

**DoReMi** Integrating Low Dose Research



# The EU NoE DoReMi – where are we now?

Sisko Salomaa

STUK - Radiation and Nuclear Safety Authority

FINLAND

*MELODI workshop 2011, Rome*



**DoReMi** Integrating Low Dose Research

## **MELODI**

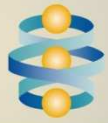
# **M**ultidisciplinary **E**uropean **L**ow **D**ose **I**nitiative

*Open RTD platform guiding priorities  
in low dose research in Europe*

## **DoReMi**

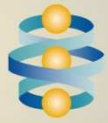
# Low **D**ose **R**esearch towards **M**ultidisciplinary **i**ntegration

*Network of Excellence 2010-2015*

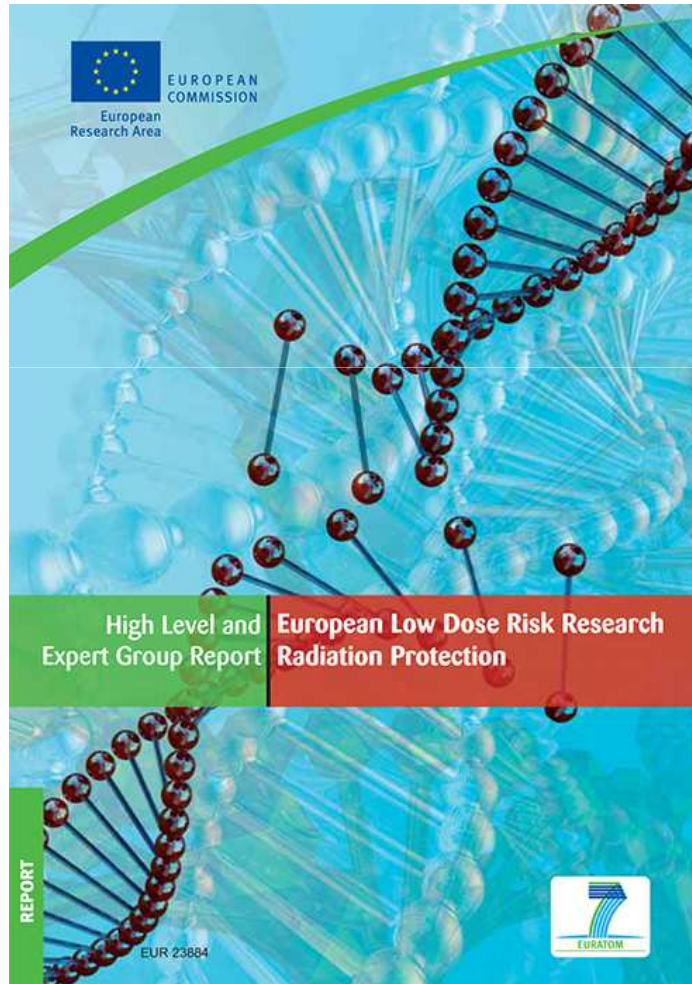


# Background

- Decline of resources across Europe (human, research infrastructures)
- Small groups, fragmented research
- Arising new issues and paradigms demand multidisciplinary approaches and new competencies
- Uncertainties remain for low dose risk
- Need to focus on key questions for RP
- No single group, institute, country can solve the scientific issues alone



# HLEG Report 2009

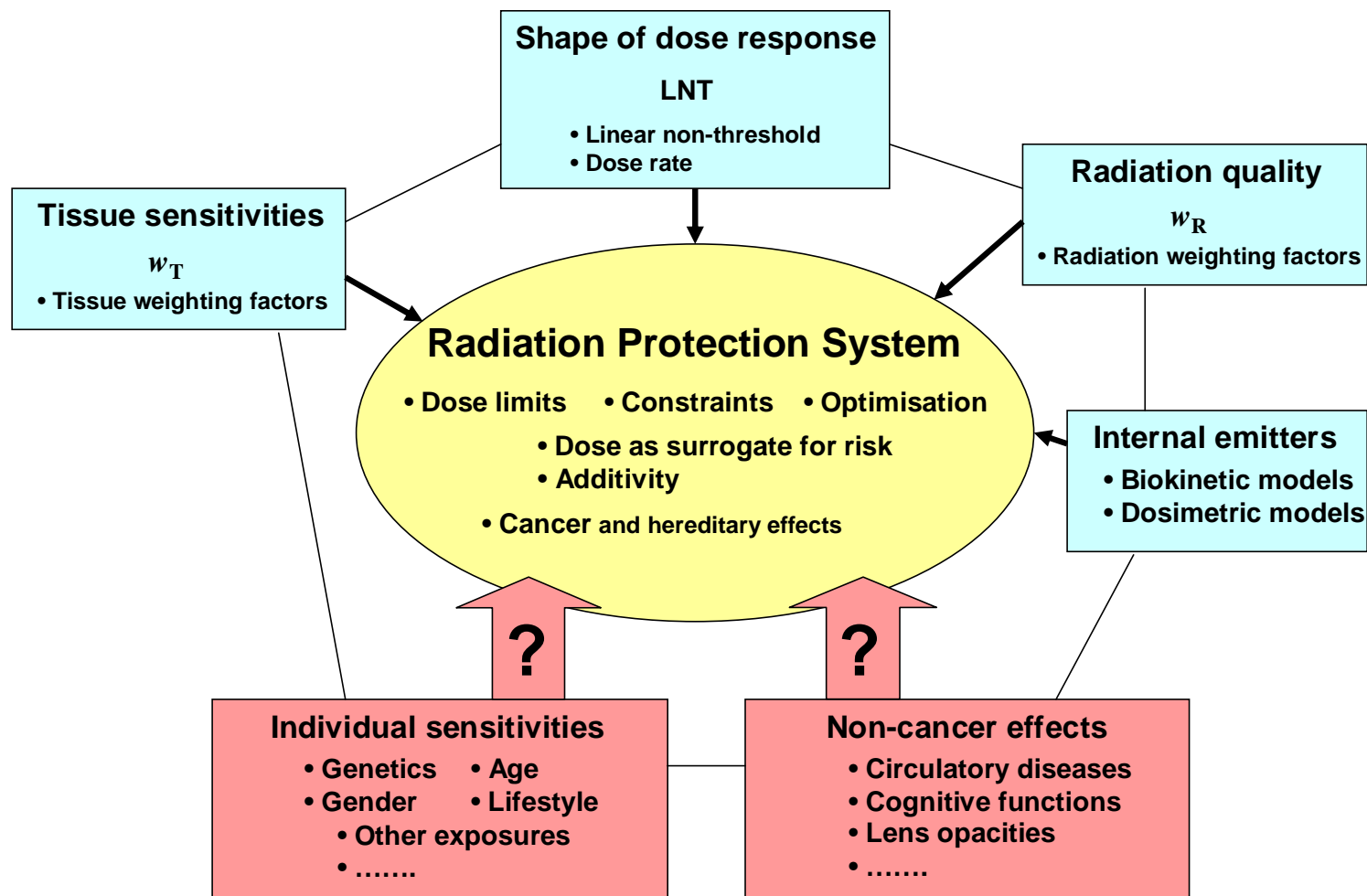


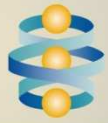
See Cordis for EC Report  
EUR 23884

[www.melodi-online.eu](http://www.melodi-online.eu)



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





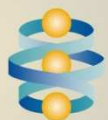
# MELODI

## Multidisciplinary European LOw Dose Initiative



[www.melodi-online.eu](http://www.melodi-online.eu)

- Letter of Intent: BfS, IRSN, CEA, STUK, ISS...
- 15 founding members
- 5 new members (2011)
- Association
- A roadmap for the MELODI platform development
- Relationship between MELODI and DoReMi
- SRA



1.	<ul style="list-style-type: none"><li>• <b>BfS</b> Federal Office for Radiation Protection, Germany</li></ul>
2.	<ul style="list-style-type: none"><li>• <b>CEA</b> Atomic Energy and Alternative Energies Commission, France</li></ul>
3.	<ul style="list-style-type: none"><li>• <b>HMGU</b> Research Center for Environmental Health, Germany</li></ul>
4.	<ul style="list-style-type: none"><li>• <b>HPA</b> Health Protection Agency, United Kingdom</li></ul>
5.	<ul style="list-style-type: none"><li>• <b>IRSN</b> Institute for Radiological Protection and Nuclear Safety, France</li></ul>
6.	<ul style="list-style-type: none"><li>• <b>ISS</b> Direttore, Dipartimento Tecnologie e Salute Director, Technology &amp; Health Department Istituto Superiore di Sanità, Italy</li></ul>
7.	<ul style="list-style-type: none"><li>• <b>ITN</b> Instituto Tecnológico e Nuclear, Portugal</li></ul>
8.	<ul style="list-style-type: none"><li>• <b>National Institute for Nuclear,</b> Chemical and Biological Protection, Czech Republic</li></ul>
9.	<ul style="list-style-type: none"><li>• <b>RIVM</b> National Institute for Public Health and the Environment, Netherlands</li></ul>
10.	<ul style="list-style-type: none"><li>• <b>SCK.CEN</b> Belgian Nuclear Research Centre, Belgium</li></ul>
11.	<ul style="list-style-type: none"><li>• <b>Stockholm University</b> Centre for Radiation Protection Research, Sweden</li></ul>
12.	<ul style="list-style-type: none"><li>• <b>STUK</b> Radiation and Nuclear Safety Authority, Finland</li></ul>
13.	<ul style="list-style-type: none"><li>• <b>TEXNIO</b> Universitat Rovira I Virgili, Spain</li></ul>
14.	<ul style="list-style-type: none"><li>• <b>KVSF</b> Kompetenzverbund Strahlenforschung, Germany</li></ul>
15.	<ul style="list-style-type: none"><li>• <b>Universidad Madrid</b> Universidad Autónoma de Madrid, Spain</li></ul>

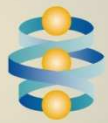
**Creation of the  
MELODI  
Association  
with  
15 Founding  
Members**



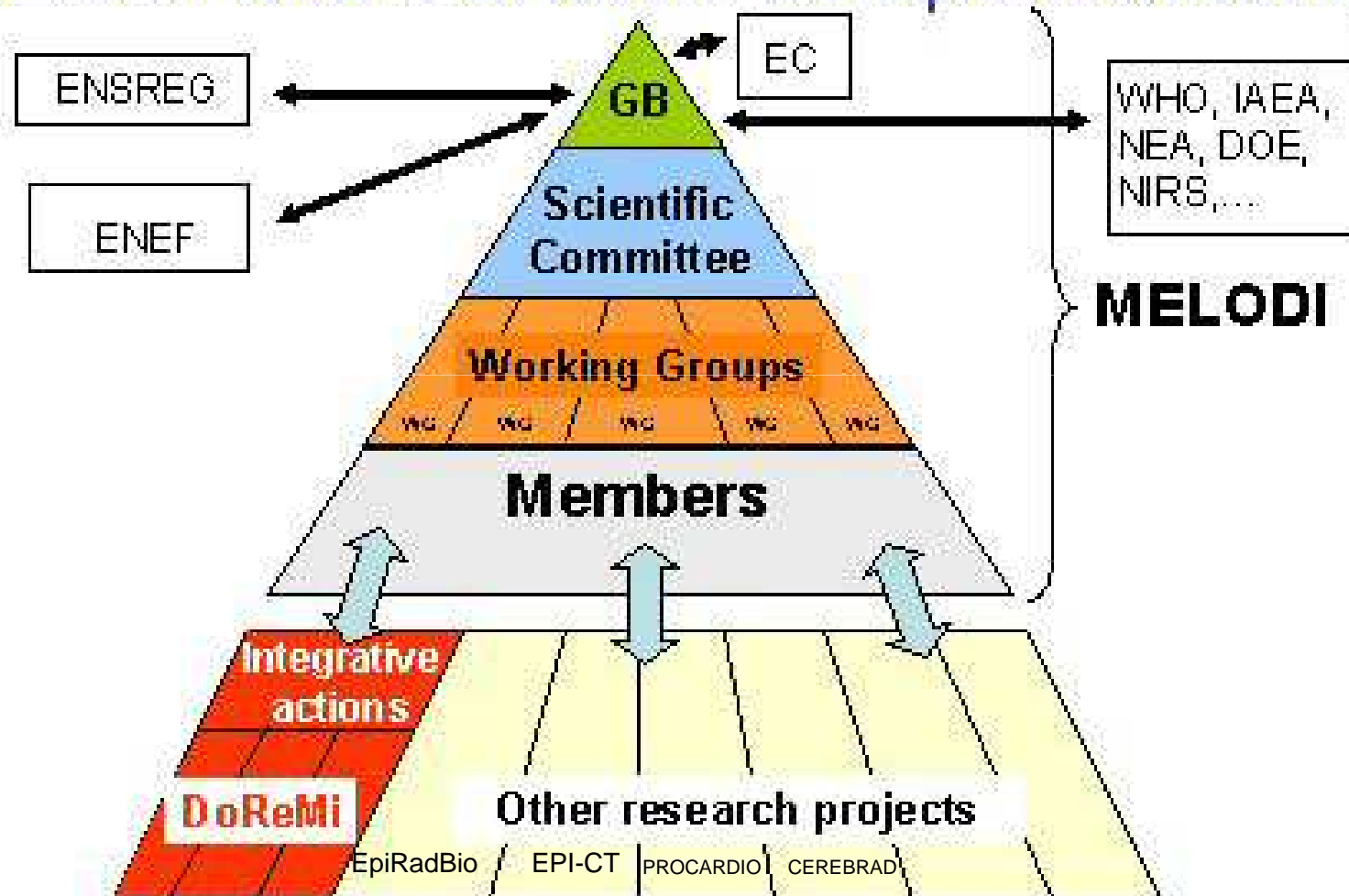
## New MELODI members 02.11.11

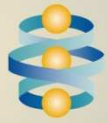
- Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA, Italy)
- Centre for Research in Environmental Epidemiology (CREAL, Spain)
- Institute of Radiation Physics (IRA, Switzerland)
- Swedish Radiation Safety Authority (SSM, Sweden)
- Frédéric-Joliot-Curie National Research Institute for Radiobiology and Radiohygiene (NRIRR, Hungary)





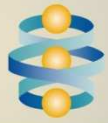
# MELODI and DoReMi: complementarity





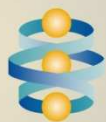
# The three goals of MELODI

- 1. To impulse low dose risk research in Europe, through an open and integrative Strategic Research Agenda approach**
- 2. To create a forum for dialogue with EU institutions and stakeholders**
- 3. To interface with international partners (WHO, IAEA, USA, Japan,...)**



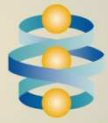
## Aim of DoReMi

- To promote sustainable integration of low dose risk research in Europe
- To act as operational tool to establish the MELODI platform
- To address the key policy questions identified by the HLEG Report by research, training and dissemination activities



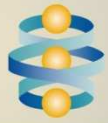
## Consortium

No	Beneficiary name	Acron ym	Country	No	Beneficiary name (new members 2011)	Acron ym	Country
1	Radiation and Nuclear Safety Authority (Coordinator)	STUK	Finland	13	Universitaetsklinikum Erlangen	UKER	Germany
2	Institut de Radioprotection et de Sûreté Nucléaire	IRSN	France	14	Johann Wolfgang Goethe Universitaet, Frankfurt am Main	GUF	Germany
3	Helmholz Zentrum München	HMGU	Germany	15	Universitaet Rostock	UROS	Germany
4	Commissariat à l'Energie Atomique	CEA	France	16	Norwegian University of Life Sciences	UMB	Norway
5	Health Protection Agency	HPA	UK	17	Norwegian Radiation Protection Authority	NRPA	Norway
6	University of Pavia	UNIPV	Italy	18	Nasjonalt Folkehelseinstitutt	NIPH	Norway
7	Istituto Superiore di Sanità	ISS	Italy	19	Agenzia Nazionale per le Nuove Tecnologie, l'Energia e lo Sviluppo Economico Sostenibile	ENEA	Italy
8.	Belgian Nuclear Research Centre	SCK-CEN	Belgium	20	Institute for Environmental Sciences	IES	Japan
9	Bundesamt für Strahlenschutz	BfS	Germany	21	Dublin Institute of Technology	DIT	Ireland
10	University of Stockholm	SU	Sweden	22	Erasmus Universitair Medisch Centrum Rotterdam	Erasmus MC	Netherlands
11	Centre for Research in Environmental Epidemiology	CREAL	Spain				
12	Institut Curie	IC	France	<b>Next competitive calls for new partners in 2012 and 2014</b>			



## DoReMi links with scientific community

- **Competitive calls** for new partners are open for all scientific community (2010, 2012, 2014)
- **External experts** invited in exploratory workshops
- **[www.doremi-noe.net](http://www.doremi-noe.net)**
- Electronic newsletters
- Surveying national research and training activities and funding opportunities
- **Infrastructures** (development and access)
- Education and Training – **training courses**

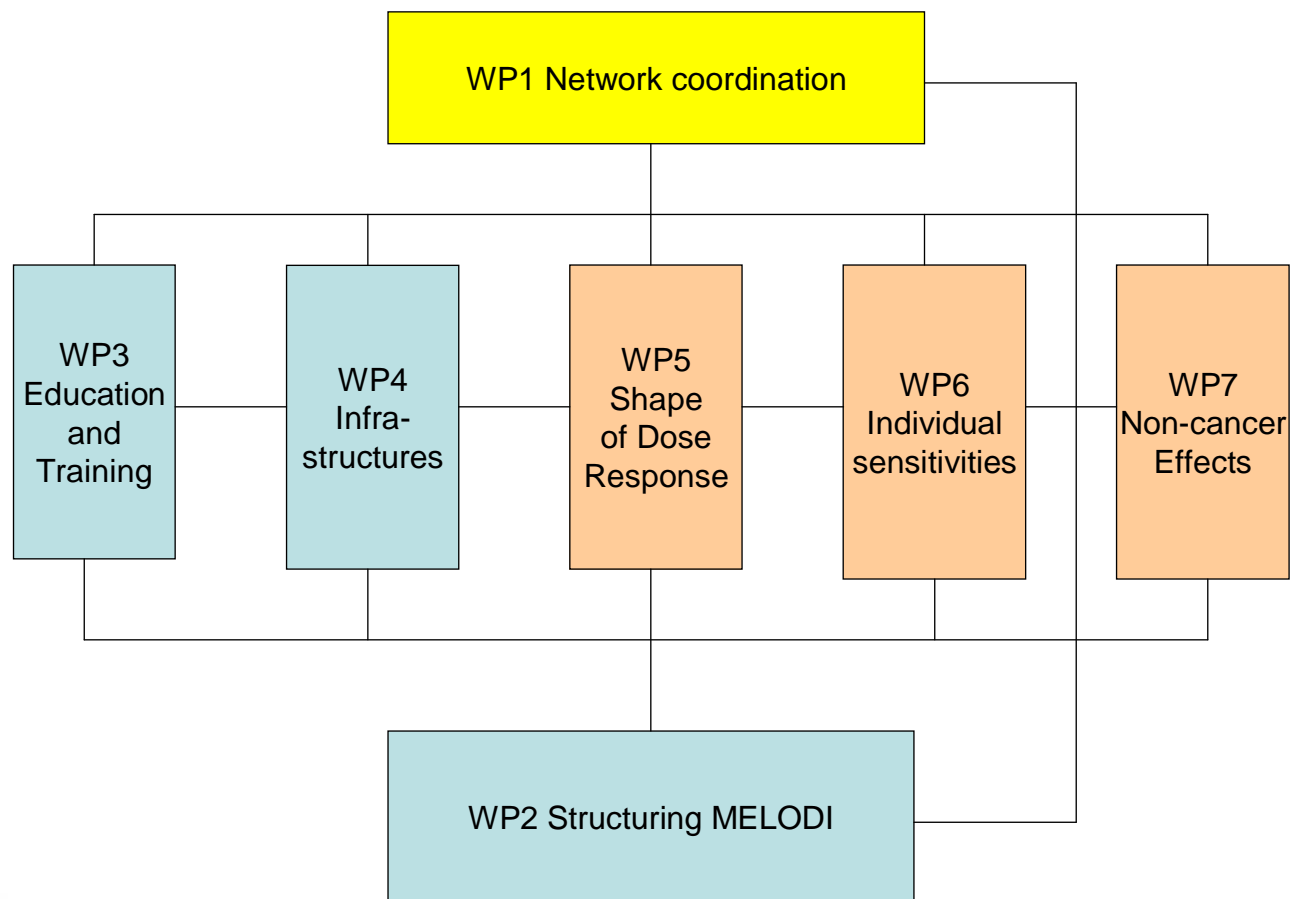


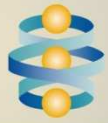
# Where are we now?

## DoReMi early activities



# Work package structure



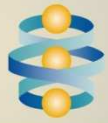


# Structuring MELODI - Milestones

**Dietrich Averbeck, WP2**

- DoReMi started in January 2010
- First version of TRA July 2010
- MELODI established in October 2010
- Draft MELODI SRA in October 2010
- First call for new partners autumn 2010
- Ten new partners joining DoReMi July 2011 > n=22
- TRA Statement August 2011
- MELODI SRA Statement October 2011
- Next DoReMi competitive call February 2012

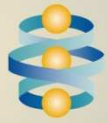




# Shape of dose response for cancer

**Simon Bouffler, WP5**

- Two overarching aims:
  - To improve knowledge of low dose/dose rate radiation cancer risk in humans
  - To improve low dose/dose-rate risk projection models based on knowledge of the processes that drive carcinogenesis
- A work plan centered on five inter-related tasks has been established
- Extension of the work through the external call



# Shape of dose response for cancer

- Low dose rate cellular stress (started)
- Mechanisms of leukaemogenesis (started)
- Modelling of cancer risk (started)
- Non-targeted and systemic effects
  - Research needs discussed in workshops
  - Feasibility studies on 3-D systems (started)
  - New task on modulation of inflammation by low and moderate doses was included after competitive call
- Priorities and feasibilities related to internal emitter risk have been discussed in workshops.



## WP5: Shape of Dose-Response Curve for cancer

### Mechanistic studies

Cellular stress responses, fibroblasts & stem cells (Task 5.1)



Non-targeted phenomena & systemic effects (Task 5.2)



AML development (Task 5.3)



Integrative models for cancer risk projection (Task 5.4)



Integrated studies on internal emitter health risks (Task 5.5)

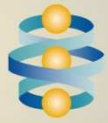


2010

2012

2014

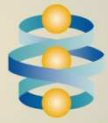
2016



# Individual sensitivities

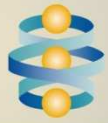
**Mike Atkinson, WP6**

- The overall aim is to determine the contribution of individual sensitivity towards the risk of developing cancer following exposure to low and protracted low dose rate ionizing radiation
- The influences of inter-individual differences are being addressed at three levels using
  - population studies
  - animal models
  - mechanistic approaches



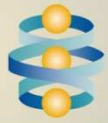
# Individual sensitivities

- Experimental studies to define the contribution of both highly penetrant and low penetrant genetic differences to modifying individual sensitivity have been initiated
- HMGU has initiated a large scale study on the genetic component that determines sensitivity to radio-iodine induced thyroid cancer
  - a range of complementary in vitro studies on the biological effects of thyroid cell irradiation



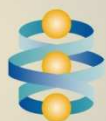
# Individual sensitivities

- Identification and validation of biomarkers of radiation exposure and effects for use in future molecular epidemiological studies of radiation-induced cancer in exposed cohorts
  - Workshop and review paper (CREAL)
- Identification of metabolite biomarkers defining individual responses to radiation exposure using Raman spectroscopy
  - New expertise in the biophysical analysis of individual plasma samples (DIT)



# Individual sensitivities

- Epigenetic markers and biological processes in radiation-induced cancer was examined in a workshop (June 2011).
  - The main conclusion was that epigenetic processes play a key mechanism in mediating the interaction between the environment and the individual.
  - The meeting recommended that a research strategy on epigenetic processes be adopted into the next TRA.
- Effects of individual variations in the radiation response over multiple scales (cell, tissue and organism) were discussed in systems biology workshop in Stockholm (October 2011)



## WP6: Individual sensitivities

**Task 6.1 – Review of potential biomarkers for radiation: potential use and validation through pilot studies in appropriate cohorts (based on WP4 review)**



**Task 6.6 - Implementation of the DoReMi strategy for a large scale molecular epidemiological study to quantify genetic contribution to individual susceptibility**



**Task 6.2 Identification of genetic modifiers of individual cancer susceptibility and their mechanisms of action**

*- Mouse models for genetic susceptibility to thyroid cancer*



*- Identification of modifier genes by classical linkage analysis / High throughput analyses: mRNA, miRNA, protein, metabolites / In vitro multicellular models: responses at 4 hrs/24-48hrs / - Analyses of DNA repair defects/IR sensitivity*

.....

**Task 6.3 Modeling individual variability**

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**Task 6.4 Genetic modifiers of carcinogenesis /low dose & low dose-rate effects**



**Task 6.5 Contribution of genetic and epigenetic mechanisms that influence susceptibility to radiation induced cancer**

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**Task 6.7 Planning expansion of research portfolio through workshops**



**Task 6.8 Prediction individual radiation susceptibility with Raman micro-spectroscopy**



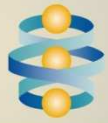
**2010**

**2012**

**2014**

**2016**





# Non-cancer effects

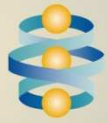
Jean-René Jourdain, WP7

## Short-term research activities

- Exploratory workshops and pilot studies on
  - mechanisms of vascular effects (Dec 2010)
  - mechanisms of lens opacities (Sept 2011)
  - mechanisms of cognitive and CNS effects

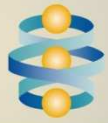
## Medium- to long term research activities

- Research projects on vascular effects (open call 2010)
- Research projects on lens opacities (open call)
- Research projects on cognitive and CNS effects (open call)



## Non-cancer effects

- The feasibility study towards a systems biology approach of radiation response of the endothelium is well in progress.
  - Cell culturing and protracted irradiation at low dose rates (1.4 or 4.1 mGy/h) have been performed at the Stockholm University
  - Several DoReMi partners contribute to the investigation of a wide range of endpoints.
- A pilot epidemiological study of lens opacities among a cohort of interventional radiologists and cardiologists is progressing.
- A pilot study of external irradiation versus internal contamination effects on neurogenesis was initiated.

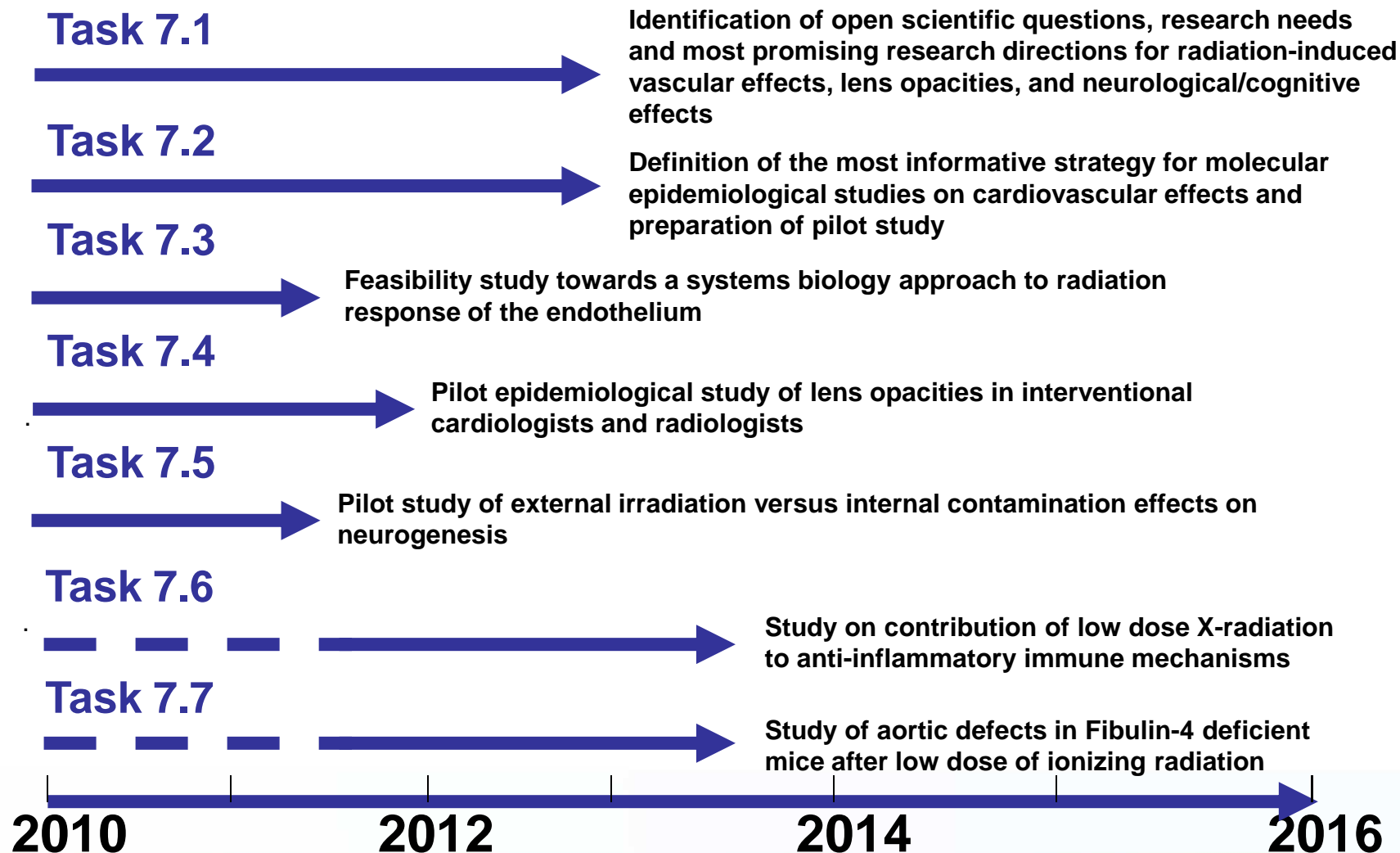


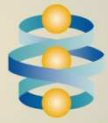
# Non-cancer effects

- Two new projects started in July 2011
  - Contribution of low-dose X-irradiation in anti-inflammatory immune mechanisms
  - Aortic defects in Fibulin-4 deficient mice after low dose of ionizing radiation



## Non cancer effects (WP7)

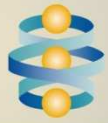




## The need for a Training and Education network to involve the wider EU community

Report of the High Level and Expert Group on European Low Dose Risk Research (see <http://www.hleg.de/fr.pdf>):

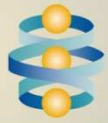
- “Many EU member states have lost key competencies and are no longer capable of independently retaining their current research activities in radiation sciences”.
- “MELODI will respond to these needs and aim at establishing an integrated approach to E&T in radiation research in Europe. Particular consideration will be given to the better integration of research and teaching at Universities and at non-university research organisations”.



# Training and Education

**Andrea Ottolenghi, WP3**

- Provides T+E support for the project
- Provides an education environment for the next generation of researchers
- Can sponsor education initiatives up to 2015
- **Longer term goal of continuing sustainable T+E programme**



## DoReMi-sponsored short course modules

### First series 2011

February 14 – 25, 2011: Human radiation genetics (including in utero and cognitive effects), as well as space health effects. SCK-CEN, Mol, Belgium. Organiser: Sarah Baatout

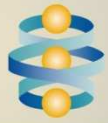
February 28 - March 11, 2011: Molecular radiation carcinogenesis. HMGU, Neuherberg, Germany. Organiser: Mike Atkinson

March 14 - March 25: Radiation epidemiology and radioecology, HMGU, Neuherberg, Germany. Organisers: Mike Atkinson and Klaus Trott

March 28 - April 8: Cellular effects of low doses and low dose-rates with focus on DNA damage and stress response. SU, Stockholm, Sweden. Organiser: Andrzej Wojcik

May 2 - May 13: Interdisciplinary radiation research focussing on radiation protection. BfS, Neuherberg, Germany. Organiser: Ulrike Kulka

May 30 - June 10: Modelling radiation effects from initial physical events, UNIPV, Pavia, Italy. Organiser: Andrea Ottolenghi



## Second series 2012

Radiation-induced effects with particular emphasis on genetics, development, teratology, cognition as well as space-related health issues. SCK-CEN, Mol, Belgium. Organiser: Sarah Baatout

Training course in molecular mechanism of radiation carcinogenesis. HMGU, Neuherberg, Germany. Organiser: Mike Atkinson

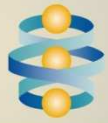
Radiation epidemiology and radioecology.  
HMGU, Neuherberg, Germany. Organisers: Dr. Michael Rosemann

Cellular effects of low doses and low dose-rates with focus on DNA damage and stress response. SU, Stockholm, Sweden. Organiser: Andrzej Wojcik

Interdisciplinary Radiation Research Focussing on Low Doses. BfS, Neuherberg, Germany. Organiser: Prof. Wolfgang Weiss

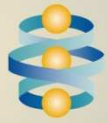
Modelling radiation effects from initial physical events.  
UNIPV, Pavia, Italy. Organiser: Andrea Ottolenghi





## DoReMi/MELODI Training and Education Workshop (Rome, 2<sup>nd</sup> November)

- Introduction to DoReMi T+E objectives
- DoReMi-sponsored courses
- Presentations on related training activities
  - European MSc in radiobiology will come to end 2012 (Trott)
  - National MSc and Doctoral programmes (UK, DE, FR, NO)
  - Other training networks
- Erasmus Mundus
- Networking beyond DoReMi
- A proposal for a T+E forum



## **Initiating the DoReMi/MELODI Training and Education Networking Forum** – linking with universities and training networks

### ***What will it consist of?***

#### *Forum Steering Committee*

- Formed from the existing DoReMi Training and Education Committee
- Plus up to 6 members from other educational/research institutions which are not in the DoReMi Consortium
- Organisation and coordination of the forum.

#### *Annual one-day forum*

- One-day workshop held in conjunction with the annual MELODI International Workshop -> next one in Helsinki 11 September, 2012
- Participation by those providing training in low dose risk (universities, other training networks etc.)



## WP3: Training and education support for the TRA

Formation of an expert advisory Training and Education Committee



Continuing optimisation of targeting and topics for short training modules



Internal calls for training modules of 1-3 weeks at the MSc or PhD level



Review need to support Bologna-accredited MSc course



Depending on outcome of review: Open call for a university to develop Bologna-accredited MSC course, or alternative initiatives.



Develop a mechanism for facilitation of multi-institution training and research collaboration



Transfer T+E funding support from DoReMi to MELODI

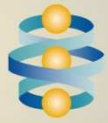


2010

2012

2014

2016

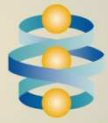


# Infrastructures

**Laure Sabatier, WP4**

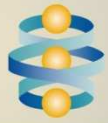
Availability of suitable infrastructures for low dose risk research is specifically addressed by DoReMi.

- Irradiation facilities
- Epidemiological cohorts
- Databases
- Biobanks
- Platforms for analyses



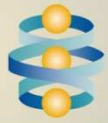
# Infrastructures

- A survey on existing facilities was carried out
- A need for a facility for low dose rate exposure of animals was identified.
  - two new partners possessing low dose rate irradiation facilities, one in Norway and one in Japan, were recruited in the consortium via a competitive call.
- For smaller experiments, a small low dose rate set up in Stockholm could be used.
- Two other needs for irradiation facilities were also identified:
  - a facility for internal contamination
  - facilities for radiation quality such as microbeam facilities and heavy ions facilities



## Infrastructures

- A survey and a subsequent workshop was organised to identify exposed cohorts that will permit future molecular epidemiological studies
- Information on 60 studies on persons exposed to low dose radiations were obtained
  - 26 related to an occupational exposure
  - 10 to an environmental exposure and
  - 24 to a medical exposure
- Only for 16 of them, biosamples had been collected
- Availability and usefulness of biosamples for radiobiological studies to be evaluated later



# Infrastructures

- The next workshop and web survey will consider what infrastructures and platforms for analysis are needed to carry out the research agendas planned for DoReMi/ MELODI
- A process to sustain STORE databases will be studied.
- Access to other national and European infrastructures will be discussed as an alternative to the improvement of individual lab platforms.



## WP4: Infrastructures

### Task 4.1 Survey of existing low dose risk research

Review of existing/planned structures (months 1-12)



### Task 4.2

Report on needs (>months 1-12)



### Task 4.3

Establish Roadmap for infrastructure



### Task 4.4

Toolboxes for infrastructure (IS) access (month 36)



### Task 4.5

Call Agenda and budget for IS access months 24 and 36)



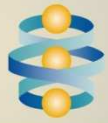
2010

2012

2014

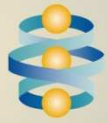
2016





## Added value of integration

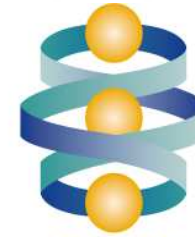
- From isolated studies, single disciplines and fragmented research towards a multidisciplinary joint program addressing key questions
- Strategic Research Agenda guiding joint activities
- Obtaining critical mass
- Integrating scientific disciplines
- Managing infrastructures
- Managing knowledge
- Training next generation of scientists



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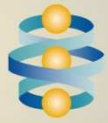


# ***ISS and ENEA***

*Uelio Macellari*

*Giustina Simone*

***Thank you for the wonderful  
programme and venue!***



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Welcome to

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