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Conference Report

The Gordon Conference on Mammalian DNA Repair
February 1 - 5, 1993
Ventura, California

Chair: James E. Cleaver Co-Chair: Michael J. Smerdon

The Gordon Research Conferences have established a recent series entitled, "Mammalian DNA Repair", held biannually in southern California during the winter season. The fourth in this series was held in Ventura, February 1 - 5, 1993, chaired by James E. Cleaver. This conference series has established itself as a strong, active forum for workers in the mammalian repair field to meet on a recurring basis. The level and quality of this series was established by its first chair, Dr. Bea Singer, followed by Dr. Tony Pegg and then Dr. R. B. Setlow.

Following the established tradition, the recent conference spread over a wide area of current topics that are of importance in mammalian DNA repair. The objective of this series of conferences has not been to exclude bacterial studies as unimportant, but to recognize the maturity and distinctiveness of the mammalian and vertebrate fields and develop programs that can be encompassed within a one week (nine session) meeting in the Gordon conferences format. The recent conference was organized to draw upon specific topics that are of immense current interest in DNA repair. It involved a number of topics including specific new and instructive themes from *E. coli* and yeast that can be used as models for vertebrate mechanism of repair, and recent studies with lower eukaryotes, insects and vertebrates of a wide variety. One session focused on a range of organisms (fish, snakes, flies, worms and plants) that are currently undergoing rapid growth into major research fields in DNA repair. These organisms compliment studies on mammalian DNA repair by illustrating different strategies giving differing relative importance to various repair pathways that various creatures can undertake to handle genetic damage from radiation and chemicals. There were several sessions devoted to the genes involved in mammalian DNA repair including those associated with the human genetic diseases Fanconi anemia, ataxia telangiectasia, xeroderma pigmentosum, and Cockayne syndrome. All of these were presented by individuals who are major participants in research in these areas and have been involved in pioneering work in cloning the genes involved in these disorders and their sequencing and functional analysis.

The conference began with a session devoted to high resolution studies based upon new techniques for producing site-specific photoproducts and chemical lesions that allow highly precise information to be obtained about the relationships between damage, repair, interruption of transcription, and mutation. On the second day, one session highlighted a burgeoning area of DNA repair in which the genes and gene products primarily identified through their repair function have been found to play additional roles in regulating the transcription of other genes. This applies not only to constitutive genes, but to damage-inducible genes such as the *gadd* genes and the DNA

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damage-specific binding proteins. One session was devoted to new work on the genetic and biochemical analysis of double-strand break repair *in vitro* and *in vivo*. The genes involved in these functions were discussed in detail by Drs. Evans and Jeggo. John Thacker described an *in vitro* assay for double-strand break repair which appeared to involve more exonucleolytic degradation of broken ends than occurs inside cell nuclei. Radiation-induced and enzyme-induced DNA double strand breaks appear to be repaired in mammalian cells by a non-homologous event which is quite different from the mechanisms involved in yeast and bacteria. In particular, homologous exchange between chromosomes was found to be vanishingly insignificant compared to non-homologous end-rejoining. One speaker who was planned for this DNA breakage session had to cancel for health reasons at the last moment, and his conference presentation was replaced by three short talks from students or junior investigators who are working in a similar area. This replacement appeared to be very well received, although it is not customary to have multiple short talks in Gordon Conferences.

A major discussion arose in the gene cloning session concerning the number of gene loci involved in single complementation groups in relation to the clinical symptoms seen in DNA repair deficient diseases. Dr. Steven Lloyd presented evidence for two distinct genes in xeroderma pigmentosum group A, identified on chromosome 8 and 9. Chromosome 9 contains mutations in all known XP Group A patients, but there may be secondary regulatory functions from the chromosome 8 gene. Evidence for correcting factors for XP Group C was presented involving chromosomes 3 and 5, although one might be a possible artifact from chromosome translocation. This discussion of gene numbers was followed by a talk from the floor by Dr. Clark Lambert who highlighted the mathematical analysis underlying gene frequencies in complex diseases in order to provide a theoretical framework for understanding the complexities of these disorders. A novel enzyme activity involved in DNA repair which may be associated with transcription effects, the intra-dimer phosphodiesterase was presented by Dr. Mac Paterson which also aroused considerable controversy.

A major session was devoted to new techniques of gene targeting in transgenic animals. This was an opportunity for many investigators to present recent work that is incomplete but which revealed some of the technical difficulties and long-term view required in these experiments. Anticipated results in these experiments where specific genes were to be inactivated by insertions and point mutations in known repair genes were related to the complex human repair disorders that we hope will become better understood. An elegant study by Dr. Tsuzuki from Japan demonstrated both positive and negative mechanisms of genetic alteration for the 0^6 alkylguanine transferase repair gene.

As a banquet speaker on the last evening, Dr. Deneb Karentz gave a survey of DNA repair and field work carried out by her with NSF and DOE support on the ultraviolet exposure and DNA damage associated with the Antarctic ozone hole. This was particularly well received and highlighted the importance and difficulties of ecological work that can be carried out on various species.

The final morning highlighted a wide variety of different DNA repair strategies carried out in eukaryotes that included the plant, *Arabidopsis thalian;* the fly, *Drosophila melanogaster;* the worm, C. *elegans;* and fish, *Xiphophorus;* together with a series of venomous and non-venomous snakes. These vertebrate and non-vertebrate organisms were particularly interesting and ended the conference on a high note, illustrating important new research directions on other organisms that can be used to highlight general problems in DNA repair. These will be of enormous interest in the near future in understanding mechanisms of genetic stability and DNA repair.

There was very active participation by the conference attendees, as is the hope for these kinds of conferences. From the 100 participants, approximately 60 posters were put up in two groups through the week and in this setting a number of remarkable novel discoveries were apparent. In particular, there were several new cloning studies on ataxia telangiectasia and the unexpected cloning of the xeroderma pigmentosum group G gene by Dr. Carlson from Geneva. This gene was cloned almost by accident during his studies of antibodies to DNA damage in lupus erythematosis patients.

The conference appeared to proceed satisfactorily, except for the usual situation of a few speakers talking longer than scheduled. Some attendees would have changed the scheduled order of subjects, and included different topics; but each Gordon conference has a definite character set by the chair.

This particular conference was well supported by Gordon Conference funds, with supplementary support from DOE, NSF, NCI, March of Dimes and Stratagene. Of the 100 attendees, approximately 25 were graduate or postdoctoral students and 23 were from outside the U.S.