

Breakout Session 2

Conclusions

Biomarkers as bridge exposure and health effects

The contribution of individual sensitivity

Systems biology approach

Plan of the breakout session:

- Biomarkers: what are they supposed to mark?
- What are the available markers, and how useful are they?
- Contribution of individual sensitivity
- Biomarkers and systems biology
- Research priorities

Biomarkers: Functional considerations

Biodosimeter: A quantifiable biological parameter that acts as a surrogate for the dose received by the individual.

Risk predictor: A surrogate measurement for the health outcomes expected from the dose received.

Disease susceptibility predictor: Identify individuals at greatest risk after exposure.

Prognostic marker: Indicator of the eventual course of a disease developing after exposure,

Note that many outcomes considered here are stochastic.

Biomarkers: Availability and functionality

- DNA-centric biomarkers
- Proteomic biomarkers
- Metabolomic biomarkers
- Cellular (ex-vivo) biomarkers

DNA-centric biomarker

Chromosomal markers such as dicentrics and stable translocations:

Pro:

- Clear indicators of high level exposure
- Time function
- Mechanism of formation can be modelled and quantified

Contra:

- Relevance to long-term endpoints unclear
- Confounders known (disease, age)
- High variability due to biology or methodology

Facit:

Biodosimeter, relevance of lymphocyte DNA damage as a predictor of outcome unclear. Accessible to a systems approach.

DNA-centric biomarkers

New DNA-based markers (γ -H2AX, telomere length changes)

Pro:

- Highly accurate predictor of exposure in vitro, in vivo shows promise at low doses.
- Simple and rapidly quantifiable (variability?)
- May be portable from lymphocyte (hair, buccal, skin, biopsy)

Contra:

- relevance for disease end points unclear (hope for either rate of resolution of foci or unresolved foci as a more meaningful parameter)

-Facit:

- Quantification needed, evaluation of predictive capacity unclear
- Interindividual variation not known

DNA-centric biomarkers

Micorarray of transcriptome (or microRNA)

Pro:

- Quantifiable data sets
- Rapid and accurate, low methodological variability
- Relevance to disease due to functional classes of genes
- Appears to be a good indicator of low dose effects
(is there a tipping point between high and low doses)
- Many tissues can be assayed if biopsied

Contra:

- Acute expression changes may not be relevant in long-term

Facit:

Pathway information can be derived for a systems approach. The projection to diseases is not good at moment.

Proteomic biomarkers

High throughput immunoassay, proteomic profiling

Pro:

- Best markers can be selected for rapid analysis
- Highly quantifiable for systems approach
- Functionality can be selected (eg ATM kinome)
- A non-DNA end point
- Low dose responses seen (100mGy)
- Independent from lymphocytes but may be limited to serum.

Contra:

- Only a fraction of actual proteome known
- Intra individual variation uncertain

-Facit:

- A nascent technology that shows great promise but not yet

Metabolomic biomarkers

Pro:

- Rapid and cheap
- Can focus on selected component (lipids, sugars, ROS)
- Selectivity to a end point may be possible (cardiovascular)
- Quantifiable and therefore amenable to systems approach

Contra:

- Relevance for biological end points?
- Set up costs

-Facit:

- Metabolomic profiling shows promise in several disease states
- Integration lacking due to newness of methods

Cellular (ex-vivo) biomarkers

Lymphocyte based assays performed ex vivo
(e.g. apoptosis indicators, DNA damage markers)

Pro:

- Rapid indicator of a realistic radiation end point
- Quantification possible

Contra:

- Relevance for long-term end points uncertain.
- High intra individual variability

Facit:

Lymphocyte based assays may predict acute hypersensitivity

Disease predictive markers:

Cytogenetics good evidence from cohort studies for differences
But not tested for predictive value

cDNA Arrays show very controversial evidence. Breast cancer therapy predictor array (Veridex) may or may not be reproducible. Ovarian cancer and lymphoma arrays show promise.

SNP arrays may be of use in breast cancer but classical predictive markers (ER, HER2 etc) not seen.

Recommendations and conclusions

The long-term health effects, and inherent individual sensitivity, require long term follow up biomarker studies.

Vehicles exist, such as RAPPER or CT scan cohorts, and should include sample storage for biomarker studies.

Review of the biomarker models suggests no single marker adequate for predicting risk of long-term effects. A systems approach combining different end points seems most logical strategy to follow.

Research priorities:

Disease biomarkers and exposure marker searches have failed to fish out useable biomarkers.

A systems approach that models both initial events and long term outcomes / stable changes should be followed.

Biomarkersystemics ?????

Thanks..... to all participants in the workshop and my apologies if I have misrepresented or omitted some of the key points.

