DoReMi - Low Dose Research towards Multidisciplinary Integration

TRA Statement

Status: Final version, 22 September 2011

Introduction and purpose of this statement

The DoReMi Network of Excellence (www.doremi-noe.net) was formed on January 1st, 2010 based on principles set out in the High Level and Expert Group (HLEG) report (www.hleg.de) as an important step in the establishment of the Multidisciplinary European Low Dose Risk Research Initiative, MELODI (www.melodi-online.eu).

This statement of the DoReMi Management Board updates the DoReMi Transitional Research Agenda prepared in April 2010, submitted July 1st, 2010 to EC and published in September 2010. The purpose of the TRA was to guide the planning, prioritization and facilitation of DoReMi research activities. DoReMi has been running for 18 months and held its first periodic meeting in July 4-6, 2011. Consequently, this statement provides a summary of the progress made within DoReMi and other relevant initiatives, and then uses this information to formulate research priorities for the forthcoming 18 months. It thus serves for the DoReMi Joint Programme of Research (JPR) and also provides guidance for internal and external calls proposed by DoReMi.

Progress to June 2011

The scientific work of DoReMi falls into workpackages (WPs) 5-7 while capacity building is facilitated in WPs 3 and 4. DoReMi ran a successful external call in this period, and as a consequence 10 new partners joined as of 1 July 2011.

In WP5 – Shape of the dose response and tissue sensitivities for cancer - work has been successfully initiated on cancer mechanisms and modelling including dose-rate dependency of cellular senescence, the use of 3D tissue models for exploration of non-targeted effects, key events in radiation-induced myeloid leukaemogenesis and mechanistic modelling of cancer risk. Workshops identified priorities for research on non-targeted and systemic effects (June 2010), and on internal emitter risk research (March 2011). Following the external call, work on gene expression patterns at low doses and inflammatory responses to radiation over a wide range of doses in *in vitro* and *in vivo* models has been added, work on neutron leukaemogenesis has been included by *ad hoc* funding.

EC iniatives such as EpiRadBio (incorporation of biological information into risk models for specific solid cancers), EPI-CT (guidance towards optimisation of doses in paediatric CT scans), SOLO (health risk estimates for internal plutonium and external exposure in exposed populations in Southern Urals), ANDANTE (a multidisciplinary study to refine RBE estimates for neutron carcinogenesis) are all expected to carry out work relevant to WP5..

In WP6 – Individual variability in cancer risk - work has been initiated to identify genetic susceptibility factors for ^{131}I-induced thyroid cancer in the mouse, and to characterize the radiation response of human model cell systems carrying gene variants that have been associated with varying degrees of radiosensitivity. A workshop (November 2010) discussed integration of mechanistic and molecular research into epidemiological studies considering existing and new epidemiological cohorts in Europe and radiation biomarkers, the validation of stored biosamples and estimation of study power. Review articles summarising these activities are being drafted. A workshop held in Stockholm in June 2011 highlighted the potential importance of epigenetics in determining radiation cancer susceptibility. Following the external call new work seeking susceptibility biomarkers by Raman spectroscopy will be incorporated. Furthermore, work on low dose sensitivity to radiation induced brain tumours in the mouse will be initiated.

The projects MULTIBIODOSE and BOOSTER, funded by the EC Security programme will be of relevance for biomarker identification along with aspects of EpiRadBio and EPI-CT.

*In WP7 – Non-cancer effect*s - significant efforts have been made to reach consensus among scientists from diverse disciplines on radiation risk to the vasculature, including definition of research priorities and approaches to improve the risk assessment. To this end an international workshop was held in December 2010. Experimental studies to identify the transcriptional and proteomic responses of vascular endothelial cells to low dose radiation are underway. A pilot epidemiological study of lens opacities among interventional radiologists and cardiologists has been initiated. Preliminary work has also started on the effects of external and internal low dose exposure on neurogenesis in rodents. As a result of the external call, work on dose-responses for anti-inflammatory effects of X-irradiation and their mechanisms, and on the aortic defects in fibulin-4 deficient mice will now be included in WP7.

Relevant research is also underway or planned in EC projects such as SOLO (information on circulatory disease risk) and other projects currently in negotiation with EC, PROCARDIO and CEREBRAD (epidemiological and experimental studies of cardiovascular and cerebrovascular diseases).

In WP3 – Education and training - The specific objectives for the first 18-month period of the project have been to investigate the current training and education needs and the availability of institutions within the EC where training is offered, and to explore possible mechanisms for networking and the sponsorship of courses. A Training and Education Committee (TEC) was set up with membership from DoReMi partners to provide input and help with setting policy and priorities. Course sponsorship was piloted by opening an internal call for 2-week courses to be hosted by partner institutions, on topics of their special expertise. Six courses were funded in the first 6 months of 2011, and they were judged very successful, both in terms of personal gain, and in attracting students and graduate researchers from a wide range of backgrounds. This call will be repeated each year, with the benefit of experience and feedback gained. In order to ensure the Europe-wide involvement in a training and education network the most promising approach appears to be to run the network on a cooperative voluntary basis through an extended TEC that will include interested experts from outside the DoReMi consortium. Plans are underway to operate through the mechanism of regular workshops, possibly held in conjunction with the annual MELODI International Workshop. An exploratory DoReMi/MELODI training and education meeting is planned in conjunction with the 2011 MELODI Workshop in Rome.

In *WP4 – Infrastructures* - surveys of available infrastructures were performed: first, a critical review of existing and planned European epidemiological cohorts and prospects for use in molecular epidemiology studies. The survey was based on detailed questionnaires, and an international workshop held in May 2010. A manuscript reviewing the cohorts and their use for radiation protection research is in preparation. Second, a major survey on irradiation facilities available within the network was obtained via online questionnaires. Low dose/dose rate irradiation facilities were identified as poorly available within DoReMi, except in Sweden. Following the external call, the network secured access to low dose/dose rate irradiation facilities through the new partners in Norway and Japan (ENEA working with IES). Links have been established to the EC project STORE on data- and biobanking, STORE activities are recognised to be of importance for all DoReMi WPs and the long term sustainability/integration of European low dose research.

Cross cutting issues

Three cross cutting issues were identified in the HLEG report and are recognised in DoReMi, these are i) radiation quality ii) tissue sensitivity and iii) internal emitters. Each of these

receives attention in current DoReMi work. The sensitivity of different tissues is addressed through the range of cancer and non cancer disease sites being considered. Internal emitter studies are identified as a task in WP5, and also as a feature in the work of WP7 and in proposed pilot studies in WP6. Radiation quality is addressed in WP5 neutron AML work, risk modelling work and in the context of WP7 work on neurological effects of internal and external irradiation.

A cross cutting epidemiological group has been contributing to DoReMi from the outset. This group assures a coherence regarding epidemiological issues included as parts of WP4, WP5, WP6 and WP7.

Assessment of current outstanding research and capability needs

The brief items below provide a summary of the major issues requiring attention in the short term identified by DoReMi through its workshop activities, research experience and in the course of the 1st periodic meeting.

WP5 – Shape of dose response and tissue specificity for cancer

WP5a Following the internal emitter workshop, it was recognised that estimates of internal emitter risk could be improved by integrated studies that will require further collaboration between a wide range of scientists. The workshop identified population studies of nuclear workers, Chernobyl residents, Techa River residents and uranium miners to be of greatest importance.

WP5b Work to identify robust early biomarkers of radiation-associated disease is required.

WP5c Work to characterise initial radiation events, identify and quantify DNA and other relevant lesions and to explore their consequences would be of value in studies of radiation quality.

WP5d DoReMi is now supporting work on modulation of inflammatory reactions by radiation, additional research on radiation effects over a wide dose range on immunological effects, tumour immunology in particular would be beneficial.

WP6 – Individual variability in cancer risk

WP6a Further work is needed to establish the quality of archived materials from epidemiological cohorts with a view to use in molecular epidemiology before finalising the choice of cohort for the planned pilot integrated molecular epidemiological study.

WP6b Further consideration of the role of epigenetics in determining individual cancer risk is required.

WP6c Prospects for using next generation DNA sequencing for identification of susceptibility genes need to be assessed.

WP6d Work to identify and validate biomarkers of individual cancer risk is required.

WP6e Expertise in mathematical modelling of systems biology is needed for future studies.

WP7 – Non cancer effects

WP7a Following a planned workshop (September 2011) support for integrated dosimetric and epidemiological studies of lens opacity (cataract) risk will be needed alongside experimental work to explore mechanisms and dose-effect relationships.

WP7b Further consideration on the existence of radiation-induced vascular effects at whole body dose below 500 mGy and/or heart dose below 1 Gy is required. The most suitable cohorts to determine whether vascular risk exists at such dose exposure need to be defined, a further workshop is expected.

WP7c Beside experimental work done to better understand the effects of low dose exposure on neurogenesis, an exploratory workshop addressing the neurological and cognitive radiation-induced effects will be organised by DoReMi in 2012.

WP3 – Education and training

WP3a Detailed assessment is needed of the value of a Bologna compliant MSc course in radiobiology in the light of a full review of the availability of such training EU-wide.

WP3b Promotion of the development of further short courses on specific (and when appropriate, specialised) topics as well as on the generalities of low dose radiation risk research would be beneficial.

WP4 – Infrastructures

WP4a The critical review of existing and planned European epidemiological cohorts showed that several cohorts are of great interest for either the quantification of cancer risk (WP5), of individual sensitivity (WP6) and of non cancer risks (WP7) at low doses. The quality of biological material collected and stored for several of these cohorts needs validation.

WP4b Surveys of radiation source availability in the EU beyond the DoReMi partnership are needed in order to include radiation qualities and infrastructures that are still lacking within DoReMi (i.e. GANIL, Caen, France) can provide only 20 -100 MeV/U).

WP4c The benefits and costs of establishing common research platforms for 'omics' technologies versus facilitating access to large European dedicated platforms (i.e. ESFRI) need further consideration following survey and workshop activity.

WP4d Provision of support to critical epidemiological cohorts including those with lifespan follow-up dedicated to public health within which radiation effects could be considered.

Cross cutting issues

All topics highlighted above include consideration of different tissues, radiation qualities and internal emitters.

DoReMi Roadmap to integrate research and capability needs for months 19 – 36 (up to 2013)

The priority research and capability needs listed above require inclusion as part of DoReMi. In parallel to current ongoing work, the table below provides a view of the actions anticipated to integrate these priority areas. Many of the highlighted areas provide scope for consideration of the cross cutting issues of tissue sensitivity, radiation quality and internal emitters.

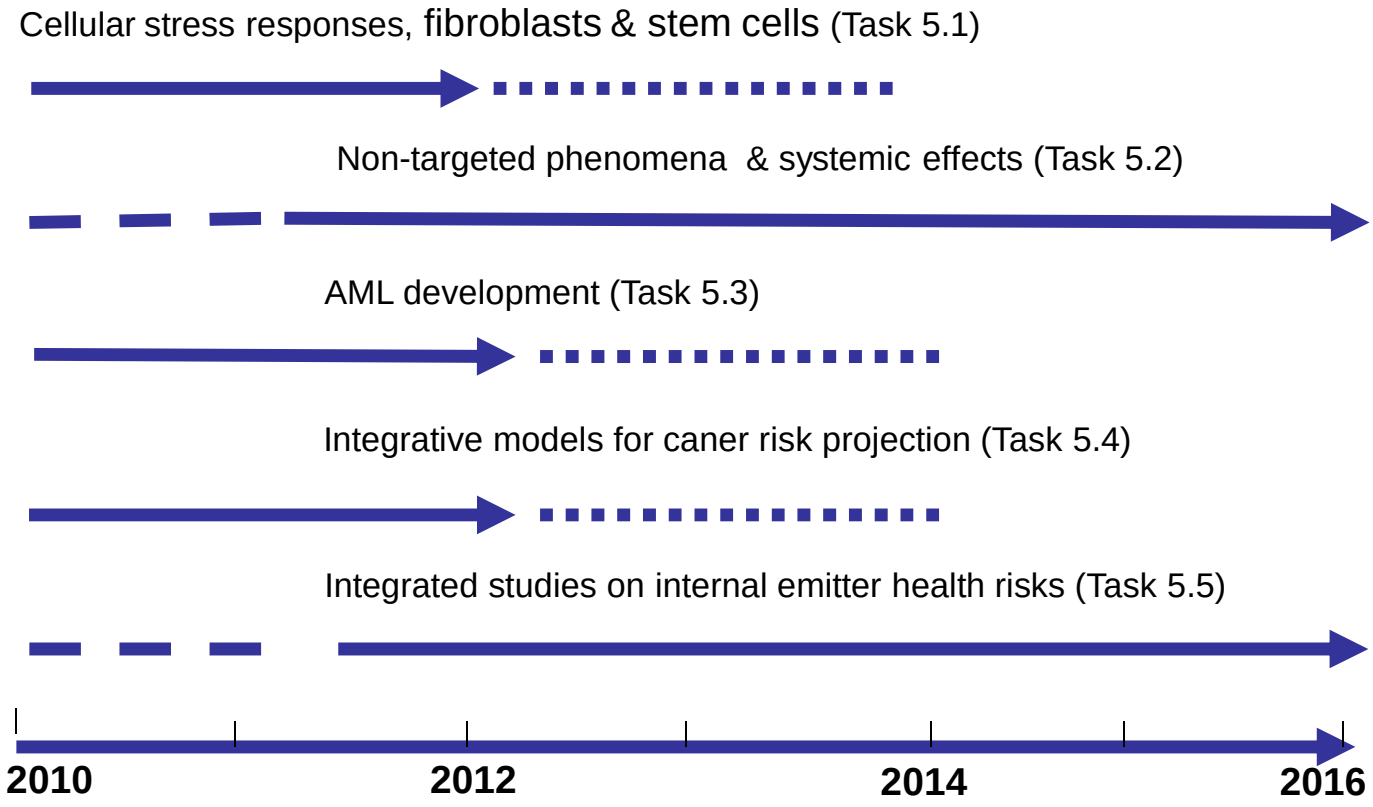
Concluding remarks: The DoReMi statement pinpoints actual priorities for the next 18 months of DoReMi following regular updating of the DoReMi TRA. It is thus an important step in the development of low dose radiation risk research in Europe and the establishment of long-term sustainability by the MELODI consortium.

Appendix: Roadmaps for the WPs 5, 6 and 7 and WPs 3 and 4

The following graphs propose the present roadmap for DoReMi. The scheme will be regularly updated (WP2, DoReMi MB and EAB) according to forthcoming new knowledge and newly developing research lines.

WP5: Shape of Dose-Response Curve for cancer

Mechanistic studies



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 indivual 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

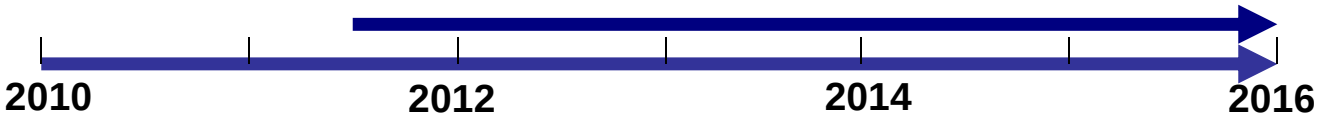
Task 6.3 Modeling individual variability

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

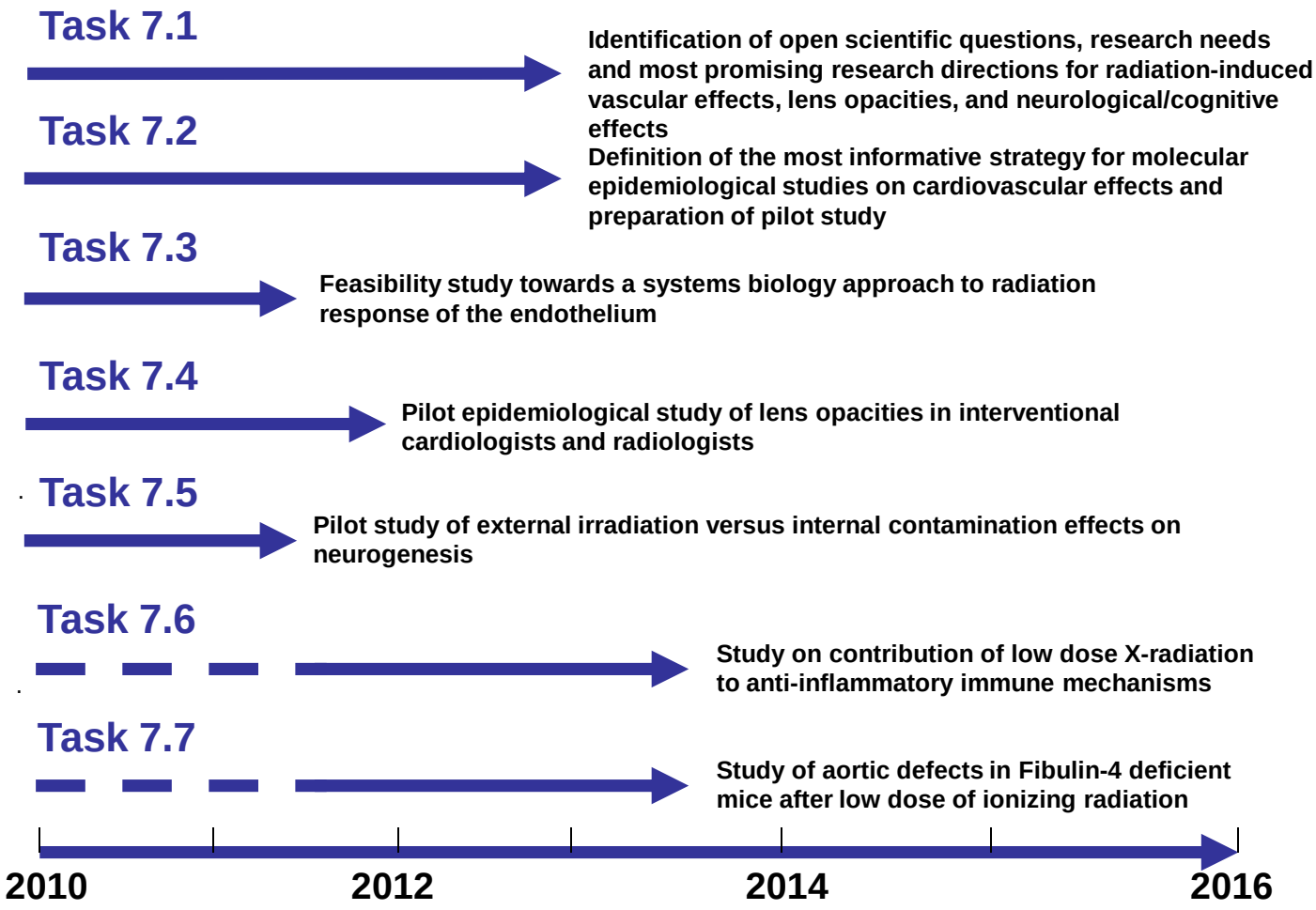
Task 6.5 Contribution of genetic and epigenetic mechanisms that influence susceptibility to radiation induced cancer

Task 6.7 Planning expansion of research portfolio through workshops

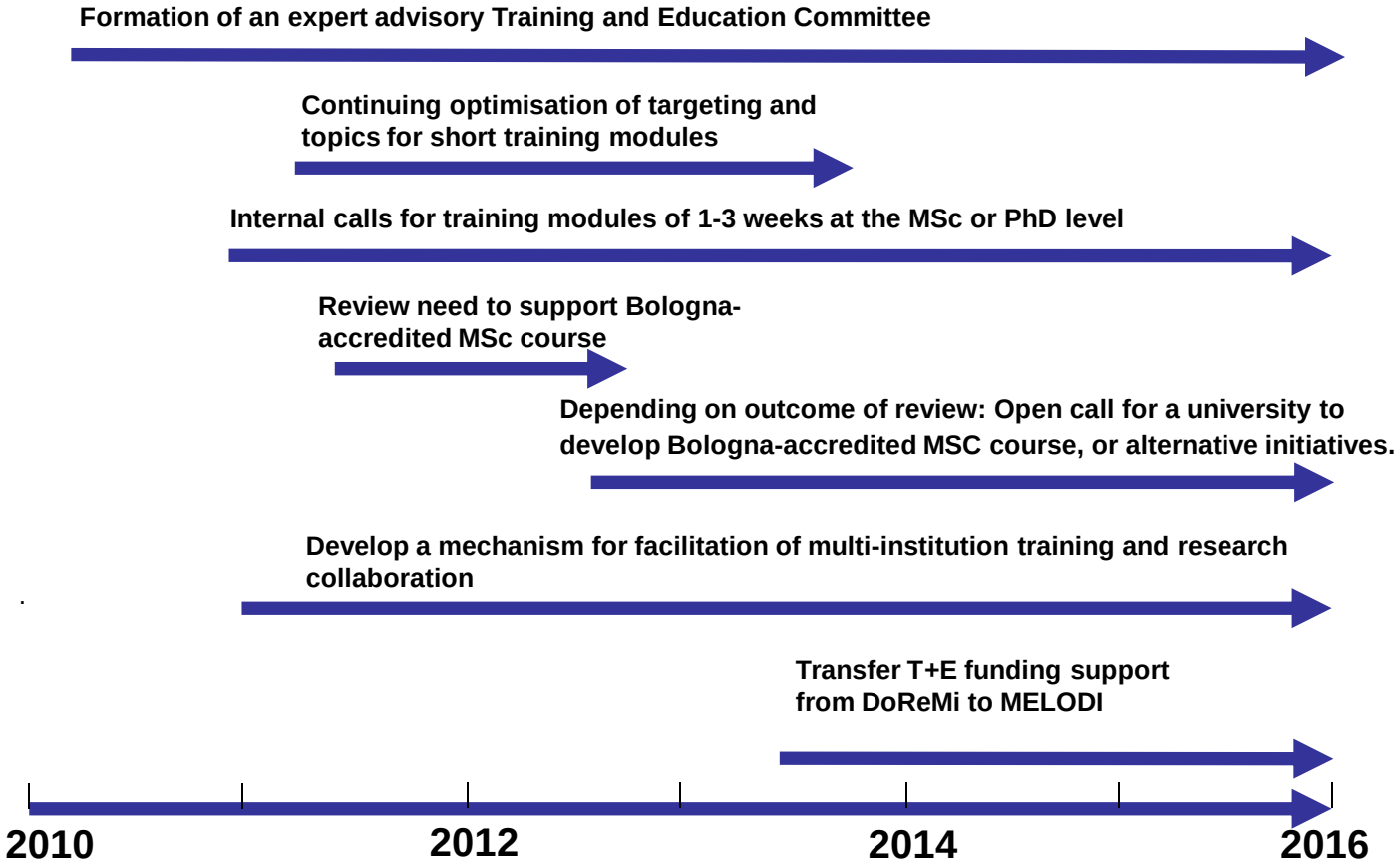
Task 6.8 Prediction individual radiation susceptibility with Raman micro-spectroscopy



WP7: Non cancer effects



WP3: Training and education support for the TRA



WP4: Infrastructures