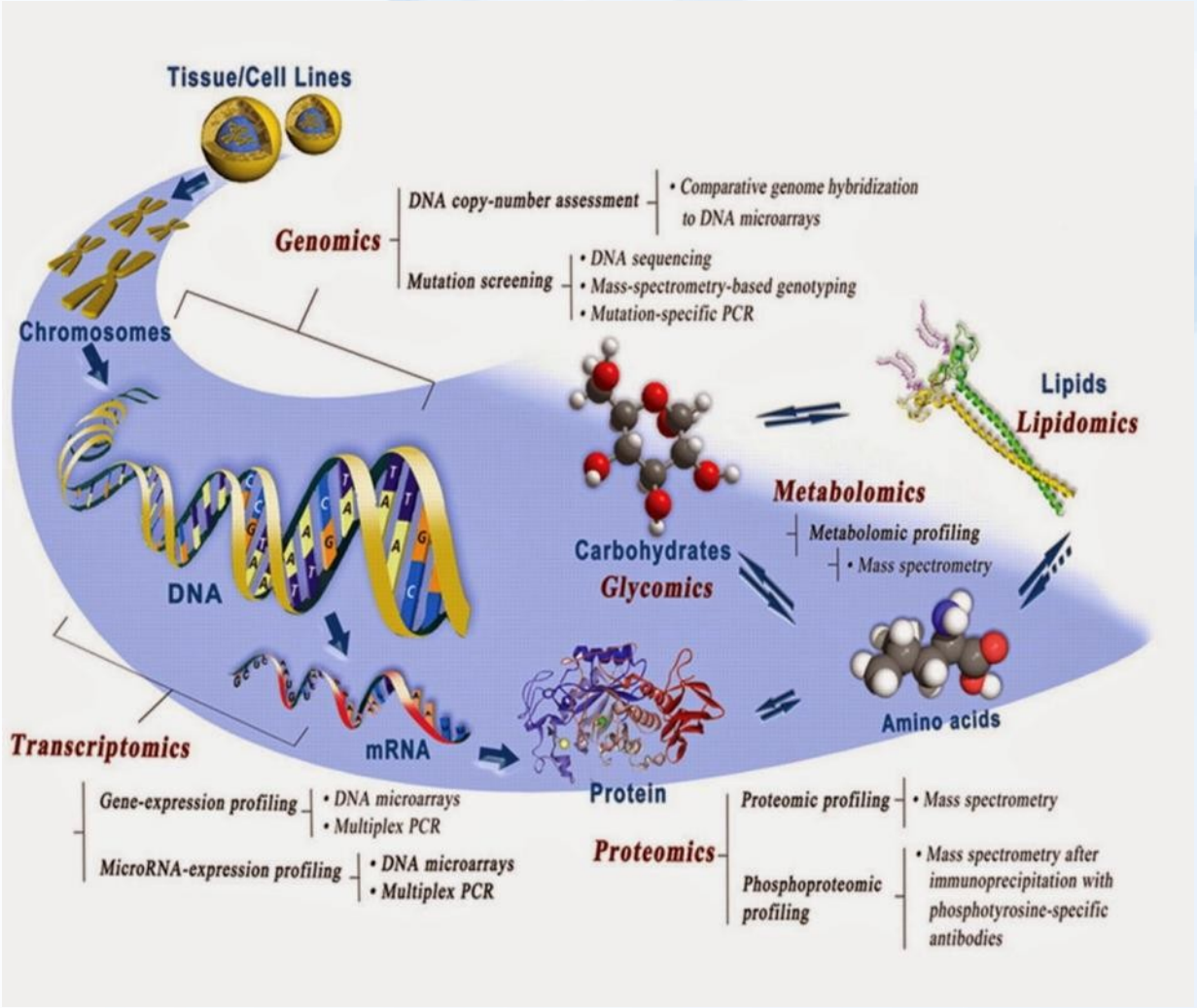
- **“Omics” techniques (**Systems biology)
  - Result of rapid technological advances (microarrays, next generation sequencing, HPLC-mass spectrometry techniques etc.)
  - Simultaneous and „instant“ assessment of thousands of parameters (biological / toxicological responses) at different levels
  - „Big data“generated ➔ bottleneck is data analysis (bioinformatics, self-learning machines, artifical intelligence?)

- **Genomics**
  - Genes (DNA) - relatively stable
    - not responding to immediate environmental changes (e.g. Toxicants)
    - „slow“ changes possible
      - Epigenetics (e.g. DNA methylation)
      - Mutations (evolution) → Single Nucleotide Polymorphisms (SNPs)
  - Used as “biomarkers of susceptibility” (SNPs / personalized medicine)
- **Other omics**
    - mRNA levels (transcriptomics)
    - proteins (proteomics)
    - metabolites (metabolomics), etc....
  - Resposive to stress (including toxicants, therapy etc.)

Biomarkers at different biological levels – „omics“ approach

OMICs (1) – from genes …. to … functions





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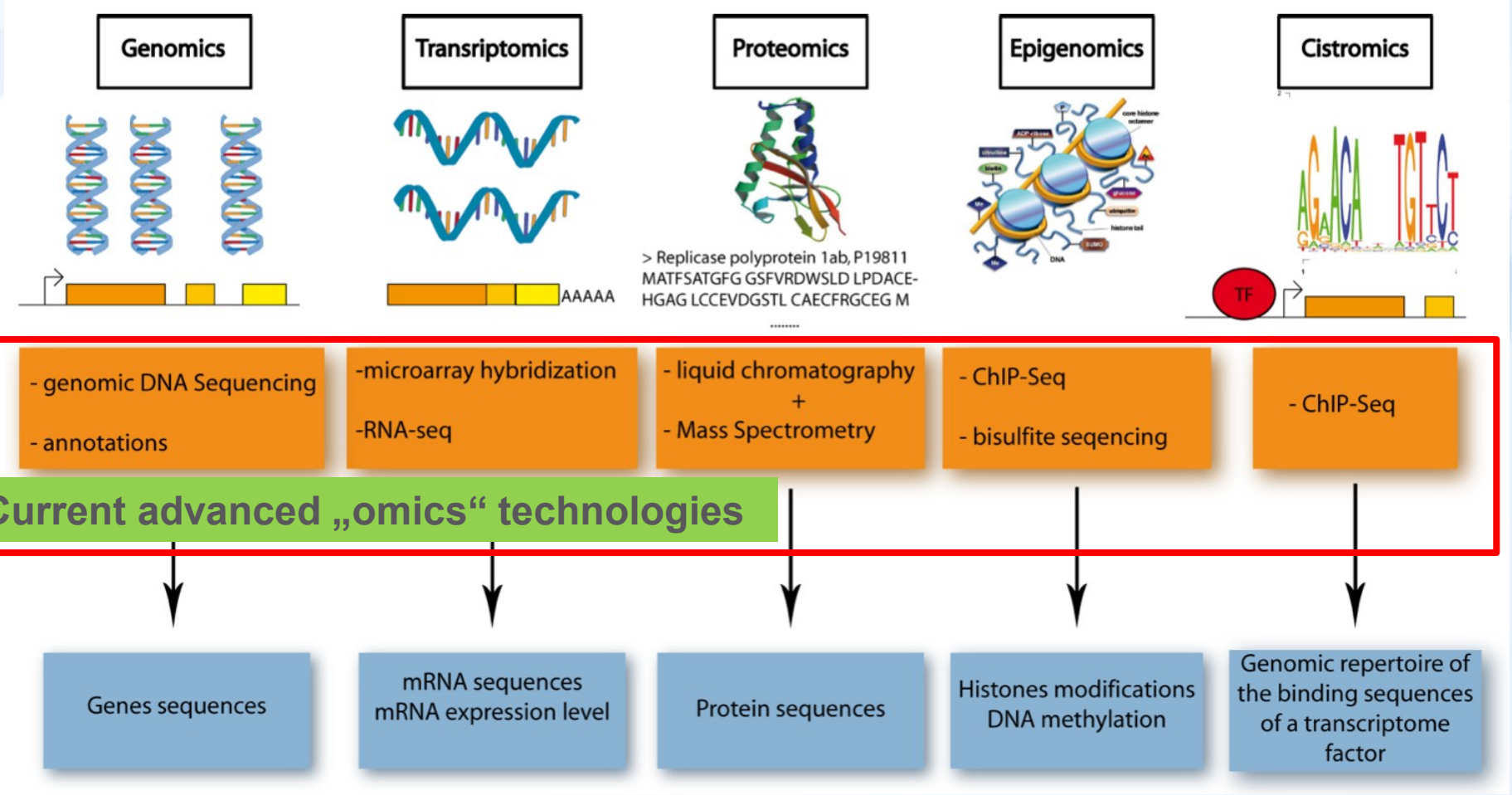
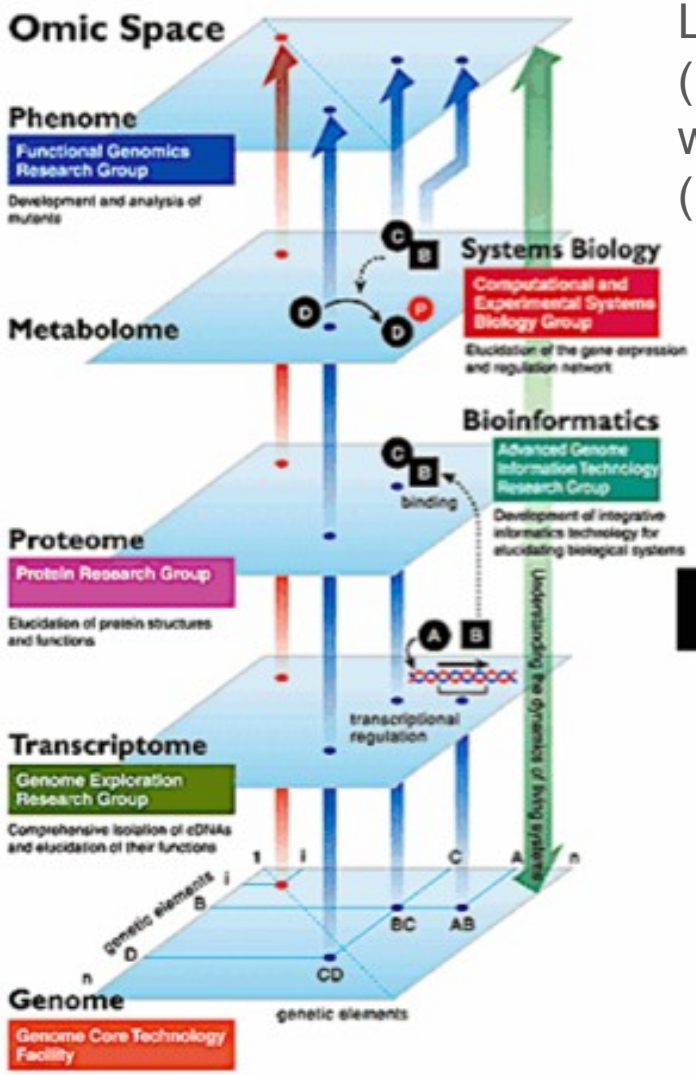
Biomarkers at different biological levels – „omics“ approach

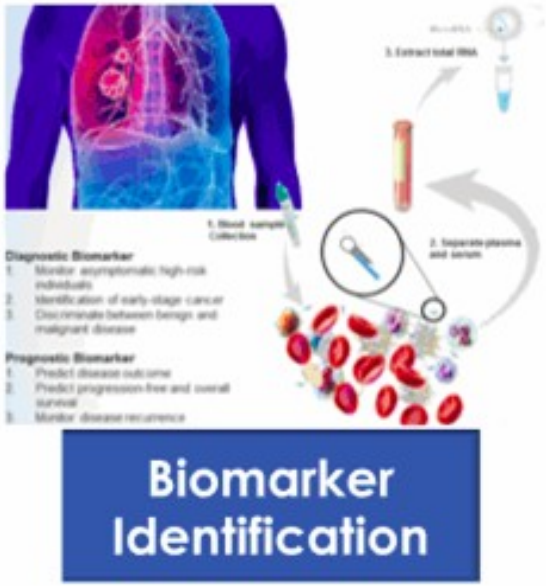


Biomarkers at different biological levels – „omics“ approach

OMICs (2) – … including PHENOTYPE (phenomics)

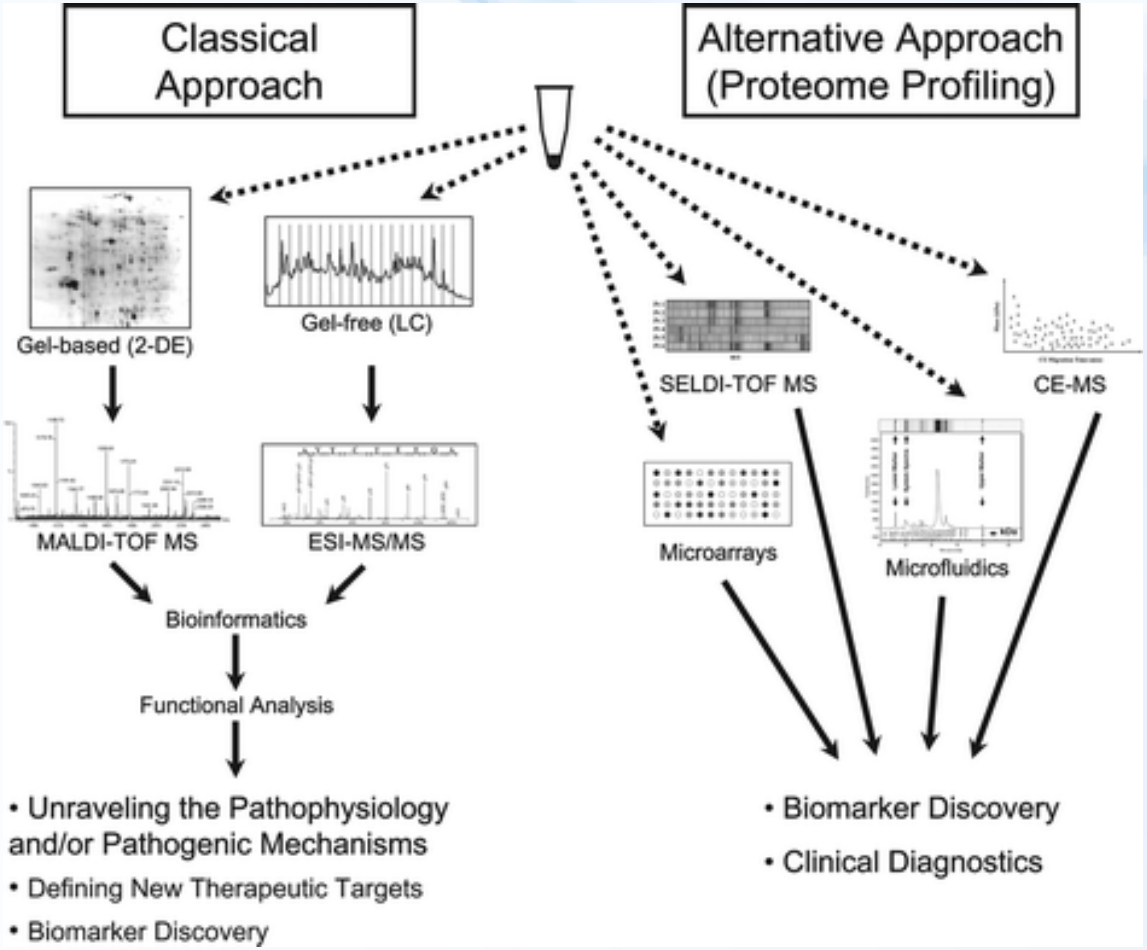


Linking „outcome“
(health, intoxication, **phenotype**)
with mechanistic changes
(i.e. „biomarkers“)



Biomarkers develoment using „omics“ approaches

- **Different approaches towards new biomarkers**
  - Hypothesis driven
  - Data driven - omics
    = screening followed by correlations *(example figure – „proteome“)*



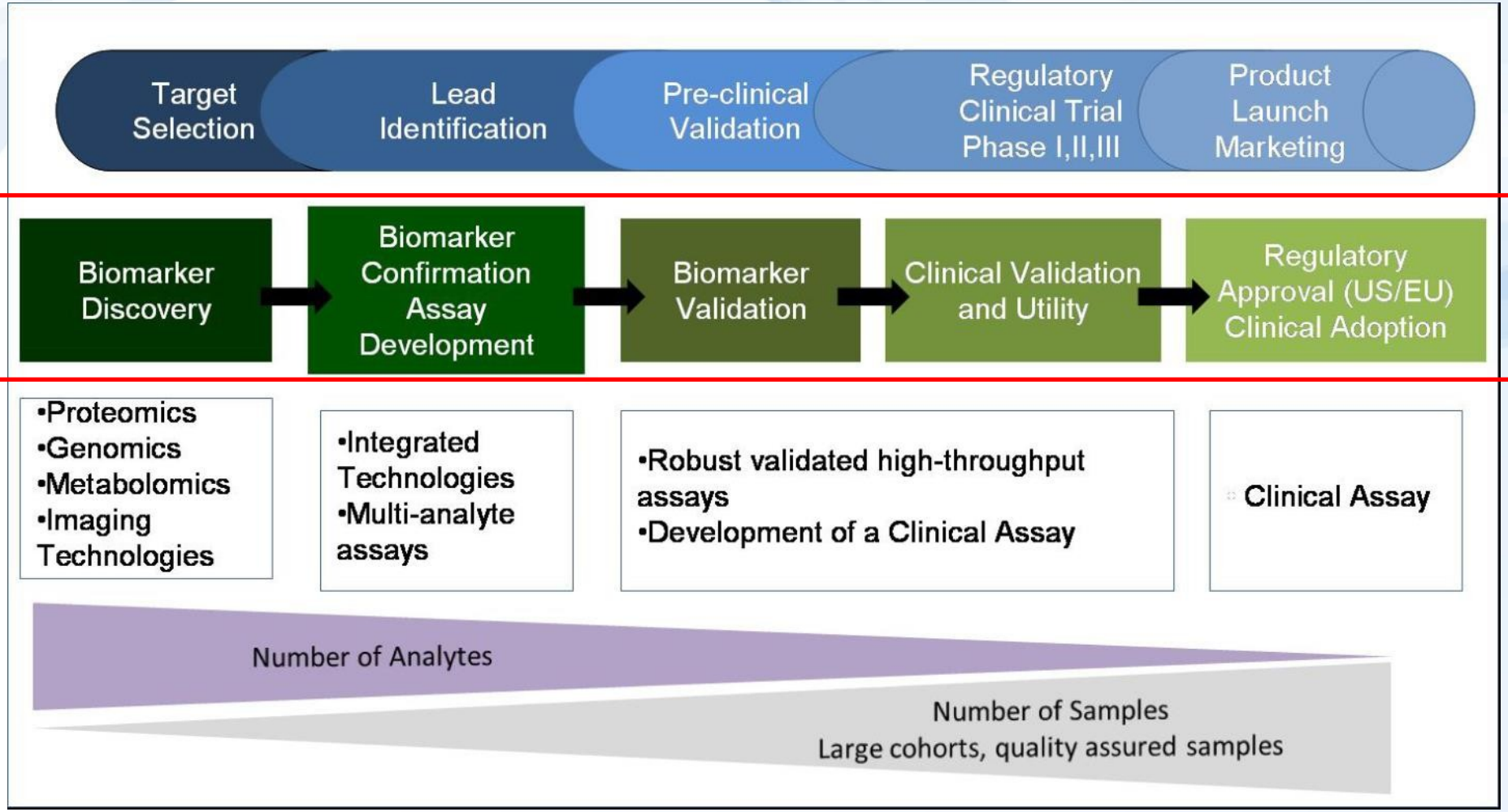
Biomarkers develoment using „omics“ approaches

- **Steps towards biomarkers**
  1. „Big omics data“ generated (easy and fast)
  2. Correlations (bioinformatics) with health outcomes (bottleneck) →eventual identification of suspected biomarkers
     - e.g. Toxicant activates genes → higher level(s) of specific mRNAs (or higher protein levels)
     - E.g. Complex effects at several levels → modulation of profile(s) of certain metabolites
  3. Characterization and validation of biomarkers (bottlenec: time and cost demanding)
     - Experimental - stability of biomarker responses throughout different stress levels (exposure doses, exposure duration, various conditions, males x females …. Etc)
  4. Qualification and approval (clinical and epidemiological studies)

→ Despite of decades of omics era, there are **only rare (if any) examples of biomarkers derived by omics** currently applied in practice

More detailed view: 5 steps leading to biomarker use in practice

DISCOVERY → VALIDATION STEPS → APPROVAL

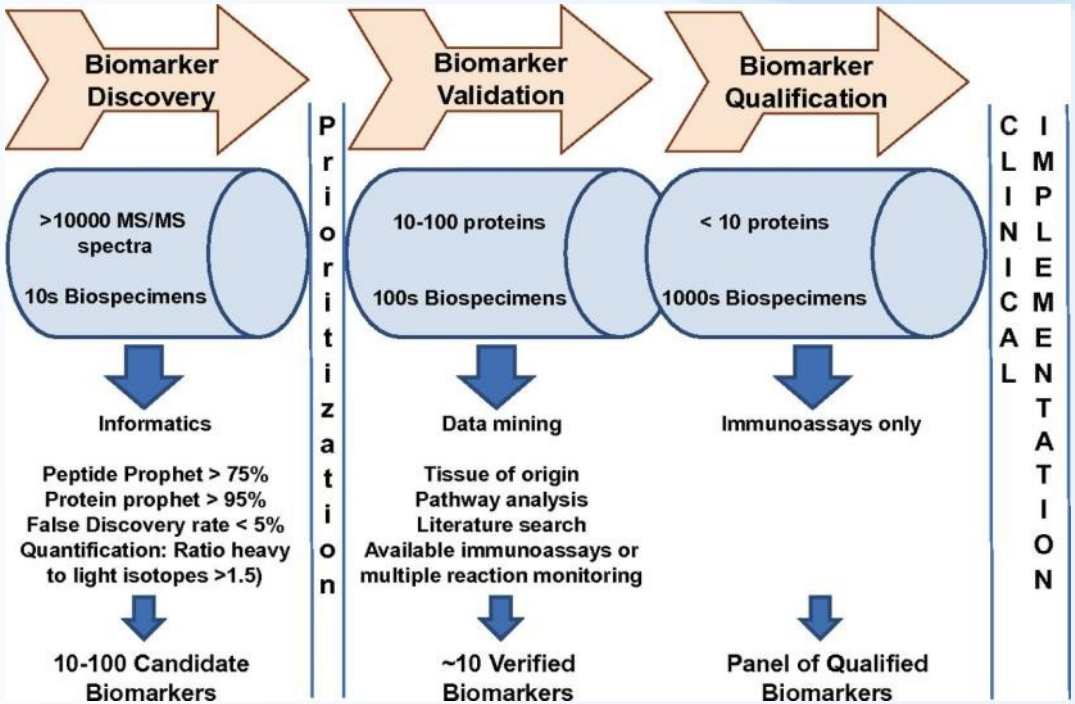


Detailed zoom = example: proteomics

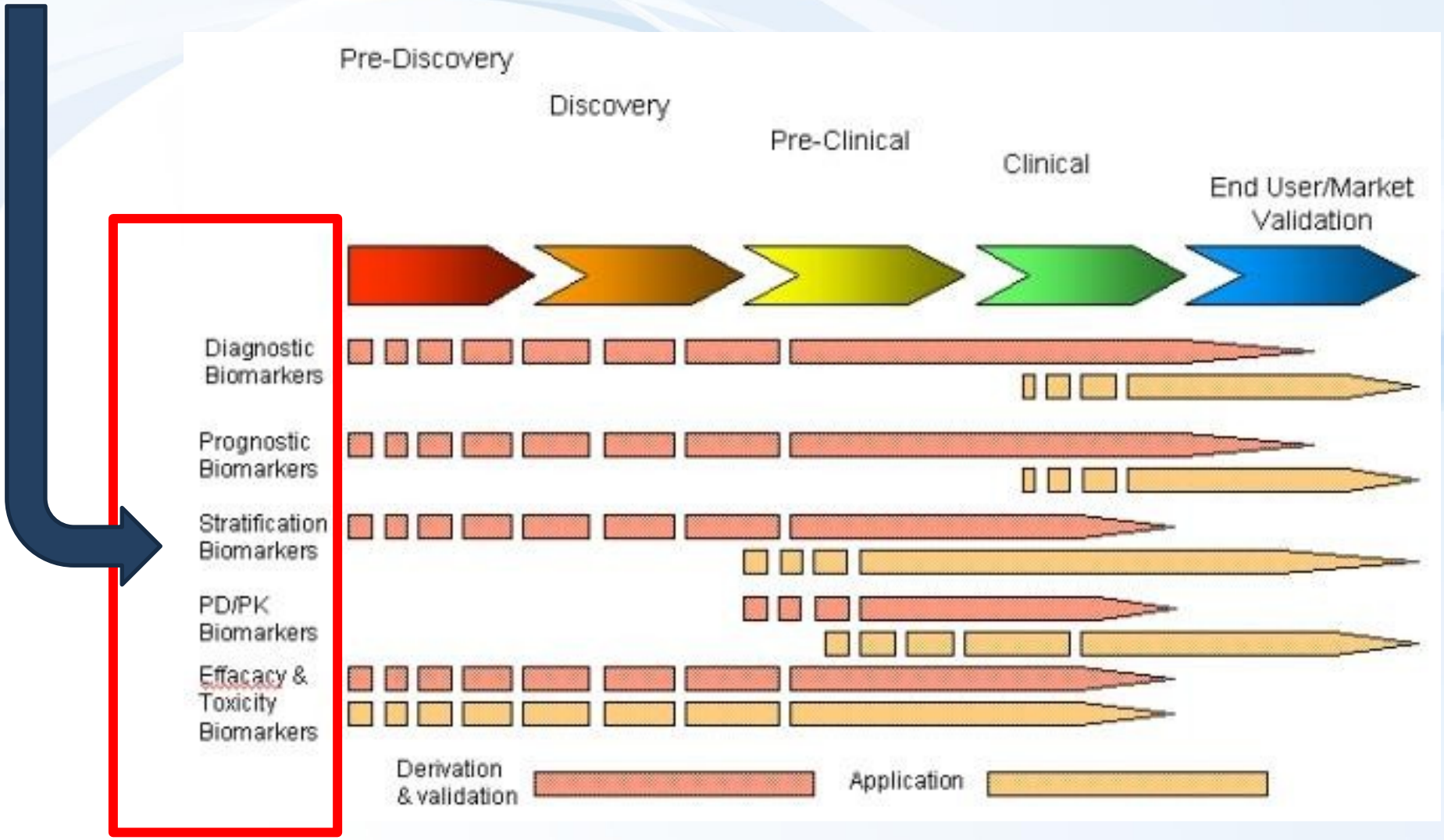
1. **Biomarker development**
   - High numbers of endpoints (e.g. proteins)
   - Low numbers of samples compared (e.g. 10 controls vs 10 “treatments”)

2. **Biomarker characterization and validation**
   - Decreasing number of markers
   - Increasing numbers of specimens (biological samples)

3. **Biomarker qualification and approval**
   - Individual markers
   - Analytical methods validated and well established



Biomarkers have potential for different applications ... such as:



Biomarkers have potential for different applications ... such as:

- **Biomarkers in research**
  - Search of “potential” therapies/drugs
    - Changes in biochemical responses provide information on efficiency and mechanism of action
  - Identification of “early markers” of chronic diseases
    - Early diagnosis (e.g. identification of developing cancer, coronary disease...)

- **Biomarkers in medicine**
  - Identification of **status** of an individual
    - Healthy vs Disease
  - Assessment of therapy/treatment
    - Efficiency – Did treatment improved situation? (improvements in biomarker responses)
    - Adverse or side effects of therapy

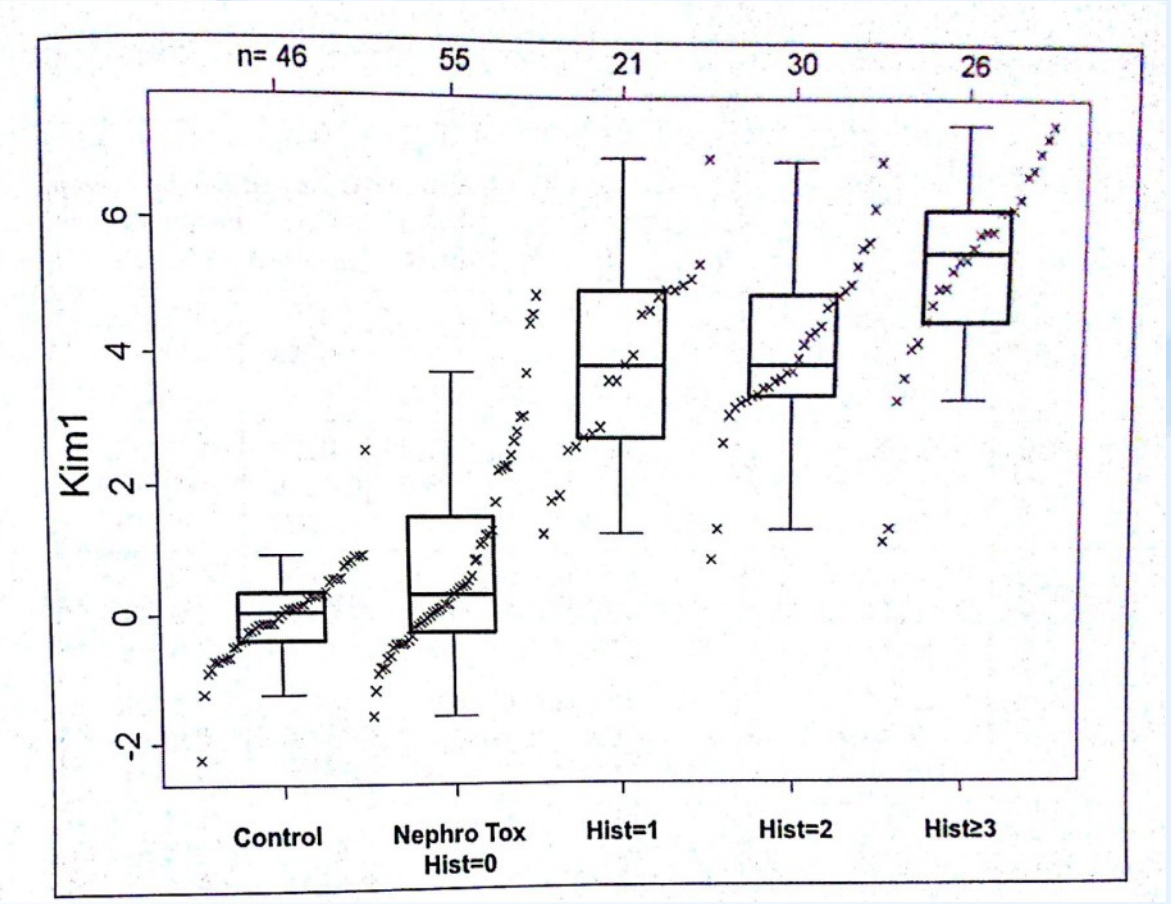
- **Biomarkers in toxicology**
  - Identification of status
    - Intoxicated (exposed) vs Controls
    - Forensic toxicology (e.g. consumption of drugs of abuse, alcohol etc)
  - Early warnings of future health consequences
    - Biochemical changes are detectable before the actual health problems

Biomarker „validation“– example

Good characterization and critical assessment needed during validation.

Example: Kim-1 protein related to kidney injury by toxicants

- Kim-1 levels significantly elevated only at manifested clinical signs = histopathology grades 1-3 („**diagnostic**“ biomarker = status)
- **Poor „prognostic**“ potential (overlap of Controls and initial toxicity condition (histo-grade 0)



Summary and overview

Class on toxicity mechanisms (MoA) and biomarkers

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Class summary and take home message

* Molecular effects of toxicants = MoAs (1)
* Propagate to higher levels (2),
* … where they induce measurable “responses” - biomarkers (3)

1

MoAs

* Molecular interactions
* Key targets ...:
  - DNA, RNAs
  - proteins (and their functions)
  - membranes
* Complex mechanisms
  - Oxidative stress
  - Signalling and hormones
  - Detoxification

2

Biological organization

3

Biomarkers

- types
- examples
- methods

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Summary on toxicity mechanisms (MoA) and biomarkers

For excellent performance and successful exam student should:

1. have an **overview** of different types of MoAs (see also point 2 below) and be able to **link** MoAs to higher level effects (toxicity)
   - *Example: inhibition of AcCholE enzymes (mechanism) → propagates as neurotoxicity (effect)*

2. know some **details for selected example MoAs** for different toxicant targets
   = based on your own interest select one example from each of the following categories, learn details, be able to discuss (i.e. know details for 7 example modes of toxic action)
   1. nucleic acids
   2. proteins
   3. membranes (lipids)
   4. cellular
   5. Complex 1 – detoxification/metabolization
   6. Complex 2 – intra- and inter-cellular signalling, hormones
   7. Complex 3 – oxidative stress

3. have **understanding of biomarker** issues
   - What is a biomarker and what properties it should have (or not to have)?
   - Why we search for them = how can they be used?
   - What different types and groups of biomarkers can be recognized?
   - What are suitable matrices for sampling and further analyses?
   - What approaches are applied in biomarker discovery („hypothesis“ vs omics)?

4. and **know example biomarkers**
   same approach as for point 2 above = based on your own interest select one example biomarker for each of seven categories and know some details)