How can biomarkers bridge the gap between exposure and final health effects in terms of individual sensitivity?

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Health effects of exposure depend upon dose and time.

High dose exposures (therapy, spaceflight, terrorism, accidental or intentional exposures)

- Acute tissue damage
- Delayed tissue damage
- Secondary cancers
- Cardiovascular effects

Low dose exposures (workplace, diagnostics, natural sources)

- Cancer
- Cardiovascular effects
- Cognitive impairment
- Cataracts
- ?

What is the potential role of biomarkers ?

Risk of high dose exposures

- Triage
- Prevent predictable adverse outcomes
- Advise on potential clinical treatment
- Follow up
- Informed consent

Risk of low dose exposures

- Prevention of damage
- Informed consent
- Selection for follow up

Prediction of risk has a significant impact on the human rights of the individual!

Role of individual susceptibility

- Is there a common dose response curve and therefore a single risk estimate that fits all individuals?

-or are differences between individuals or even between populations ?

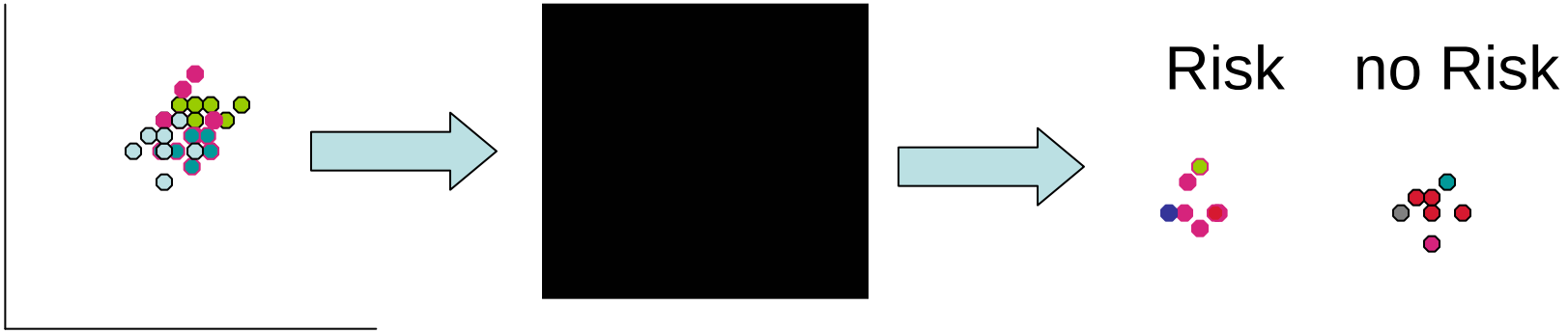
Individual differences in sensitivity to radiation occur:

- acute normal tissue response to therapy (repair defects)
- secondary cancers (Gorlin, Li-Fraumeni syndrome)

Accommodation of individual variability into biomarker-based risk projections may require a systems approach ?

How can biomarkers bridge the gap between exposure and final health effects in terms of individual sensitivity?

What systems biology can do for you (in an ideal world) ?



Biomarkers in an exposed individual

System model

Predicted risk

Did anyone notice the problems.....

1) Biomarkers of a cellular response may not predict anything, other than DNA damage.

2) Causes of radiation-induced and “sporadic” diseases are unclear, may even be different.

3) Extent of, and mechanism of, individual sensitivity unknown

4) Long term health effects may have multiple confounders that may even change during latency.

5) No systems model of adverse radiation response.

Biological uncertainties in the search for biomarkers

- Do DNA damage indicators predict anything?

- What is the mechanism by which radiation causes disease after a long latency ?

- What measurable changes precede development of the disease ?

- How do individual differences influence the processes ?

But the journey starts with one step….

Candidate biomarkers may include:

- DNA mutations fixed into the genome

- Ultrastructural changes (protein foci, chromosome breaks, translocations, micronucleii)

- Transcriptional and translational shifts, protein modification

- micro RNA & epigenetic changes (genome and chromatin)

- Metabolite changes (e.g. lipid peroxides, ROS/NOS)

The challenge to develop a systems approach

- Shift from descriptive to mechanistic viewpoint

- Must start quantitative radiation biology

- Partnerships of experimentalists and theoreticians

- Replace DNA “centricism” and model-based dogma

- Re-evaluate if there is a “unifying” mechanism of health effects

- Need to integrate responses at different scales

- Do we need to confuse the issue with individual differences?

Assessment of risk,.....in the dose region from fractions of mGy to a few tens of mGy, would be greatly facilitated by knowledge of the ***shapes of the dose-response relationships*** for radiation induced cancers in humans.

.....not available and not likely to be obtained by direct observations.

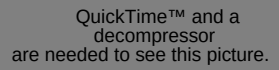
UNSCEAR 1986

But maybe a systems approach can provide this information ?

Or maybe we need to start

to understand

the proteomics ?



3rd RadSysBio Rovaniemi: Suggested topics

- What biomarkers are used to predict individual sensitivity to radiation exposures?

- Are they all reliable enough? Do we need more of them?

- Could high throughput techniques be helpful in finding new biomarkers for individual sensitivity studies?

- Could we use experience of cancer biology biomarker studies for radiation protection?

- What is the role of systems biology in all this ?