DNA REPAIR 5 (2006) 986–996

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/dnarepair

Meeting report

DNA repair: From molecular mechanism to human disease

ARTICLE INFO

ABSTRACT

A comprehensive meeting on biological responses to DNA damage organized by Alan Lehmann, Deborah Barnes, Wouter Ferro, Robert Fuchs, Jan Hoeijmakers, Roland Kanaar, Leon Mullenders and Bert van Zeeland, was convened at Noordwijkerhout, The Netherlands, from April 2 to 7, 2006. This article summarizes information presented by speakers at the seven plenary sessions. Poster sessions with organized discussions constituted a fundamental aspect of the meeting—as did a marvelous evening of musical entertainment by a talented group of conferees.

1. European funding for research in DNA repair and the Noordwijkerhout meetings: a historical perspective (by Alan R. Lehmann)

In 1972, Dirk Bootsma of Erasmus University, Rotterdam and Paul Lohman, then at the TNO labs in Rijswijk, The Netherlands, paid a visit to Bryn Bridges and his colleagues at the recently established MRC Cell Mutation Unit at the University of Sussex. Bootsma and Lohman had become aware that the European Community had instigated two new research programs in Radiation Protection and Environmental Protection and funds were available to support collaborative research in these areas between scientists from different member states of the EC. They proposed applying for these funds for a collaborative DNA repair project between Erasmus University, the TNO Laboratories and the MRC Cell Mutation Unit. They further proposed convening a meeting on DNA repair that would bring together European and other scientists working in this area, to be held in a recently converted seminary in Noordwijkerhout, located in the middle of the tulip fields in The Netherlands.

From these small beginnings blossomed continuous EC funding for collaborative DNA repair-related research under a variety of different EC programs, and a series of now internationally renowned meetings, which have taken place approximately every 5 years at Noordwijkerhout, also largely funded under EC programmes. I have been privileged to be involved in these collaborative projects since 1973 and to participate in all the Noordwijkerhout meetings. Both EC funding and the meetings have played a major role in enabling European research in DNA repair to be at the forefront internationally and to remain competitive with that in the USA and elsewhere.

EC funding is available under a variety of different programs, each with its own "funding modality". It requires a certain amount of persistence to wade through the Eurospeak, for example, to learn the difference between "milestones" and "deliverables", in order to complete an application form for EC funding, but a successful application can be a great stimulus to collaborative research between laboratories in different countries. The first European project in DNA repair funded in 1973 was supported by the Euratom radiation protection program and involved just three laboratories. Euratom has funded research in repair and responses to ionizing radiation damage continuously since that time. A currently funded 10 million Euro "integrated project" now involves seven DNA repair labs and a further 20 laboratories investigating epigenetic and carcinogenic effects of radiation.

An EC funding mode termed Concerted Action provided money specifically for exchanges of personnel between laboratories, for small meetings and for larger conferences rather than funding research projects per se. Three such Concerted Actions, between 1990 and 2001, involving between 27 and 40 different participating laboratories, supported numerous exchanges as well as the Noordwijkerhout meetings in 1991, 1996 and 2001. The Human Capital and Mobility Program, subsequently renamed Research Training Networks, is another productive program through which funding is provided to different laboratories for collaborative research, in which the country of origin of the funded Ph.D. students or postdocs (known as early stage researchers or experienced researchers in current Eurospeak!) must be different from that of their host

laboratory. Despite some irritatingly restrictive EC rules, these programs have stimulated young researchers to carry out part of their research training in different countries, thereby broadening their scientific and social outlooks.

The first Noordwijkerhout meeting in 1973 was a relatively small affair with about 70 participants and the facilities at the conference centre were relatively frugal. Each successive meeting has grown in size. For the 2006 meeting, even without wide advertising, there were about 300 participants and a substantial number of applicants had to be declined to keep the meeting at this manageable size and retain its ethos. In order to ensure the involvement of all participants poster sessions have always formed an important part of the proceedings. Unlike many meetings, at which posters are displayed in a crowded room for just one evening, the posters at Noordwijkerhout are displayed throughout the entire meeting. Posters are divided by topic into nine groups and each topic is assigned two chairpersons, who organize poster discussion sessions, in which important issues arising from the posters are debated. The 2006 meeting once again received high acclaim, one participant stating "... a great meeting. Honestly, the best that I have been to in years." The 2006 meeting was largely funded from another EC-funded Integrated Project on DNA Damage and Repair mechanisms within the Life Sciences, Genomics and Biotechnology for Health Program involving 15 participating laboratories, funded at a level of 11.5 million Euro.

2. Opening session

Philip Hanawalt (Stanford University) chaired the opening session, beginning with an expression of appreciation to Dirk Bootsma, a farsighted pioneer in the field of DNA repair, who initiated this remarkable series of meetings more than three decades ago. Phil called attention to Dirk's seminal scientific contributions and his profound impact upon the community of DNA repair, as a mediator of good fellowship and cooperation among researchers.

Steve Jackson (Cambridge University) provided an overview of the cellular responses to double-strand breaks (DSB) and the consequences of defects in those responses. He focused upon detection of DSB and how signaling events are triggered to mediate DSB repair. He concluded with examples of how knowledge of the DNA damage response is contributing to development of drugs selectively toxic to cancer cells.

Steve gave a balanced treatment of the dual aspects of the DNA damage response, which include both the recruitment of DNA repair proteins and the initiation of "checkpoint" events. A question of interest is how damage recognition and binding are prioritized between repair enzymes and checkpoint proteins. He discussed a new core NHEJ protein, XLF, similar to XRCC4, which likely regulates XRCC4-DNA ligase IV. Reference was made to the fact that loss of XLF/Cernunnos causes a new human disease, characterized by radiosensitivity and severe-combined immune-deficiency.

Steve then explained how phosphorylation of histone H2AX yields a protein species termed γ-H2AX, which is required for focus formation by many DNA repair proteins. The phosphorylation of H2AX by ATM, ATR, or DNA-PKcs is essential to link the DNA repair machinery to sites of chromosome breakage. Using γ-H2AX as "bait" a member of Steve's group fished for binding proteins, which revealed MDC1 that binds via its C-terminal BRCT domain. Subsequent work showed that MDC1 is needed for efficient DSB repair, in a possible "tethering role", and that MDC1 is a binding partner of the MRN complex and is recruited by MRN to sites of damage, where it regulates ATM-mediated phosphorylation events.

Jan Hoeijmakers (Erasmus University) reviewed the global genomic repair (GG-NER) and transcription-coupled repair (TC-NER) subpathways of NER, and the accumulating evidence that GG-NER deficiency promotes carcinogenesis, while defective TC-NER does not. Defective TC-NER is associated with excessive apoptosis and accelerated aging phenotypes. He alluded to the multiple phenotypes of XPD mutants and the case of trichothiodystrophy (TTD) in particular, in which the consequent TFIIH instability leads to a temperature-sensitive transcription defect. Mouse models have been important to the elucidation of the complex relationships of GG-NER and/or TC-NER defects to cancer and aging. *Xpd/Ttd* mice, partially defective in both GG-NER and TC-NER, have reduced cancer levels but manifest premature aging, while *Xpd/Xp-Cs* mice are highly cancer-prone with even more pronounced aging phenotypes. The complete deficiency in both GGR and TCR in $Ttd^{-/-}$ $Xpa^{-/-}$ mice further aggravates premature aging; lifespan is reduced to ~3 weeks from ~1.5 years for the *Ttd* single mutant. Similar results were obtained with $Csb^{-/-}$ $Xpa^{-/-}$ crosses, in which enhanced retinal degeneration, indicative of endogenous oxidative damage, was noted. *Ercc1* mice also manifest a particular phenotype of premature aging, in which apoptosis is increased in the liver. The application of microarray analysis revealed down-regulation of the IGF1/GH somatotrophic axis (involved in metabolic control and anti-oxidant responses to endogenous DNA damage), in $Csb^{-/-}$ $Xpa^{-/-}$ double knockout mice. In humans as well as in mice IGF/GH is down-regulated with age. Hoeijmakers suggested a rationale for the down-regulation of GH in adulthood as a "preservative" strategy to reduce metabolism and extend life span. Hoeijmakers concluded that the strong correlations of the severity of the repair defects with the clinical evidence for premature aging provide support for the DNA damage theory of aging.

3. Session 1: nucleotide excision repair and links with transcription

It is widely believed that transcription-coupled repair (TCR) is signaled by blocked transcription elongation due to DNA damage on the transcribed strand of transcriptionally active genes. **Kiyoji Tanaka (Osaka University)** examined blockage and/or bypass of transcription by RNA polymerase II using an in vitro transcription elongation system that includes purified human RNA polymerase II and oligo-dC tailed templates containing a single lesion on the transcribed strand. He reported that cyclobutane pyrimidine dimers (CPD) and (6-4) photoproducts ([6-4]PP) completely block transcription elongation at the DNA damage site, while several types of oxidative DNA damage, including 7,8-dihydro-8-oxo-guanine (8-oxoG), partially blocks transcription elongation. He reported that the transcription factor TFIIS enhances the transcriptional bypass of oxidative DNA damage and that TFIIS-deficient yeast strains are hyper-