Multidisciplinary European LOw Dose Initiative

MELODI

Individual sensitivity (susceptibility) to cancer induced by low doses and low dose rates

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Presentation plan

- ***Question 1: What are the key research tasks ?***

-Discussion

- ***Question 2: What tools and techniques are needed ?***

- Discussion

- ***Question 3 & 4: What is the importance of tissue sensitivity ?***
  What is the relevance of radiation quality / rate ?

-Discussion

- ***Question 5: MELODI ?***

Question 1: What are the key research tasks - I ?

- Can we identify groups (cohorts) that are:
  - at risk and/or are informative ?
  - have quantifiable exposure ?

- Which cohorts reflect risk of exposure:
  - CT scan and mammography, proton therapy, workers, fliers/pilots, others ?

- How do we identify biomarkers and surrogate end points for:
  - exposure (definitions of dose)?
  - end points of cancer ?
  - susceptibility at genomic, expression of phenotype and epigenetic levels?

Question 1: What are the key research tasks - II ?

- Can we assume susceptibility established **between** groups can be of value in finding susceptible individuals **within** a group ?

- Can we identify relevant **sub-populations** within an exposed group, and are these **split by effects** of age, gender, ethnicity, lifestyle and environment (weighing by relevance) ?

- Are susceptibility effects filtered by the epigenome ?

- Are **mechanisms** of susceptibility the same in different groups ?

- Are mechanisms /pathways same for **different qualities / rates** ?

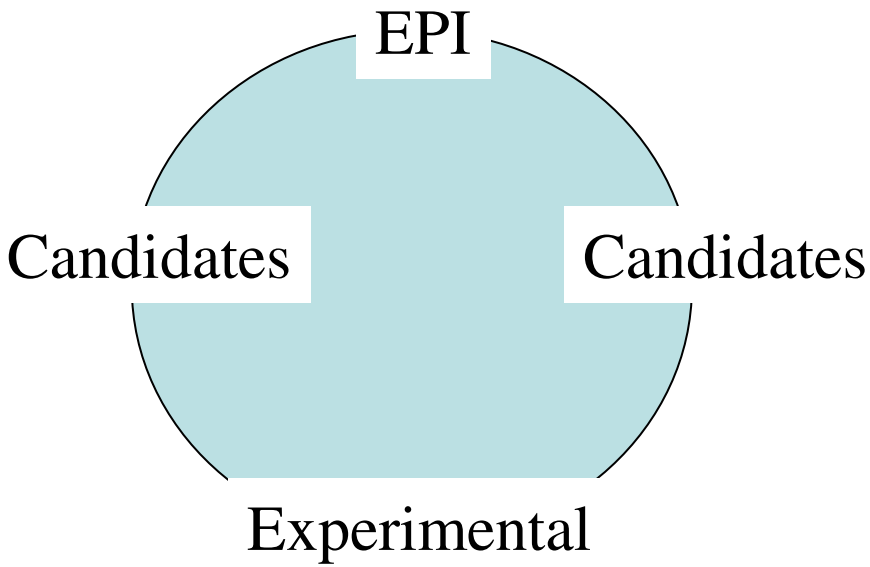
- How **susceptible** is susceptible ?

DISCUSS - Key research tasks

- ✓ Need cohorts with exposure, biomaterials, end points?
- ✓ Need for biomarkers / surrogate end points ?
- ✓ Should we try to go from study of group to individual ?
- ✓ Do we study effects of age/gender etc ?
- ✓ When do we start to quantify susceptibility ?
- ✓ Do we assume a common mechanism of susceptibility ?

Question 2: What tools and techniques are needed to address the questions -I ?

An integrated molecular epidemiological and experimental approach provides the best answer.



Question 2: What tools and techniques are needed to address the questions - II ?

➢Need model systems at cell, tissue and animal level for integrating with epidemiology:

- non-mammalian may be relevant, but only if end points have relevance to cancer.

➢Epidemiology and controversy:

- Supported by both groups on an integrated basis.
- Need planning and think tanks from both fields.
- Weak interaction at moment.
- Concerns that informative cohorts don't exist.
- Cannot supply answers at individual level.
- Ethical issues.
- Value of old cohorts challenged.

Question 2: What tools and techniques are needed to address the questions - III ?

Stem cell / progenitor models of radiation cancer to study:

- sensitivity at level of division, differentiation and cancer

Systems biology and mechanistic modelling (no experts present)

- to provide data, but only start when data available

Individual reaction to radiation:

- cellular/tissue organ level reaction needs clear end points with relevant to cancer. Consider tissue complexity, stressor response, NTE.

Dosimetry:

- differences in response due to differences in dose ? Lack of experts in community for good dosimetry.

DISCUSS - What do we need ?

- ✓ Do we try to integrate epidemiology and experimental research ?
- ✓ Are non mammalian models relevant ?
- ✓ Criticism of power / cost of molecular epidemiology ?
- ✓ Is it time for increasing stem cell and systems biology effort ?
- ✓ When do we start to quantify susceptibility ?
- ✓What do we do about dosimetry ?

Question 3: What is the importance of tissue sensitivity ?

- Response of different tissues needs integration at whole animal level. Inflammation and Immune response to be studied.

- Stem cell response in different tissues

Question 4: What is the relevance of radiation quality and rate ?

- we must get away from all using Faxitron (need alpha, neutron, Proton and HZE studies).

- Susceptibility to different qualities may not be same.

- Suitable cohorts for quality analysis

- Dose rate effects needed, dose as a measure of exposure

DISCUSS - Tissue sensitivity and radiation quality

- ✓ How much emphasis on tissue differences is appropriate ?
- ✓ Do we focus on intact animal models (inflammation / Immunity or on stem cells, or both ?
- ✓ Should we ban the use of X-rays as an experimental model ?
- ✓ Do we study effects of sensitivity for different qualities ?
- ✓ Can we study quality by epidemiology ?
- ✓ Do we look for an alternative to dose ?

Question 5: MELODI

1) Must work to maintain coherence of RTD strategy with the broad goals of RP by informing/ training scientists.

2) Must maintain competence and keep RTD on track by organising summer schools, web seminar/communication platform.

3) Exchange of staff (including RP!).

4) Frequently revisit SRA and keep open eye for hot topics.

5) Must help in recruiting new experts (Clinicians, bioinformatics and toxicologists).

Thank you to all participants for the open and constructive dialogue.

This presentation reflects a synthesis of the opinions presented,
but not all topics raised have been included in this summary.

We apologise if any opinions have been misrepresented.

Mike, Rafi, Anna and Kai.

Coordinated research activities within Europe

- Research programme must integrate activities.
- Planned studies must be achievable with available resources.
- Should address the key questions defined by HLEG.
- Possibly exploit synergy with US / Japan.
- Create added value (sustainable competence, collaboration, integration with other programmes (national / international).