

**P056** Unified mechanisms for DNA repair from assembled enzyme DNA structures characterized by integrated X-ray solution scattering and crystallography

**John A. Tainer**

*Lawrence Berkeley National Lab, Skaggs Institute for Chemical Biology, & The Scripps Research Institute*

The Base Excision Repair (BER) pathway is initiated by damage-specific DNA glycosylases, which excise the lesion base, followed by damage-general repair steps, including strand cleavage, synthesis, and ligation. To understand substrate recognition and the catalytic mechanism for the initial steps of oxidized based repair by pyrimidine N-glycosylase/AP-lyase, we determined structures of an *Archaeoglobus fulgidus* (Af) Nth complex with DNA containing 5-hydroxy-5-methylbarbituric acid and thymine glycol as base moieties, respectively. Furthermore we determined comparable structures of the Af OGG, the N-glycosylase/AP\_lyase that repairs the major mutagenic lesion 7,8-dihydro-8-oxo-guanine (8-oxoG). Based on our results, we propose a universal mechanism for damaged base removal and subsequent phosphodiester backbone cleavage that may be general to bifunctional DNA N-glycosylase/AP-lyase enzymes that catalyze  $\beta$ -elimination. BER is completed by the coordinated activities of the structure-specific repair and replication nuclease Flap EndoNuclease (FEN-1), the trimeric processivity factor termed the Proliferating Cell Nuclear Antigen PCNA, and DNA ligase. Structural characterizations of FEN-1-PCNA, PCNA-DNA, and ligase-PCNA complexes suggest a unified model for DNA-substrate recognition and control of DNA ends in the completion of BER.