Report from the MELODI SRA Expert group

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Strategic Research Angenda- Plenary Session

Cité Internationale Universitaire de Paris

17 boulevard Jourdan, 75014 Paris

Introduction

A **Working Group** for the **Strategic Research Agenda** (SRA) of MELODI was nominated in May 2010 by the MELODI Governing Board:

- Chair **Dietrich Averbeck** (IRSN, CEA,France), leader of WP2- DoReMi

  David Lloyd (HPA, UK)

  Peter O'Neill (University of Oxford, UK

- Provides link with the DoREMi TRA

- Four meetings Working Group have taken place since May 2010.

Mission of the SRA Working Group

- to develop the long-term strategic research agenda (SRA)
- to make recommendations for setting up the MELODI Scientific Advisory Board

Progress of SRA (1)

MELODI – Multidisciplinary European Low dose Initiative

- **First draft of Strategic Research Agenda (SRA) submitted to MELODI GB on 11th October 2010**

- **First draft of SRA to be presented at the 2nd MELODI workshop in Paris.**

Progress of SRA (2)

Since the EC call for low dose risk, announced on 20th August refers to the SRA,

- **consultation on the draft SRA is an important issue.**

➢ The SRA is complementary with the Transitional Strategic Agenda (TRA) of DoReMi

➢ It relies on the input of open minded and interested scientists from the general scientific community.

Overall aims

- **Consolidation of the European protection framework in the area of low dose exposure to ionizing radiation**

- **Development of a Multidisciplinary European Low Dose Initiative – (MELODI platform) to ensure long term commitment (>20 y) to low dose research in Europe**

Key scientific issues

The SRA focuses on the three issues identified by HLEG

(1) shape of dose-response curve for cancer
(2) individual radiation sensitivity
(3) non-cancer effects

together with the three overarching issues

(1) radiation quality
(2) tissue sensitivity and
(3) internal emitters

Key Questions

- How robust is the current system of radiation protection and risk assessment?
- How can it be improved?
- *What are the areas of greatest uncertainty in radiation research?*
- *What are the areas of greatest uncertainty in radiation protection?*
- *Prioritise the underlying scientific questions*

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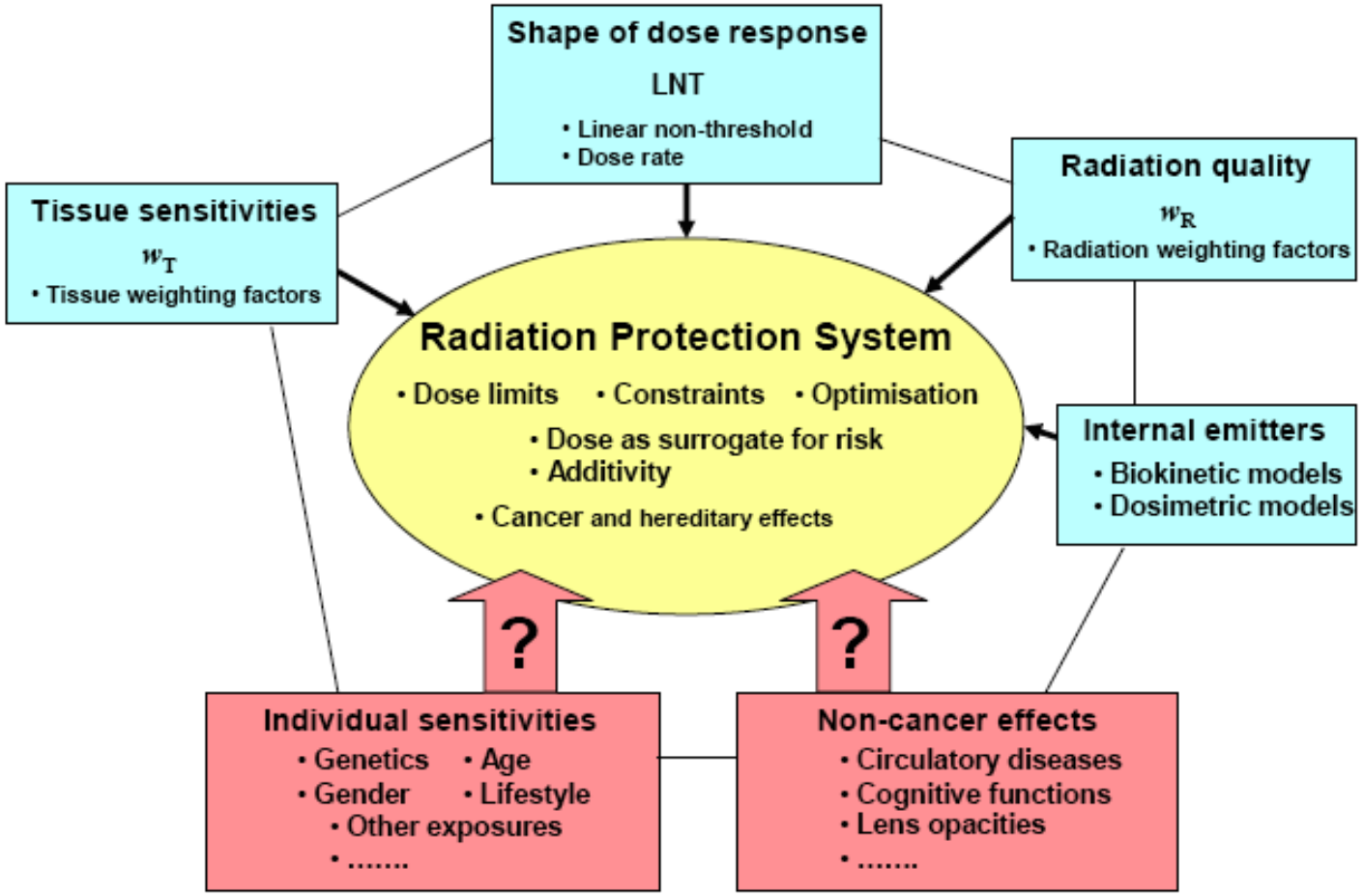
Key Questions

High Level Expert Group

How robust is the system of radiation protection and risk assessment?



Major Considerations

- Multidisciplinary integrative low dose research in Europe
- Attract new scientific competences and scientists from complementary disciplines
- Sustainability of infrastructures, education and training
- Interaction and communication with stakeholders and the public.

Methodology adopted by the SRA Working Group

- Initially, the SRA is based on the scientific issues from
  - -HLEG,
  - -Transitional Strategic Agenda (TRA) of DoReM
  - -MELODI workshops.

- Meetings involving experts from
  - the field of low dose radiation research
  - related fundamental and applied research domains

to consolidate strategic issues on radiation protection and low dose health risks

Scientific consensus on Health Effects

The current scientific consensus on health effects which should be addressed are:

- Cancer – including secondary cancers
- Heart disease
- Neurological effects
- Effects on the central nervous system (CNS)
- Lens opacity
- Adverse effects to normal tissue from radiation therapy (out-of-field effects)

DoReMi

Network of Excellence (NoE) on Low Dose Research towards Multidisciplinary Integration (DoReMi)

The 7 Work packages of DoReMi :

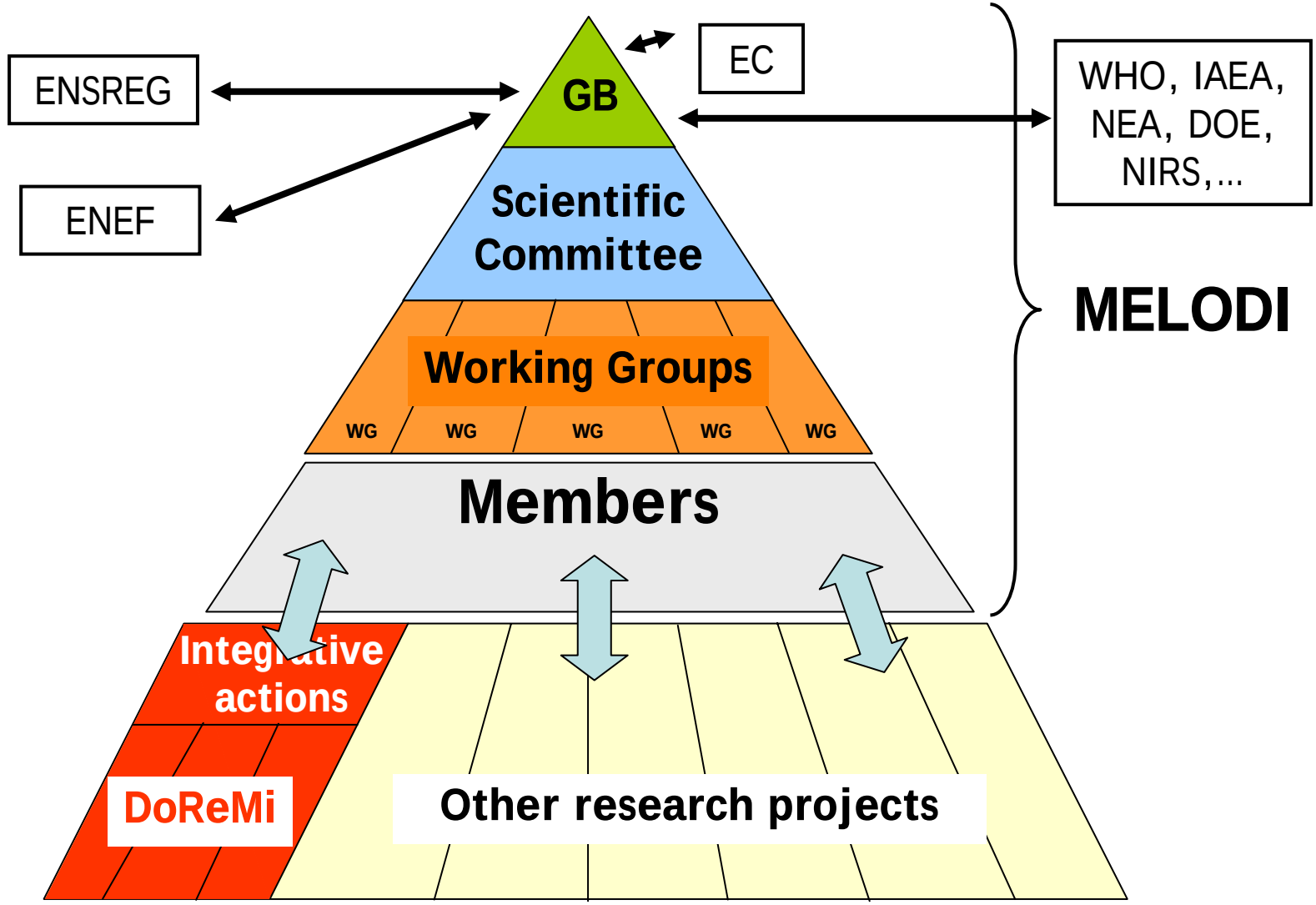
- WP1: Coordination and management,
- WP2: Structuring MELODI,
- WP3: Education and Training,
- WP4: Infrastructures,
- WP5: Shape of dose response for cancer,
- WP6: Individual radiation sensitivity for cancer (and non cancer)
- WP7: Non-cancer effects.

DoReMi

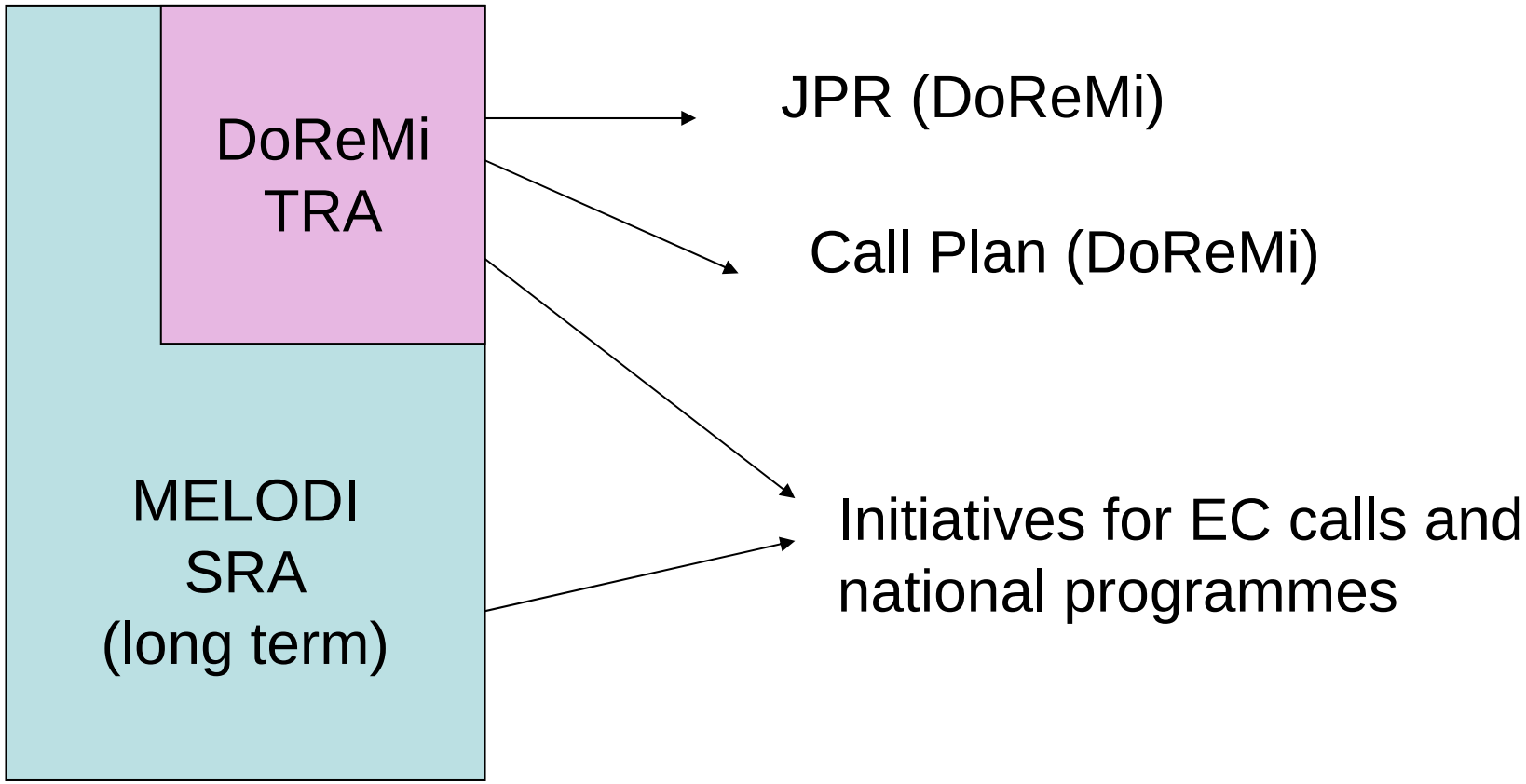
- **DoReMi** is a transitional initiative providing EU financial support and scientific feasibility studies to facilitate and accelerate the integration process within the **MELODI platform**.

- **MELODI** is the vehicle for development of a new long term institutional European entity capable of sustainability and promotion of low dose radiation research on health risks and radioprotection.

MELODI and DoReMi: Complementarity



Scope of TRA and SRA



2. Scientific Vision (1)

2.1.The present situation

- The present system of health risk evaluation and radiation protection is based on current scientific knowledge and societal considerations of acceptance.

- For high radiation doses where epidemiological studies are particularly significant the radiation protection system is reasonably well established.

Scientific Vision (2)

Uncertainties still exist and continue to need attention:

- **the shapes of dose response curves for different types of cancers and non-cancer diseases**
- **biological effectiveness of different types of radiation**
- **sensitivity of different cell types and tissues**
- **sensitivity to *in utero* irradiation**
- **variations in radiosensitivity between children and adults**
- **Variations between gender**
- **individual radiation sensitivity and predisposition to cancers and certain non-cancer diseases**

Scientific Vision (3)

Uncertainties *(continued)*

- **non-targeted effects of radiation.**
- **radiation quality effects;**
- **fractionated exposures;**
- **effects of radionuclides and internal contamination;**
- **mixed radiation exposures;**
- **radiation versus, or combined with, chemical toxicity (interactions of radiation with chemical agents)**

Scientific Vision (4)

The baseline needed

- one should have extensive knowledge on the unperturbed living system, the basic homeostatic equilibrium between metabolic activity, structure and function of cells and tissues, the normal physiological and proliferative state of organs and the whole human body.

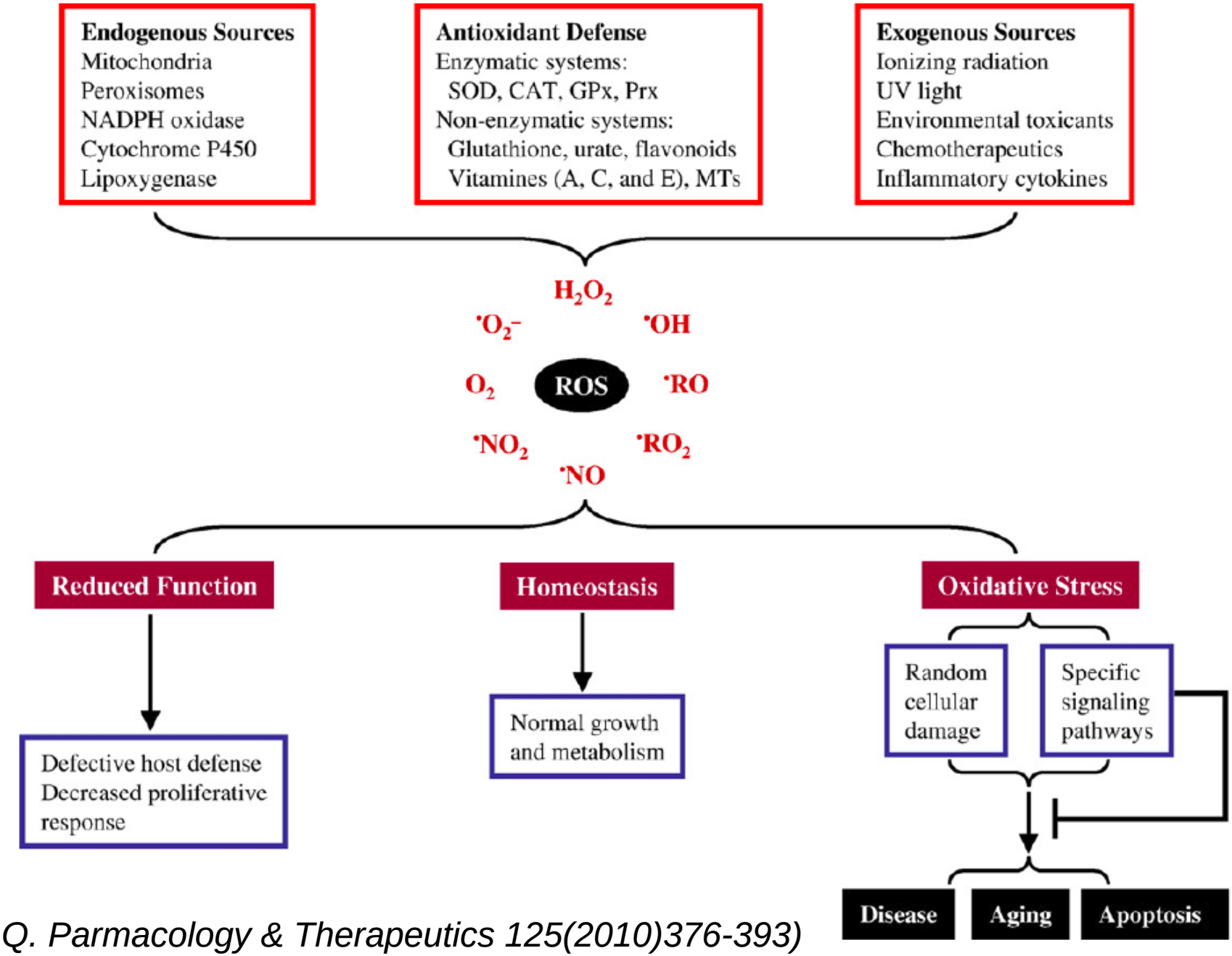
Scientific Vision (5)

The general scheme

Radiation-induced events at the level of cells or the whole organism are induced as follows:

- Energy deposition by different types of radiation in living systems will create perturbations in the homeostatic equilibrium (metabolism) as well as reversible or irreversible damage (structural changes) which may be detectable at the molecular level by sensitive physical, chemical and biological (omics) methods.
- 'Omics' should make it possible to identify specific biomarkers directly linked to radiation exposure.
- For health risk assessments, the most important question will be which type of radiation exposure, radiation dose and dose-rate will give rise to a pathological outcome such as cancer and non-cancer diseases in the short or long term. Also, it should be possible to identify specific biomarkers that can predict or are precursors of pathological developments towards defined diseases.

Oxidative stress and biological consequences

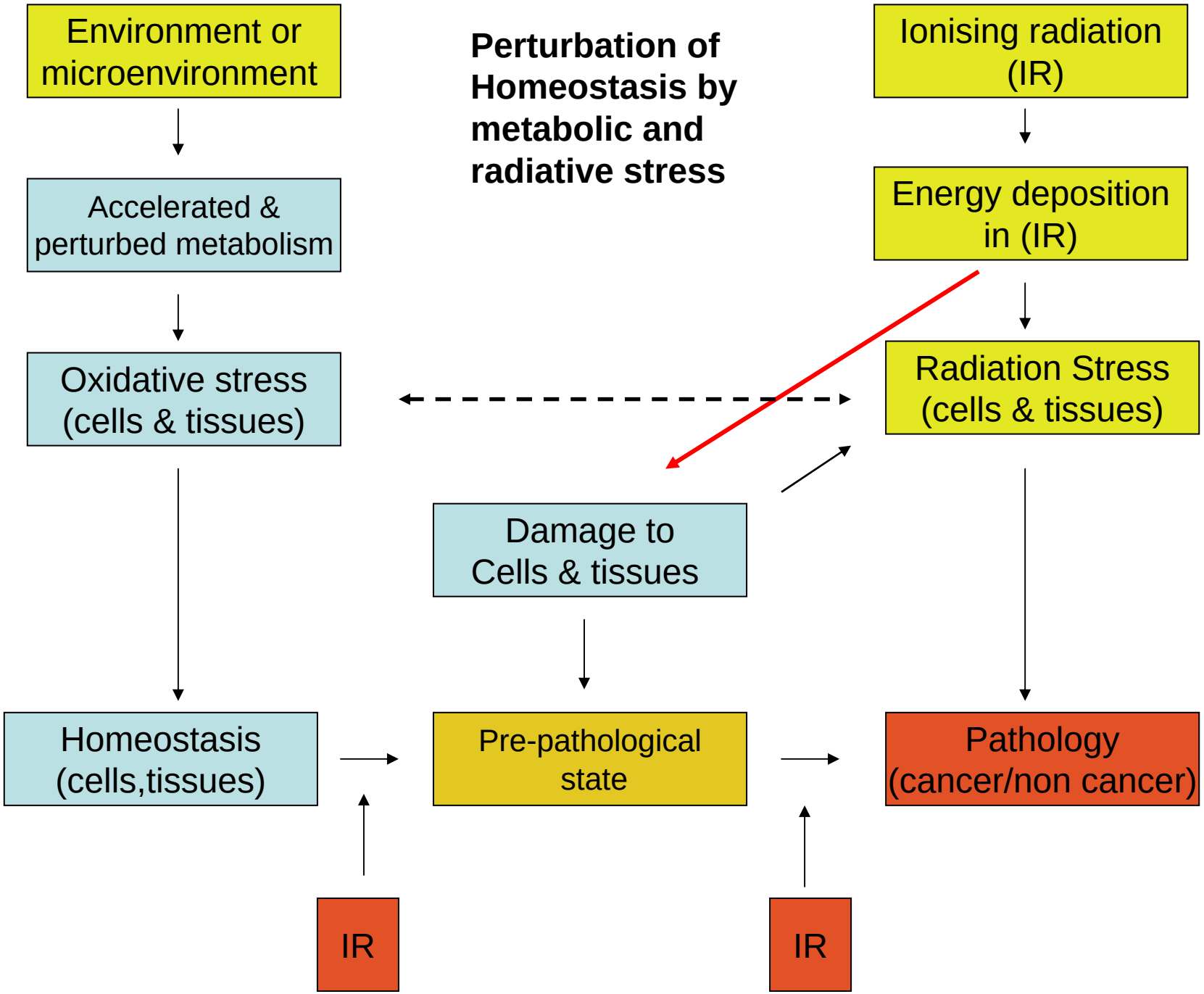


(Ma Q. Parmacology & Therapeutics 125(2010)376-393)

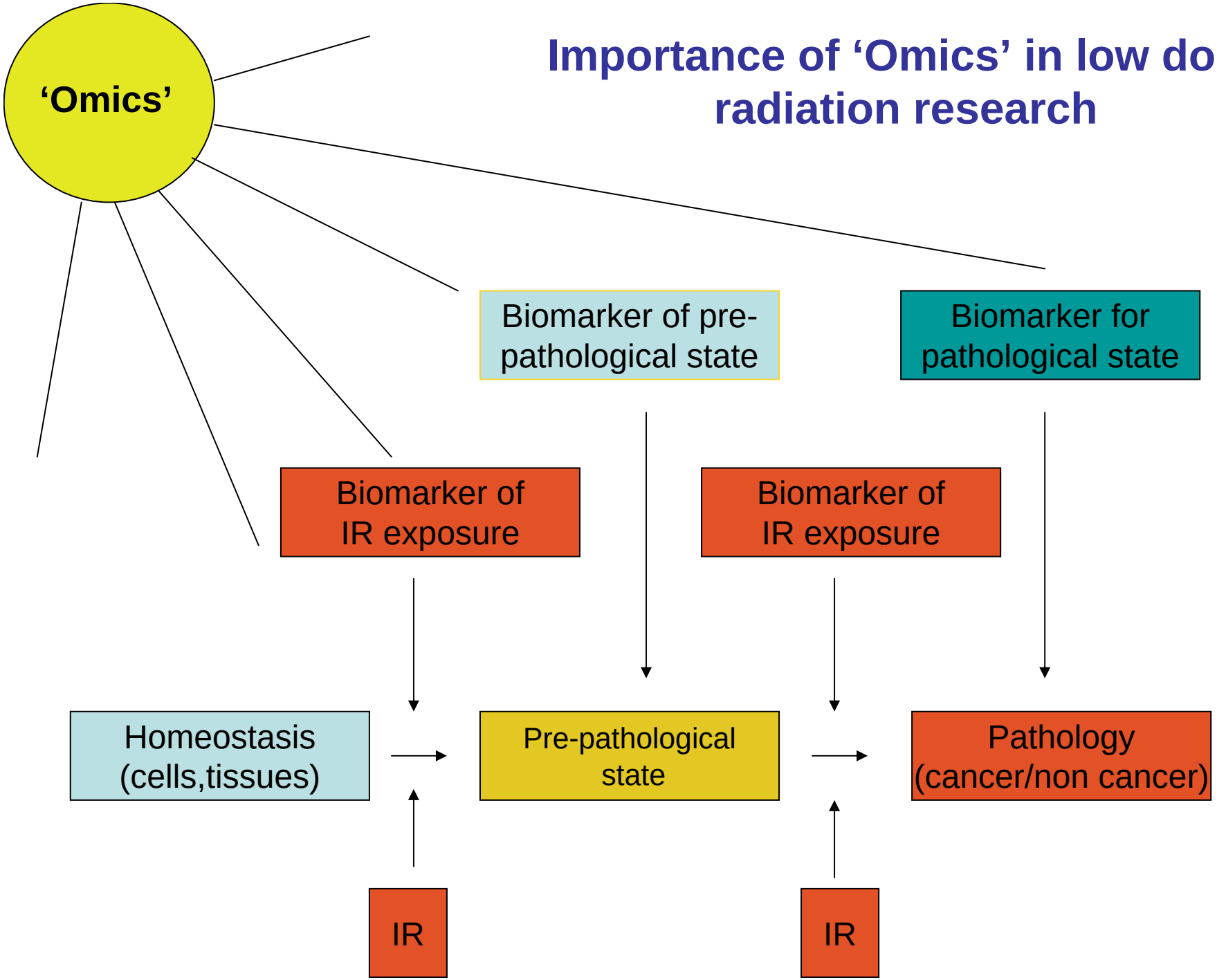
Scientific Vision (6)

The general scheme

- The scientific challenges will be to define the borderline between normal metabolism, normal physiological responses and a disease-prone perturbed metabolism as a precondition of pathology that may be induced by low dose ionising radiation.
- Some types of radiation-induced damage are similar to those induced by other types of stresses (heat, solar UV, chemical pollution, endogenously).
- Types of damage that are potential signatures of ionising radiation effects, i.e. may be attributed to observed biological (pathological) effects of ionizing radiation, need to be identified including approaches based on microdosimetric analysis of different radiation qualities. Their contributions to the detrimental health effects of radiation need to be assessed.
- Further, concomitant exposures to radiation and other types of stresses and/or the possible interactions/synergisms with different types of agents have to be taken into account.


Environment or microenvironment
Perturbation of Homeostasis by metabolic and radiative stress
Ionising radiation (IR)
Accelerated & perturbed metabolism
Energy deposition in (IR)
Oxidative stress (cells & tissues)
Radiation Stress (cells & tissues)
Damage to Cells & tissues
Homeostasis (cells,tissues)
Pre-pathological state
Pathology (cancer/non cancer)
IR
IR

Importance of ‘Omics’ in low dose radiation research



Scientific Vision (7)

The general scheme (continued)

- In some instances, comparative studies between the pathological effectiveness of certain chemical agents and ionising radiation exposure should be very informative in placing the importance of ionising radiation into context with other pollutants.

Many parameters have to be considered including:

Ionising radiation issues

- types (α, β, γ, protons, neutrons, X-rays, heavy ions);
- energy distribution and deposition;
- radiation track structure and microdosimetry;
- dose and dose rate
- dose fractionation;
- external exposure;
- internal contamination exposure**.**

Scientific Vision (8)

Biological effects on cells and tissues:

- damage to all cell constituents;
- normal (oxidative) metabolism and energetic status;
- proliferative (differentiation) and developmental status;
- genetic and epigenetic background; hereditary effects;
- age; effects of gender;
- specificity of cells and tissues;
- specific cellular structures and metabolism functions;
- perturbed metabolism in diseased cells (cancer, non-cancer);
- intra-intercellular signalling, inflammation; allergy
- normal and disease perturbed tissue (organ) physiology;
- regulatory systemic, immunological and hormonal effects;
- other confounding factors due to environmental exposures to physical agents (temperature, electro-magnetic fields), chemical and biological agents (virus, bacteria).

Scientific Vision (9)

Fundamental molecular interactions associated with ionising radiation (1):

- One of the most important future challenges of low dose research is to establish to what extent ionising radiation perturbs normal cellular metabolism at the cell, tissue and organ level as well as perturbing the equilibrium of normal systemic signalling (homeostasis) of the human body and as a consequence promotes or induces pathological conditions.
- Ionising radiation of different qualities vary considerably in their ability to induce direct structural and indirect radiation effects (oxidative, free radical mediated stress), and also, by definition, the rate by which free radicals and cellular damage are produced (effects of dose rate) may condition short and long term radiation effects.

Scientific Vision (10)

Fundamental molecular interactions associated with ionising radiation (2):

- The local distribution of the free radicals produced in cells and tissues, the pre-existing cellular oxidative stress and the available arsenal of antiradical and antioxidant defence systems (under genetic and epigenetic control) will determine the final biological outcome.
- Thus, the basic metabolic, proliferative, genetic, epigenetic, immunological, hormonal and physiological status of cells and tissues need to be investigated as an important pre-determinant for low dose radiation-induced insults.

Scientific Vision (11)

Fundamental molecular interactions associated with ionising radiation (3):

- It will be of outmost importance to launch research to define quantitatively the levels of oxidative stress in cells, tissues and organs that are part of normal homeostasis and those levels that can be achieved by low ionising radiation exposure and if they may be regarded as precursor conditions to perturb the homeostasis for the development of cancer and non-cancer diseases.
- Additionally, it will be important to determine relevant molecular and structural changes induced uniquely by ionising radiation directly and that are in the long term persistent and contributing to cellular, tissue and organ dysfunction. The roles of different cell types, stem cells, progenitor and germ cells will need to be defined.

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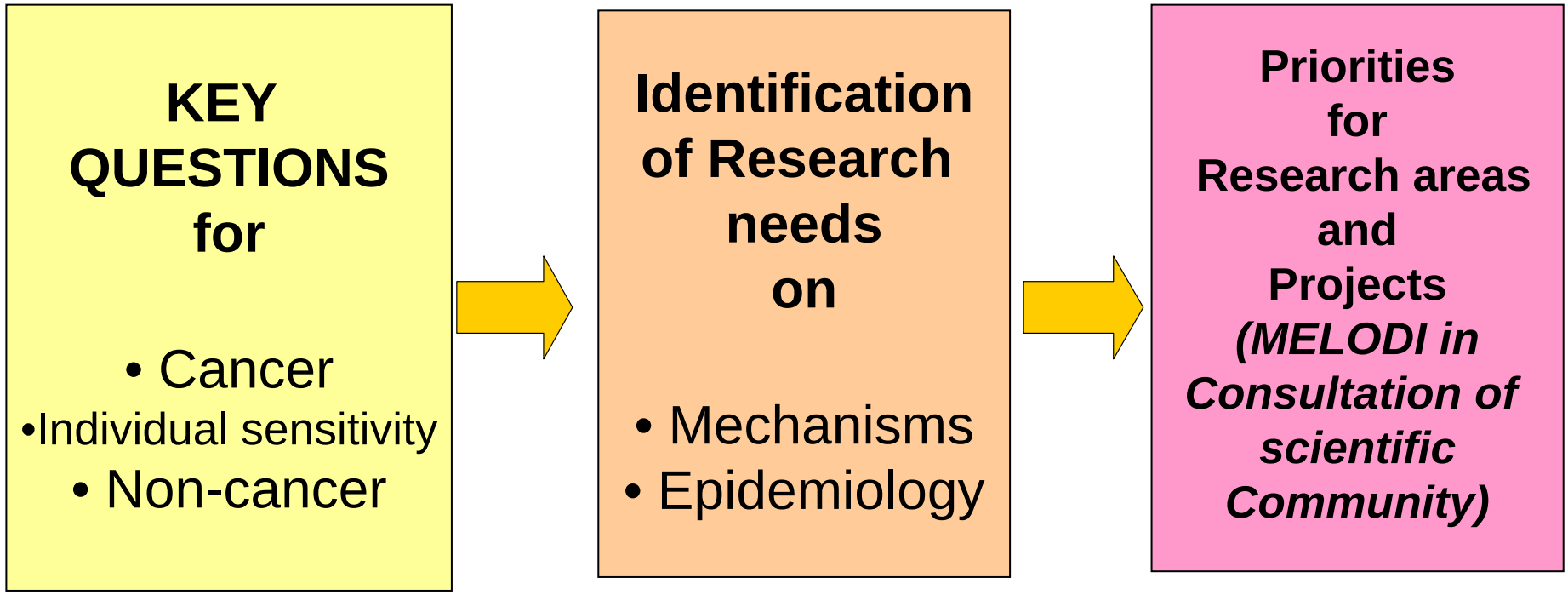
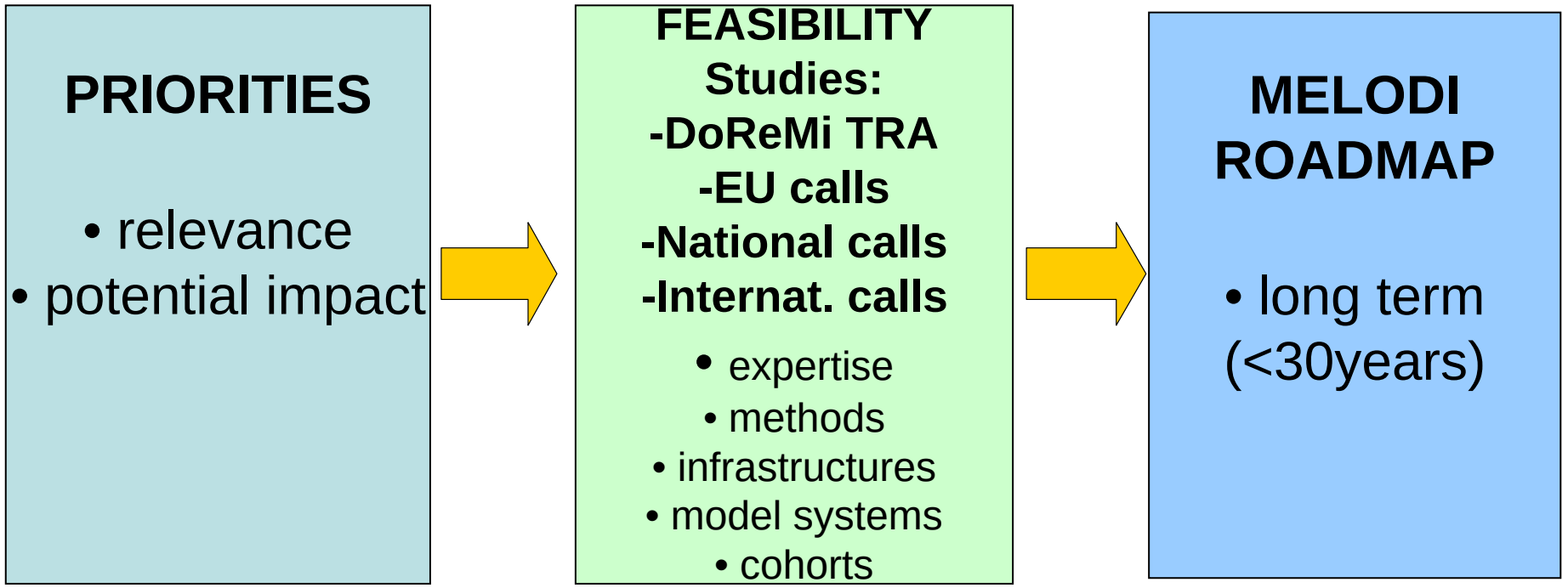
MELODI SRA Process (1)



MELODI SRA Process (2)



Scientific questions (1)

(1) Shape of the dose-response curves for cancer

- **Mechanisms**
  - What is the dependence on track structure and microdosimetric features of the tracks spatial distribution of energy deposition events? – interplay between spectrum of damage induced and its repairability in modulating the shape of the dose response curve.
  - What is the dependence on dose rate and LET?
  - What are the **molecular biomarkers** that can be validated and used in molecular epidemiology to define pathological impact and disease? – both cancer and non-cancer
  - Are **molecular biomarkers** available or may suitable biomarkers be developed for radiation-induced carcinogenesis (molecular signatures) in animals and humans and as biological dosimetry of human exposure?
  - What is the implication of irradiation of **stem cells** in carcinogenesis?

Scientific questions (2)

(1) Shape of the dose-response curves for cancer

Mechanisms (continued)

- Can the processes underlying radiation-induced carcinogenesis be **modelled** for different types of cancers?
- To what extent does the sensitivity to cancer induction differ for exposures during various **developmental stages** (e.g. *in utero*, young children, adults)?
- What is the effect of radiation quality and the sensitivity for **different tissues** for radiation-induced carcinogenesis and disease?
- What are the mechanisms underlying the appearance of secondary cancers or out-of-field low dose radiation effects in humans?
- Can good **animal models** be developed to analyse radiation-induced cancers other than acute myeloid leukaemia or are good animal models available?

Scientific questions (3)

(1) Shape of the dose-response curves for cancer

Mechanisms (continued)

- What is the impact of **non targeted effects** on radiation-induced carcinogenesis? - cellular signalling at low dose and low dose rate; adaptive responses to radiation
- What is the relationship between **oxidative stress**, DNA damage complexity, chromosomal damage, translocation, DNA damage signalling, perturbed cell cycle regulation, senescence, apoptosis and the induction of cancer (and non-cancer diseases) by radiation?
- What is the role of **epigenetic** effects including chromatin remodelling on health effects induced by radiations of different quality?
- What is the impact of **immunological status** (systemic factors) on radiation-induced pathological responses (inflammation, cancer, non-cancer)?

Scientific questions (4)

(1) Shape of the dose-response curves for cancer

- **Dosimetry**
  - How can the information on dosimetry and biokinetics of **internal emitters** be improved to understand radiation-induced short and long term effects?
  - What are the most important **radionuclides** to focus on (scoping of internal emitter studies) to gain better understanding of their short term radiotoxicity and long term effects (cancer and other pathologies)?
- **Omics and systems biology**
  - How can research based on ‘omics’ contribute to a systems biology approach to processes underlying radiation-induced carcinogenesis and non-cancer diseases? - Involvement in homeostasis?
  - How can ‘omic’ approaches enhance our understanding of the effects of radionuclides?

Scientific Vision (5)

(1) Shape of the dose-response curves for cancer

Epidemiology

- What are the cohorts that can be used for molecular epidemiological approaches to understand low dose radiation effects (cancer, non-cancer)?
- Is it possible to launch an epidemiological study on low dose induced second cancers?
- Is it possible to launch an epidemiological study on out-of-field low dose radiation effects in humans?
- Can existing biobanks (STORE, GENEPI) be used in molecular epidemiological studies?
- Can specific epidemiological studies be conducted to reveal and analyse specific radiation responsive cancer prone tissues?
- Can feasibility studies be performed on non-cancer effects (cardiovascular, lens opacities, neurological effects)?

Scientific Vision (6)

- ***(2) Individual radiation sensitivity***

An overriding priority is for this research to include ethics considerations.

Mechanisms

- What is the evidence that individual sensitivity plays a significant role towards cancer and **non-cancer pathologies** through modulating radiation response to exposures at low dose and dose rates? - Links to cancer predisposition.
- Are there **genetic and/or epigenetic modifiers/biomarkers** available that allow determination (monitor, predict) of individual sensitivity to radiation, cancer and disease development?
- Which mammalian and non-mammalian systems should be able to validate candidate **biomarkers** related to individual radiation sensitivity?
- To what extent are **inflammatory and immunological factors** involved in individual radiation responses?

Scientific questions (7)

- ***(2) Individual radiation sensitivity***

Mechanisms

- To what extent do **non-targeted radiation responses** differ in different individuals?
- What are the factors involved in individual sensitivity and dependent on **genetic background**, age, gender and lifestyle?
- Can a multilevel approach using cells in culture, tissue cultures, non-mammalian and mammalian models help to analyse individual sensitivity?
- Can an **'omics'** approach help to elucidate individual sensitivity and be used to develop a systems biology approach?
- Can omics help to define tissue weighing factors?
- How do **stem cell and progenitor cell** biology contribute to individual radiation sensitivity and tissue responses?

Scientific questions (8)

(2) Individual radiation sensitivity

Mechanisms

- Do **genetic or epigenetic modifiers** of radiation responses affect individual radiation responses similarly at low and high LET radiation?
- Is individual radiation sensitivity dose rate dependent?
- Can risk assessments for individuals be developed on the basis of molecular indicators for cancer and disease? – leading to **genetic profiling** of individuals?
- Are mechanisms and factors governing cancer susceptibility independent of dose rate and radiation quality, or are there differences in the degree to which risk modifiers contribute to individual risk at different dose rates and radiation qualities?

Scientific questions (9)

(2) Individual radiation sensitivity

Mechanisms

- Can the magnitude of individual sensitivities be quantitatively assessed and compared?
- Can non-mammalian and animal models contribute to a better understanding of the mechanisms involved in individual sensitivity?

Scientific questions (10)

(2) Individual radiation sensitivity

- **Epidemiology**
  - Are there cohorts available, or which can be set up, that allow establishment of direct links between molecular experimental studies and epidemiological studies (molecular epidemiology) on individual sensitivity?
  - Are there cohorts available, or may be set up, to allow modelling of individual sensitivity responses?
  - Can populations at risk be identified and distinguished by biological markers?
  - Can realistic cohorts be designed, including low dose exposures and protracted exposure scenarios (medical imaging cohorts, nuclear workers, flight crews), that allow detection of individual sensitivity by available **biomarkers**?

Scientific questions (11)

(2) Individual radiation sensitivity

Epidemiology

- Are there cohorts available, or which can be set up, that allow establishment of direct links between molecular experimental studies and epidemiological studies (molecular epidemiology) on individual sensitivity?
- Are there cohorts available, or may be set up, to allow modelling of individual sensitivity responses?
- Can populations at risk be identified and distinguished by biological markers?
- Can realistic cohorts be designed, including low dose exposures and protracted exposure scenarios (medical imaging cohorts, nuclear workers, flight crews), that allow detection of individual sensitivity by available **biomarkers**?
- Can **biomarkers, gene** markers and phenotypic traits indicate specific radiation risks in human individuals? -Ethics problems to be considered

Scientific Vision

(3) Non-cancer effects

- The system of radiologial protection is mainly based on excess risk of cancer induced by ionizing radiation. The main data on stochastic effects have been derived from situations with a very short exposure at a high dose rate, like Hiroshima and Nagasaki populations.
- Much less information is available on effects of internal exposures or long term consequences on non-cancer effects such as cardiovascular dysfunction, neurological alterations, lens opacities, or effects on other physiological functions.
- In order to tackle these important aspects there is an urgent need for multidisciplinary approaches involving cardiology, neurology, toxicology, dosimetry, radioecology, embryology, bioinformatics and biomathematics, pharmacokinetics...

Scientific questions (12)

(3) Non-cancer effects

Mechanisms

- What are the mechanisms involved in radiation-induced **lens opacities**?
- What are the mechanisms involved in radiation-induced **cardiovascular** effects?
- What are the mechanisms involved in radiation-induced effects on the **central nervous system** (neurogenesis) and **behavioural** changes?
- Are these mechanisms consistent with stochastic or deterministic dose responses?
- What are the mechanisms involved in radiation-induced effects on the **digestive system**?

Scientific questions (13)

(3) Non-cancer effects

Mechanisms

- What are the mechanisms involved in radiation-induced effects on reproduction and **trans-generational** effects?
- What are the mechanisms involved in radiation-induced effects on the **immune** system (inflammation, immunodeficiency)?
- How can systemic effects be distinguished from organ specific effects?
- What is the impact of **non-targeted effects**?
- What is the impact of radiation quality, dose and dose rate, acute and chronic exposure?
- What are the age, gender, population and temporal effects?
- What is the possible impact of synergistic and interactive effects with other agents?

Scientific questions (14)

(3) Non-cancer effects

Mechanisms

Concerning the mechanisms involved in tissue responses it has to be noted that for many years great effort has been focused on cell-level responses to radiation.**To better understand tissue responses, the key questions are**:

- To what extent are in vitro experiments on single cell types relevant in predicting responses of more complex tissues and organs to low doses. e.g. are the biological responses uniform amongst different cell types and between tissues?
- Is there a long-term adverse tissue response at low doses in tissues other than cardiovascular/cerebrovascular tissue and lens (bone, brain etc)?
- Are the risks of impairment of system level response adequately known at low doses (e.g. immune competence, cognitive ability, reproductive capacity, osteogenic regeneration)?
- Does the known genetic predisposition to cancer risk extend to non-cancer risk of tissue level responses at low doses? If so, which biological pathways are influenced by these genetic factors?

Scientific questions (15)

(3) Non-cancer effects

Epidemiology

- Do **confounding factors**: diet, smoking and many other life-style factors, plus genetic and epigenetic factors, multi-stress exposures contribute to non-cancer effects?
- What are the main non-cancer diseases to be considered after low dose radiation exposure?
- Are there suitable cohorts available? (out-of-field exposures in radiation therapy, CT scans, nuclear medicine patients, interventional cardiologists, dentists, staff preparing radiopharmaceuticals (PET imaging), workers exposed to alpha emitters (Mayak), uranium miners and others (fluorspar), aircrews)

Suggestions for Research priorities

2.4. Research Priorities

- The research priorities derived from the above listed key questions are presented in the following order: **1) radiation quality related issues and shapes of dose response curves, 2) biological mechanisms, 3) epidemiological issues.**
- This includes research on the interaction of low dose ionizing radiation with macromolecules and living matter, the biological consequences at the cellular and tissue level as well as human health risks.

Suggestions for Research priorities

(1)Radiation quality relate issues:

Energy deposition, track structure, dose, dose-rate, dosimetric issues, radiation quality effects, identification of damage, targets involved,non targeted effects…)

(2) Biological mechanisms

cell and stem cell research, ‘omics’ (transcriptomics, proteomics, metabolomics), ‘extraction’ of biomarkers:

specific for radiation exposure, pre-pathological effects (radiation-induced (oxidative) stress: identification of relevant metabolic pathways (oxidative metabolism, DNA repair, apoptotosis, inflammation, immune responses etc.), pathological effects (‘Over-stress’) (cancer, non cancers).

Suggestions for Research priorities

(2) Biological mechanisms (continued)

- **putting it all together: systems biology and modelling**
- **use of selected biomarkers in molecular epidemiology**
- **research on to links between (attributability of) radiation exposure to pathological effects (animal studies)**

(3) Individual sensitivity:

genetic and epigenetic profiling, SNPs, sequencing, detection of genetic variants, miRNA and splicing patterns, DNA repair capacities, apoptotic responses, stress profiling (mitochonrial dysfunctions, persistant damages and alteration of homeostasis)

•Details

Research priorities (1)

2.4.1. Physical issues (Radiation quality related issues)

Research on

- ionizing radiation energy deposition,
- track structure,
- definition of the dose (Monte Carlo),
- dose rate,
- dose fractionation in relation to well-identified and characterized damage to biologically important macromolecules,
- main cellular targets (aspects of antiradical protection, protective
- mechanisms in cells and tissues (reversibility, persistence, reparability, long term perturbation) in relation to tissue weighing factors,

  biological effectiveness on divers biological endpoints.

•Details

Research priorities (2)

2.4.1. Physical issues (Radiation quality related issues)

- Extensive research is needed aimed at understanding the impact of radiation quality on those aspects of cell responses which could be relevant in risk estimates for both cancer induction and non-cancer diseases.
- They should include **oxidative damage and stress, cell signalling modulation in the microenvironment and the relative roles of targeted and non targeted effects**.

•Details

Research priorities (3)

2.4.1. Physical issues (Radiation quality related issues)

- **Studies to be prioritized**:
  - *Track structure methods still need further improvements, particularly for ions of great importance and also for understanding neutron effects.*
  - *The role of the different characteristics of initial damage and repair pathways with respect to different radiation qualities, still need to be investigated particularly clustered/complex damage in conjunction with microdosimetric approaches and nature of the chromatin.*
  - *The biological significance of complex chromosome aberrations preferentially induced by high-LET radiation should be evaluated.*

•Details

Research priorities (4)

2.4.1. Physical issues (Radiation quality related issues)

- **Some criteria to be applied**:
  - Integrated studies with common theoretical and experimental approaches should preferably be aiming to understand the mechanisms related to low dose and low dose-rate effects. *(The important issues of internal dosimetry, microdosimetry and retrospective dosimetry have to be covered in association with other EU programs such as EURADOS).*
  - In vitro and non-low dose studies are recommended provided they are part of a clear strategy towards a better understanding of in vivo low dose effects.
  - Research on microbeam-induced radation effects with ions or soft X-rays) should be encouraged.

•Details

Research priorities (5)

2.4.2. Biological mechanistic issues

Research on ‘Omics’ (transcriptomics, proteomics, metabolomics).

- This involves essentially identification of pathways responding to or affected by specific types of radiation or exposure conditions (dose rate) and discrimination of the effects from normal homeostasis or background noise. This may allow useful comparisons between radiation-induced stress (radical, ROS) responses to that induced by other stressors (chemicals, infectious agents, nanoparticules..). Specific effects of different types of radiation on well identified components of biological pathways (oxidative metabolism, cellular signalling, oxidative metabolism, death pathways, DNA repair pathways, ..) should give rise to the development of **biomarkers that are specific for exposure.**.

•Details

Research priorities (6)

2.4.2. Biological mechanistic issues

Research on ‘Omics’ (continued).

- These may include markers for specific types of damage (clustered damage etc.).The link between the disruption of specific pathways and radiation-induced pathological conditions (cancer and non-cancer) may give rise to **biomarkers for specific pathologies** and to the definition of corresponding molecular signatures that can be then further developed and validated in animal models or in specific human diseases. The stability and persistence (short or long term) of these specific **biomarkers for radiation exposure and disease will be an important issue of research.**

•Details

Research priorities (7)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

Research on systems biology

- The information collected on the multiple pathways may then become part of an overall **systems biology approach** which will allow modelling of biological dose responses (cancer, non-cancer).
  - **Two types of systems biology approaches** should be considered (1) an approach to describe the overall set of pathways and interactions of components ('networks') wihin a single cell. This approach should allow understanding and predicting of the cellular responses to stress such as low dose radiation in relation to that encountered by other agents. (2) an approach to understand the inter cellular communication between cells within a tissue and communication between different tissues in the whole body.

•Details

Research priorities (8)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

Stem cell research

Research on radiation quality effects on normal and mutated (including precancerous and cancerous) **stem cells** should define their sensitivity and their developmental capacity with respect to their role in radiation-induced carcinogenesis and disease.

Research on **pathological effects** induced by ionizing radiation of different radiation qualities using a systems biology approach will give rise to extensive modelling (modelling of important biological and pathological mechanisms, link between energy deposition and both cancer and non-cancer pathologies). The models will then be validated on specific animal models (AML?) and some well designed human retrospective and prospective cohorts.

•Details

Research priorities (9)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

- Research on **individual radiation sensitivity** to cancer and non-cancer diseases should be promoted. It should cover the following items: sensitivity specific developmental stages, children versus adults, sensitivity of different cell types (stem cells and progenitor cells) in different types of tissues), redox profiles (oxidative stress) in different radiation sensitive and resistant individuals, genetic (SNPs, sequencing..) and epigenetic profiles, the DNA repair capacity, capacity to undergo radiation-induced death, the immunological, hormonal, inflammatory, general health status of radiation sensitive and resistant individuals, latencies for different pathologies.

•Details

Research priorities (10)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

- Research on **intra- and intercellular signalling** after low dose radiation appears to be important in order to define localised radiation effects linked to the cellular microenvironment and more systemic effects (involving the release of cytokines, specific mediators and clastogenic factors) linked to inflammation and disease. The possibility that these bystander effects may give rise to long term and trans-generational effects including genomic instability needs to be studied as well.

•Details

Research priorities (11)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

- Research on **radiation-induced oxidative stress** involves many inter-related responses. Different radiation qualities and dose rates are likely to be linked to specific types and ratios between different types of oxidative damage (simple and complex (clustered) damage).
- ***Oxidative stress plays an important pivotal role for inducing alterations of normal homeostasis that may lead to the development of cancer and non-cancer diseases.***

•Details

Research priorities (12)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

Research on radiation-induced oxidative stress

Oxidative stress is linked to

- signalling of cellular damage,
- perturbations of normal cellular metabolism, mitochondrial dysfunction
- normal cell differentiation
- development and cell cycle progression,
- induction of pathological diseases (cancer, non cancers), apoptosis,
- senescence, genetic and epigenetic (changes in chromatin structure)
- effects including possible radiation-induced epigenetic reprogramming ofgerminal cells, inflammatory, hormonal, immunological changes (systemic factors) in relation to the onset of pathological effects.

Research priorities (13)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

- Research on **internal emitters** following internal contamination with radionuclides needs to be promoted. It is clear that the local uptake and distribution (biokinetics) radiation quality of the emitters and dose-rate effects are of greatest importance. However, also confounding factors such as chemical toxicity, specific damage to cellular and tissue components using toxicological and nanotechnological approaches should be considered.
- It would be most profitable and relevant to focus studies on: tritium and actinides in the nuclear industry; mining industries that cause radium and thorium exposures; diagnostic, and possibly therapeutic, applications of radiopharmaceuticals in nuclear medicine

Research priorities (14)

2.4.2. Biological mechanistic issues

Research on 'Omics' (continued).

Research on internal emitters

- *Individual whole body and/or organ dosimetry is often difficult with internally deposited radionuclides but is highly important for any dose-response research.*
- *Nuclear medicine applications are possibly a rich source of experimental study because planned, monitored and controlled delivery of radiopharmaceuticals gives scope for precise dosimetry follow-up.*

Research priorities (15)

2.4.3.. Epidemiological issues

- Research on suitable human epidemiological cohorts remains a very high priority of research in forthcoming years. Epidemiological studies are considered to be essential hallmarks for the evaluation of radiation health risk taking into account the effects of factors that may modify risk of diseases, including age, gender and factors in the general environment and genetic, epigenetic factors and non-targeted radiation-effects.
- Not only promising research on existing retrospective epidemiological cohorts should be continued, but also research on new prospective cohorts should be initiated on cancer and non-cancer diseases.
- Epidemiology should be combined with molecular / biomarker assays on the study subjects .

Research priorities (16)

2.4.3. Epidemiological issues

- Until specific biomarkers for exposures and disease are validated appropriate biobanking of materials has to be considered. It might be possible to use some existing biobanks such as STORE, GENEPI.
- Cohorts have to be backed up with good dosimetry encouraging retrospective dosimetry for existing ongoing studies (eg. cytogenetics, EPR etc.) and also for newly initiated studies.
- Proper medical surveillance of the cohorts is essential. Low dose exposures from medical radiology and radiation therapy, including nuclear medicine, can be the most productive cohorts because exposure is taking place in a controlled environment with good dosimetry and controlled discrimination of exposure fields.

Research priorities (17)

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European Low Dose Initiative

2.4. Research Priorities

2.4.3. Epidemiological issues

- Cohorts such as **children exposed to CT scans**, occupationally exposed individuals such as **interventional cardiologists**, **flight crews**, radiation therapy patients with significant out-of-field exposures (conformational radiotherapy) should be considered and, of course, studied not only for cancer incidence but also the non-cancer conditions of concern.
- Links should be sought with ongoing epidemiological studies such as ALPHA-RISK (i.e. health risks from domestic alpha exposure), CHILD-THYR (i .e. risk of thyroid cancer following early life exposure to 131I), GENE-RAD-RISK (i.e. radiation exposures at early age and impact of genotype on breast cancer risk), ARCH (i.e. long term research on health consequences of radiation from the Chernobyl accident) and CHILD-MEDRAD. and CHILD-MED-RAD (i.e. health risk follow up prospective study of trans-national cohorts of patients with substantial paediatric diagnostic exposures).

Research priorities (18)

MELODI
Multidisciplinary
European Low Dose Initiative

2.4. Research Priorities

2.4.3. Epidemiological issues

- The promoted suitable epidemiological studies should be associated with (accompanied by) **mathematical modelling** taking into account mechanistic aspects in order to support low dose health risk evaluations..
- Overriding **ethical issues** should be sorted out and settled by consensual interaction with the national ethical commitees involved.
- Combined epidemiological and animal model studies may be of use in identifying risk variants. Inclusion of various functional assays for radiation sensitivity in epidemiological studies will increase statistical power for identifying risk factors in later genome wide association studies. Moreover, additional functional cohorts could come from human longevity studies (cancer susceptibility and radiation response), cancer susceptible individual and radiation therapy patients with aberrant responses.

Research priorities (19)

MELODI
Multidisciplinary
European Low Dose Initiative

2.4. Research Priorities

2.4.3. Epidemiological issues

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Justification (1)

2.5. Justification and expected outcomes

- **2.5.1. Shapes of dose response curves and radiation quality effects**.
- **2.5.1.1. Basic aspects**

The basic scheme involves the relationship between radiation energy deposition and biological effects. The qualitative and quantitative differences between low and high-LET ionizing radiation rely on the spatial (and temporal) energy deposition properties of the radiations at the nanometer, micrometer and higher scales.

The quantity absorbed dose (dose) for low dose high-LET exposures is of scarce meaning. When a low number of cells are irradiated with a significant dose associated with single radiation tracks, the interaction of irradiated with non-irradiated cells is crucial to understand risk of cancer in an organ vs the effects in a cell.

Justification (2)

2.5. Justification and expected outcomes

2.5.1. Shapes of dose response curves and radiation quality effects.

- **2.5.1.2. General knowledge gaps.**

Radiation weighting factors, w_R, as used by ICRP have been specified for stochastic effects as factors by which the mean absorbed dose in any tissue or organ is multiplied to account for the detriment caused by a specific type of radiation relative to photon radiation (ICRP, 2007). The concept of average organ absorbed dose may be inappropriate when energy deposition is highly inhomogeneous. Thus, at low average organ dose high-LET irradiation may result in a significant level of cell damage. It can be questioned whether the health effects of low doses of various radiation qualities can be evaluated by the w_R approach and whether the currently adopted w_R values are reasonable estimates for radiation protection purposes. This problem holds in particular for neutrons, since estimation of risks associated with them is only indirect, relying on scaled estimates of risk from low-LET radiation (ICRP Publication 99, 2005).

Justification (3)

2.5. Justification and expected outcomes

2.5.1. Shapes of dose response curves and radiation quality effects.

- **2.5.1.2. General knowledge gaps (continued)**
- The shapes of the dose effects curves after low- and high-LET irradiation can be very different, and the results obtained for the former cannot be extrapolated to the latter just on the basis of rescaling factors. Also, the influence of dose rate is expected to be different.
- This clearly emphasizes that specific strategies are needed for the assessment of the risk of low-dose, high-LET radiation. Furthermore, studies on the dependence of biological effects on radiation quality can be extraordinarily useful tools to test mechanisms underlying these effects.
- *Understanding whether indirectly affected cells can contribute to the effects of irradiation at low doses in a radiation quality-dependent fashion can have important implications.*

Justification (4)

2.5. Justification and expected outcomes

2.5.1.3.. Identification of knowledge gaps and prioritization.

- To improve our understanding of the role of radiation quality in carcinogenesis and non-cancer diseases experimental and theoretical mechanistic studies are needed on radiation-quality dependence of the relevant end points, starting from track structure and physical interactions with main biological targets. Critical questions are to what extent quality effects are responsible for radiation-induced (oxidative) stress and conditions its possible reversibility, how radiation quality affects the initial damage (DNA and non-DNA), and its time evolution (considering both faithful repair and mis-repair processes), intra- and intercellular signalling, and non-DNA-targeted effects.
- A deeper understanding is needed on the relevance of complex and clustered DNA damage induced by a single radiation track in chromosome aberration, mutation induction and carcinogenesis and also on the possible role of dose-rate and that of mixed radiation fields (including possible synergistic and adaptive phenomena).

Justification (5)

2.5. Justification and expected outcomes

- **2.5.1. Shapes of dose response curves and radiation quality effects**.
- **2.5.1.4. Future Research lines**
- The mechanisms that govern the possible different shapes of dose-(fluence-) effect curves at low dose still need further investigation. Especially, **radiation-quality specific studies** are needed to explore processes possibly leading to biological effects relevant to cancer and non-cancer risks.
- An **omics and system biology approach** for these radiation effects is advisable, coordinated with epidemiological studies. Experimental and modelling approaches should be combined.

Important research issues involving radiation quality effects are:

- Studies on initial damage characteristics (related to time and space evolution of track structure) and its time evolution (including DNA damage repair and misrepair processes), their conversion into chromosome and other endpoints relevant for low dose cancer and non cancer induction.

Justification (6)

2.5. Justification and expected outcomes

- **2.5.1. Shapes of dose response curves and radiation quality effects**.
- **2.5.1.4. Future Research lines**

Important research issues involving radiation quality effects are (continued):

- Studies on the radiation quality dependence of epigenetic phenomena and occurrence of genomic instability.
- Studies on the radiation quality dependence of oxidative damage and stress (generation of reactive oxygen species), cell signalling and microenvironment (cell-to-cell communication).
- Studies on mixed fields effects (possible additive or synergistic phenomena and adaptive responses).
- Studies on the role of dose/fluence rates, and the extent to which this varies with different radiation types.

Justification (7)

2.5. Justification and expected outcomes

- **2.5.1. Shapes of dose response curves and radiation quality effects**.

2.5.1.5. Expected outcomes

- The above mentioned studies should provide a better perspective of the relationship between low dose exposures for cancers (which currently steers present radiation safety regulations) and the more recently appreciated non-cancer diseases and the mechanisms by which they can be radiation-induced.

Justification (8)

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects

- This research largely **responds to public concerns** on how to protect every individual and how to define the **individual's health risks after low dose radiation exposure**. Obviously, further knowledge on individual radiation sensitivity would help to better evaluate personal risks from accidental or therapeutic low dose exposures. In radiation therapy, better knowledge on this topic should help to further limit the risk of radiation out-of-field and other side effects.
- The **development of reliable biomarkers for exposure and predisposition for disease (cancer and non-cancer) is an essential pre-requisite.** Such biomarkers are not yet close to deployment. It is likely that in the current framework of DoReMi such biomarkers will be developed.

Justification (9)

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects (continued)

- At present, **it will be necessary to store material** from on-going research cohorts. However, at the present state it is not clear what to store because we do not know what markers will emerge.
- Research on individual sensitivity constitutes an interface between fundamental research and molecular epidemiology.
- There are formidable ethics restrictions placed on this type of research in Europe and of course logistical limitations on what may be collected from human subjects. Thus, these problems have to be solved concomitantly.

Justification (10)

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects (continued)

- A critical factor is **proper dosimetry when considering retrospective or prospective cohorts.** Prospective studies from medical radiology or radiation therapy appear to be more promising because dosimetry is well specified.
- By analyzing genes and genetic polymorphisms (DNA repair, cell cycle checkpoint genes, oncogenes, genes of DNA and general metabolism, SNPs associated with micro RNA binding sites, post-transcriptional regulation of gene expression, hormonal and immune responses etc.) as well as epigenomic imprints their role in individual low dose radiation responses can be defined. This knowledge then can be used to define sensitive subpopulations in the cohorts and the effects of confounding factors such as age, sex, gender, lifestyle, physiological and reproductive status,and concomitant exposures to other physical, chemical or infectious agents.

Justification (11)

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects (continued)

- Some endpoints have shown **promise in the field of markers for individual radiosensitivity** e.g. G2 sensitivity, dicentric chromosomes or micronuclei and may need further study. However, to date, all assays have fallen short of being reliable individual predictors, and there is a considerable overlap.
- Some newer assays for markers of radiation exposure and specific DNA repair activities have shown greater promise for indicating intrinsic individual radiation sensitivity and repair capacity and this work should be encouraged. Some tests may even be predictive for long term cancer risks in human.
- These newer cytological and molecular assays have to be applied on a large scale for validation. It is possible that an integrated analysis based on a constellation of results from several markers will emerge as the most reliable way to specify an individual's sensitivity.

Justification (12)

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects (continued)

- In-bred laboratory animal models cannot represent the intrinsic variability of a human population. However, they can be useful for validation purposes.
- Specific endpoints can be examined and specific modifiers can then be further explored using suitable animal models (e.g. for osteosarcomagenesis (RB1), mammary tumours (Aps) and medullablastoma (ptch). Radiation quality and dose-rate effects should be considered as well.

Justification (13)

2.5.2. Individual radiation sensitivity

2.5.2.2. Expected outcomes

- From molecular and initial human studies over the timescale of 3-5 years there is a reasonable likelihood that some suitable biomarkers for radiation exposure and pathological conditions (cancer) will become available. Probably, several biomarkers and indicators will have to be used in suitable cohorts in combination to assess individual sensitivity.
- However, it should be realised that cohorts and other human studies require ethics approval. Experience has shown that obtaining approval in different European countries is very time consuming and introduces considerable delays to getting the actual research started. It would be a considerable advantage if the MELODI platform would explore ways that facilitate ethics approval throughout Europe overcoming national boundaries for such studies.

Justification (14)

2.5.3.Non cancer effects

- Non-cancer effects at low doses cannot be readily explained by the mutational theory (DNA paradigm) underlying the extrapolation of cancer risk from high to low doses (LNT).
- It has been traditionally assumed that the non-cancer effects and diseases show a **threshold at doses** that are well above the levels of exposure typically encountered in the public environment, at work or from medical diagnostics.
- However, some epidemiological evidence as well as various tissue responses and non-targeted effects recently observed at low doses call for new experimental (mechanistic) and epidemiological studies that address the extrapolation issue.

Justification (15)

- **2.5.3.Non cancer effects**
- At present, little information is available on the constancy of acute low dose damage recognition, signalling and response mechanisms across tissues, and on the long-term development of radiation effects in different tissues at low doses.

Justification (16)

- **2.5.3.Non cancer effects**
- At present, **cardiovascular diseases, effects on cognitive effects and lens opacities are focused on**.
- **Cardiovascular diseases**

  It has been generally accepted that high dose (several Gy) radiation exposure to the heart or other parts of the circulatory system result in long-term increases in circulatory disease risks. Over the past 10-15 years evidence has been emerging from the long term follow-up of atomic bomb survivors and other populations that relatively low dose acute exposures (< 2 Gy) are also associated with increased circulatory disease risks.
- Thus, there is increased interest to identify mechanisms for long-term radiation effects on the circulatory system and to examine possible low dose radiation circulatory disease risks in other populations.

Justification (17)

- **2.5.3.Non cancer effects**
- **Cognitive functions**
- Dose response relations for radiation effects on **cognitive functions show thresholds around 100 mGy for exposures of the foetus** between weeks 8 and 15 but the current judgement is that induction of IQ deficits at low doses is of no practical significance (ICRP Publication 103). The mechanistic understanding of the effects of radiation on the foetus is coupled to the developmental stage of the brain during the critical weeks 8-15 when the cell proliferation and migration is maximal, while the later stages seem less critical.
- Considerable interest was generated when a study on the effect of low doses of ionizing radiation in infancy on cognitive function in adulthood was published in 2004. The conclusion was that **low doses of ionizing radiation to the brain in infancy influence cognitive abilities in adulthood.**

  This discovery of a second time window (at infancy) for radiation induced adverse effects on the cognitive functions opens new aspects for much needed investigations

Justification (18)

2.5.3.Non cancer effects

- **Lens opacities**
- At high doses (0.5-2 Gy), ionizing radiation causes lens opacities in humans that may manifest as cataracts, and other changes that hamper vision. Several recent epidemiological studies have indicated that the prior assumption of a relatively high threshold dose may not be justified.
- Indications of lens opacities have been reported in US interventional radiologists, Icelandic pilots exposed to cosmic radiation, people exposed to Chernobyl fallout, and after exposure to X-rays.

  Studies on A-bomb survivors suggest that there is either no threshold or the threshold is much lower than was previously assumed.

Justification (19)

2.5.3.Non cancer effects

- **2.5.3.2. Relevant biological and physiological effects (continued)**
- Recent animal experiments have demonstrated that chronic exposure by ingestion of low doses of radionuclides may induce effects on unsuspected biological targets, such as the central nervous system,liver and major organism metabolism.
- Effects on metabolism and behaviorial changes were observed. Chronic contamination by cesium-137 is suspected to affect cardiovascular functions.
- It is likely that the underlying mechanisms involve as starting points (initial events) radical formation and radical (oxidative stress) induced lesions very similar to those implicated in cancer.

Justification (20)

2.5.3.Non cancer effects

- **2.5.3.2. Relevant biological and physiological effects (continued)**
- Subsequent stages involving different tissues, metabolic, hormonal, immunological, inflammatory and tissue micro-environmental responses) are likely to be rather specific and different from those identified for cancer. It will be important **to attract new disciplines into the field of radiation research**. In the case of non-cancer diseases, parmacotoxicologists, cardiologists, neurologists, toxicologists, ophthalmologists have to be involved.
- Suitable cohorts may be constructed from radiation diagnosis and radiation therapy patients as well as from interventional cardiologists, dentists, flight crews etc .
- ***Non cancer endpoints have thus to be included in prospective studies in addition to the cancer surveillance*.**

Justification (21)

2.5.3.Non cancer effects

2.5.3.3. Expected outcomes

- We expect to obtain relevant information on the mechanisms involved in non-cancer effects of low dose radiation exposures. In particular, a better understanding of the mechanisms will guide us to answer the important question on the existence or not of thresholds for non-cancer effects, i.e. whether the effects are of stochastic or deterministic nature.

3. NEXT STEPS

3.1. Evolution of research areas to be exploited

- It is clear that the above questions relating to key issues that the research cannot be adequately undertaken by only extending already existing fields in radiation research such as radiation physics, radiation chemistry, radiation biology, radiation therapy and diagnostics, radiotoxicology etc.
- New lines of research have to be developed based on recent achievements arising from areas outside of radiation research to broaden thinking with a view to a new dynamism.

3. NEXT STEPS

3.1. Evolution of research areas to be exploited:

- For example, there have been in recent years many discoveries on specific metabolic functions and pathways, homeostasis, signalling mechanisms, stem cell biology, cellular stress, proliferation, genetics, epigenetics, systems biology, toxicology, genotoxicology, physiology, pathology, immunology, inflammatory research, hormone research, research on cell death (apoptosis, mitotic catastrophy, autophagy), the central nervous system, recognition and behavioural effects, molecular markers for imaging, effects of nanoparticles (nanotechnology), heredity, transgenerational transmittance, diseases (medical treatments and diagnosis of cancer and non-cancers,etc.).

3. NEXT STEPS

- **3.1.1. Approaches to be considered**
  - ***Classical***
    - Cytogenetic (Multi-FISH, chromosome painting) radiation chemistry, biochemistry, radiation sources, microirradiation, genetics
  - ***Emerging***
    - Transcriptomics, Proteomics, Metabolomics, Epigenomics,
    - Development of exposure and disease specific biomarkers
    - Systems Biology (Identification of molecular pathways)
    - Inactivation of specific genes (miRNA, epigenomic silencing)

3. NEXT STEPS

- **3.1.1. Approaches to be considered (continued)**
  - ***New techniques:***
    - Molecular Imaging and MRI
    - New radiation devices: microirradiation, synchroton, heavy ions, conformational radiation therapeutic devices, radiation pharmacology, immunoradiology
    - QT-PCR
    - Nanostring nCounter
    - High throughput sequencing
    - Reproduction - hereditary transmission
    - 2 and 3D electrophoresis
    - mass spectrometry electrospray, HPLC, chromatography,
    - nanotechnology
    - Genetic an epigenetic imprinting
    - Computer assisted tomography
    - Bioinformatics

3. NEXT STEPS

- **3.1.1. Approaches to be considered (continued)**
  - **Epidemiology**
  - Classical and molecular Epidemiology
    - whole Populations
    - retrospective and prospective cohorts
    - mathematical modelling
    - Reliable medical assessment and follow-up of suitable cohorts (short and long term pathologies)
    - Genetic and transgenerational studies in mice and humans

3. NEXT STEPS

3.1.2. Infrastructures

- For low dose and low dose rate research the lack of suitable infrastructures is at present a limiting factor. A strategy for the upgrading of the infrastructures should be thus given a high priority.
- Suitable cohorts, biobanking and radiation devices are essential.

3. NEXT STEPS

3.1.2. Infrastructures

- For low dose and low dose rate research the lack of suitable infrastructures is at present a limiting factor. A strategy for the upgrading of the infrastructures should be thus given a high priority.
- Suitable cohorts (allowing evaluation of radiation insults as well as those of other agents) , biobanking (ensure follow-up of STORE and DoReMi WP4) and radiation devices (microirradiation and low dose/low dose rate installations) are essential.

3. NEXT STEPS

- **3.1.2. Infrastructures (continued)**
  - In particular, suitable sources with associated laboratory facilities able to deliver low and low dose rate radiation to cells, tissues and whole animals (both external beam irradiators and internal radionuclides) are to be identified and /or developed already during DoReMi and then made available in the MELODI context.

3. NEXT STEPS

3.1.3.Education and training

- In recent years, many European member states have lost key competences and are no longer capable of independently retaining their current research activities in radiation sciences, with implications for effectively fulfilling operational and policy needs and obligations.
- Thus, specific programmes aiming at knowledge management across generations have to be designed in order to achieve sustainable continuity and development.

3. NEXT STEPS

3.1.3.Education and training

Important aspects to be considered are:

(1) the underlying scientific programmes have to address questions that are attractive to both young scientists and faculties of universities as well as to the management of research organisations.

(2) the attractiveness of the field has to be increased by a multiple approach implemented from Summer schools to master degrees, PhD and post-doctoral European research training programmes.

(3) In the long term, such programmes cannot be successful unless they do provide job opportunities to young scientists.

(4) In the present situation, sustainability of such programmes can only be achieved by a long-term commitment of funding bodies.

3. NEXT STEPS

3.1.3.Education and training

- The MELODI platform does effectively respond to these needs and aims at establishing an integrated approach to education and training of research and teaching at Universities and non-university research organisations.
- Existing elements of education and training activities in this domain such as the European MSc course should be strengthened, making it compliant with the Bologna Process which creates the European Higher Education Area (EHEA) and is based on the cooperation between ministries, higher education institutions, students and staff from 46 countries, with the participation of international organisations.
- At present, only a few universities in Europe will have the resources to offer a full educational program at the basic as well as the advanced level of subjects such as radiation biology and radiation physics.

NEXT STEPS

Education and training

- **The following steps should be implemented**
  - Audit of radiation courses in Europe (undertaken by DoReMi) to establish a European course (and/or summer school) in radiation biology and radiation protection with conventions with European universities and institutions
  - Identification of stakeholders able to support long term sustainability.
  - Proposition of EU calls directed to education and training that promote new ways of setting up new multidisciplinary interactive courses that are Bologna compliant and based on solid conventions with leading universities and research organisations and that allow inclusion of most recent research developments in the field of low dose radiation research and the evaluation of radiation health risks.

NEXT STEPS

Maintaining the SRA (1)

- Essential that the SRA is periodically revised to take account of new developments, achievements of research from DoReMi, feedback from the consultation processes and the progressive roll out of SRA targets.
- Revision should include a statement of achievements in terms of scientific ground covered, establishment of multidisciplinary and multinational teams and development of infrastructures.

NEXT STEPS

Maintaining the SRA (2)

- MELODI should organise on a permanent basis a team tasked to periodically review and update the SRA

- The frequency of revisions needs to be aligned with main stream of budgetary procedures, including the Euratom call process.

3. NEXT STEPS

ROADMAP (1)

- **SRA Working Group considers it premature to outline a ROADMAP for MELODI until consultation at the meeting finalised.**
- **Part of the projected low dose program is realized by the DoReMi TRA covering the next 6 years**
  - involves putting into place important aspects of essential infrastructures and developing new approaches to education and training.

3. NEXT STEPS

ROADMAP (2)

The fully integrated research (SRA) will rely on

(1) attracting new partners

(2) input from non radiobiological research disciplines such as toxicology, immunology, inflammatory research, physiology, pathology, genetics, epigenetics, cardiology, neurology, ophthalmology etc.

(3) MELODI Roadmap should (end of 2010) give

- Timescales of the different research ideas
- Financial sustainability program based on feedback from the MELODI GB, the outcomes of this 2nd MELODI workshop and input of the MELODI SAC, the general scientific community and comments of the stakeholders.

3. NEXT STEPS

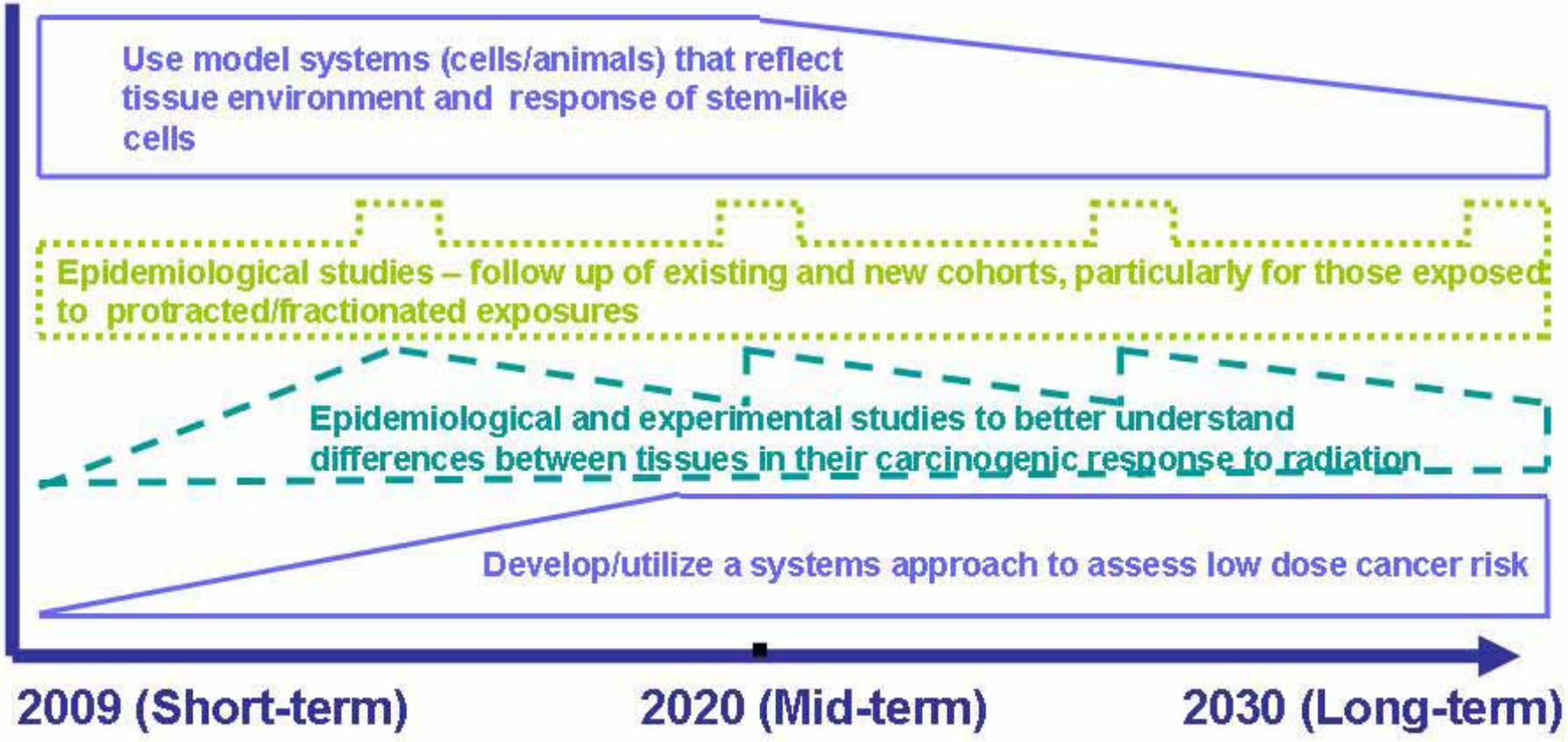
ROADMAP (2)

- **Prioritise research areas outlining a prescribed time scale.**
- **Identification of suitable biomarkers for defined radiation exposures (internal or external)**
- **Predictions for the initiation of pathological pathways and for final pathological outcomes will be high priority for research on radiation biology networking.**
- **Identification of biomarkers expected to stimulate molecular epidemiological studies and the establishment of suitable prospective or retrospective cohorts (i.e.. prospective cohort of CT scans in children, induction of secondary cancers in out-of field radiotherapeutic sites).**

Shape of dose response (cancer)

Objective: **To improve the understanding of dose-response for radiation carcinogenesis- to judge whether approaches using the LNT model might under- or over- estimate risk in different tissues**

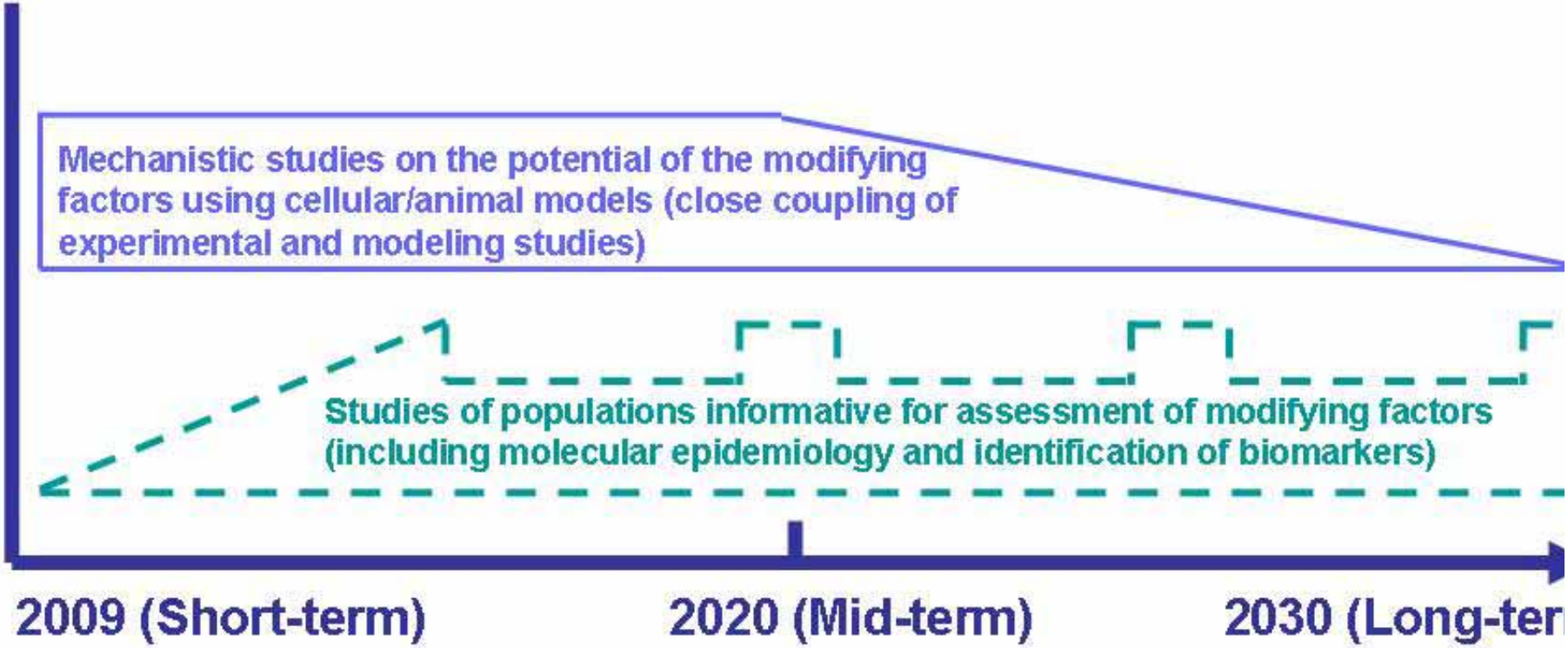
Relevance: projection of risk to low doses and doses rates – judgments on tissue weighting factors



Individual variability

Objective: **To quantify how the sensitivity of individuals (or population subgroups) to induction of health effects depends on gender and age, genetic and epigenetic factors, lifestyle factors and concomitant exposure to other agents**

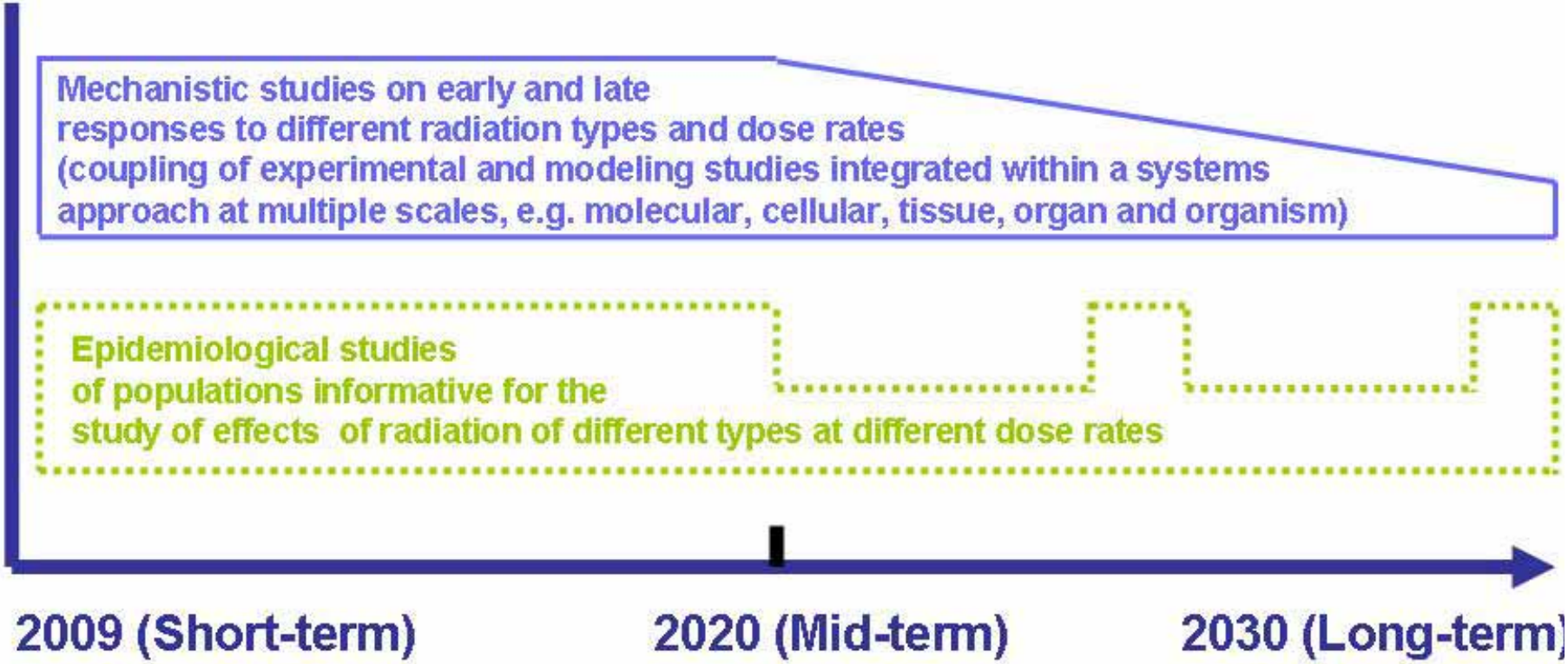
Relevance: protection of particular subgroups of population



Radiation quality

Objective: **Quantification of health effects of different radiation types and mixed fields**

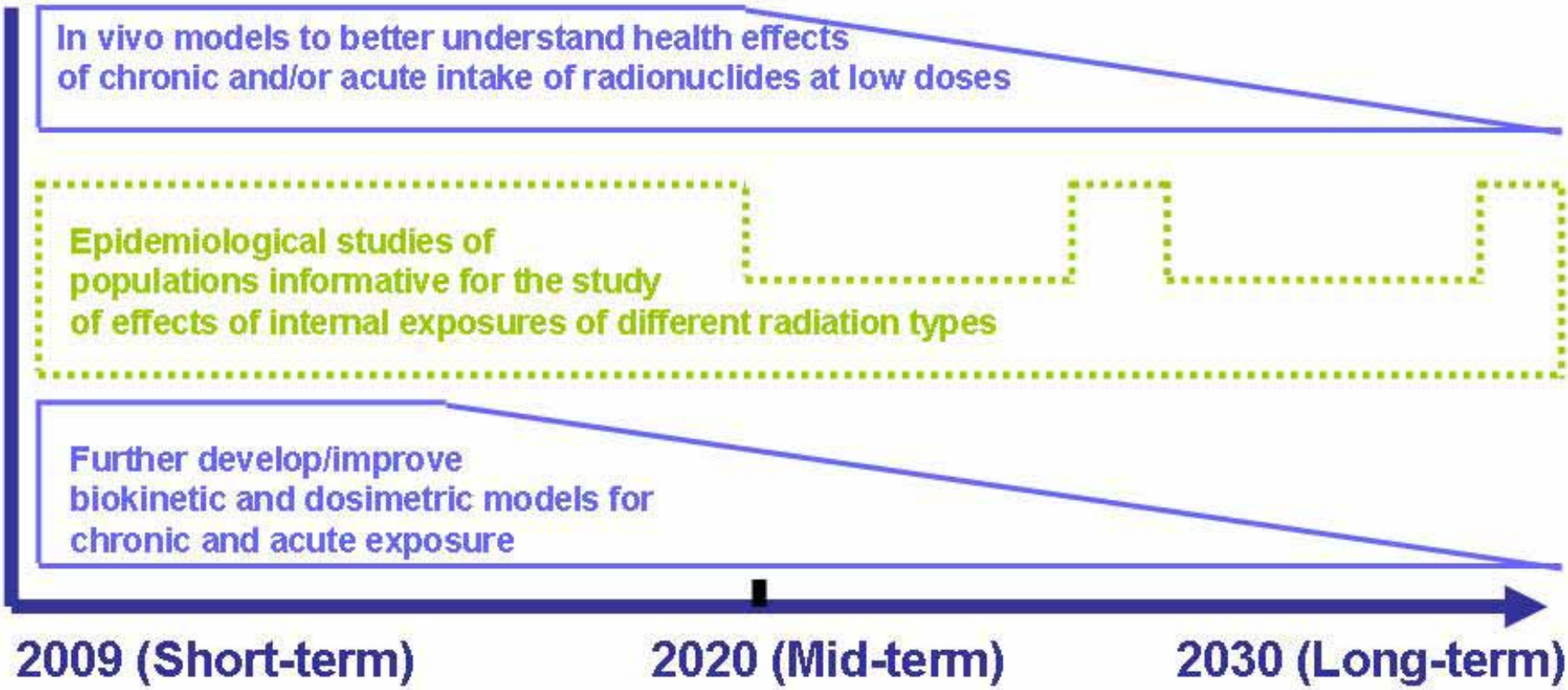
Relevance: use of radiation weighting factors in radiation protection and application of different types of radiation in medical practice



Internal exposures

Objective: **To better quantify the risk estimates from internal exposure**

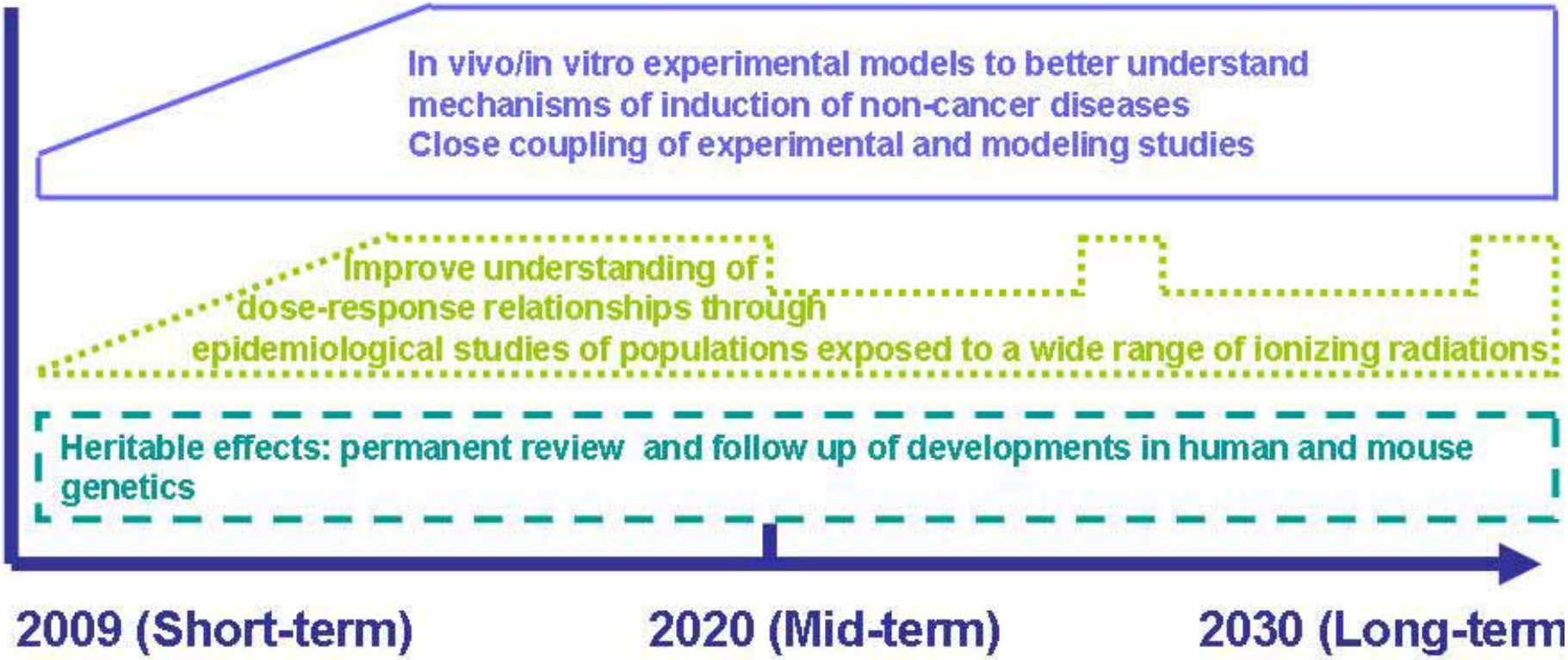
Relevance: To improve the robustness of the systems of protection



Non-cancer effects

Objective: **To better understand the mechanisms of and quantify the risks for non-cancer health effects resulting from exposure to low and protracted doses**

Relevance: Implications of contribution of non-cancer diseases to radiation risk for the system of radiation protection



NEXT STEPS

Major considerations

MELODI is promoting Multidisciplinary integrated low dose research in Europe

- to bring in ‘new blood’ and to attract young scientists
- Harmonisation of research efforts and infrastructures, education and training
- Sustainability of infrastructures, education and training
- Ongoing interaction and communication with stakeholders and the public to promote knowledge and organize sustainability of this type of research.

NEXT STEPS

On-going Consultation (1)

- A working group of experts constituted by MELODI to identify important domains of low dose research
- prioritize scientific questions relevant for low dose radiation risk research
- assess the corresponding research needs in the light of present EU funded research and other international programmes.
- promote multidisciplinary integration covering as wide range as possible of scientific areas group meetings.

NEXT STEPS

On-going Consultation (2)

It is recommended that there should be

- fully interdisciplinary working groups to re-appraise the research areas and priorities based on on-going research
- discussion forums to attract fundamental scientists from neighbouring fields
- a Series of MELODI sponsored mixed forums-conferences-seminars-colloquia.

NEXT STEPS

- **MELODI Board will finalise composition of the Scientific Advisory Committee (SAC)**
- To include a wide range of disciplines covering both the existing branches of radiation biomedical sciences and all new areas identified as being important for attraction to the MELODI programme.

Conclusion

Your comments to the first draft of the MELODI SRA are most welcome.

Thank you very much for your attention!