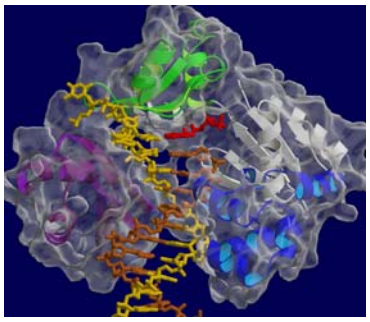
Biography

Dr. Kunkel is the Director of the Environmental Biology Program, Chief of the Laboratory of Structural Biology, and Leader of the DNA Replication Fidelity Group at the National Institute of Environmental Health Sciences, located in Research Triangle Park, North Carolina. In 26 years at NIEHS Dr. Kunkel has published nearly 300 peer-reviewed articles. His research is focused on the mechanisms by which cells ensure faithful duplication of the genome and the consequences to human health when these mechanisms are impaired or challenged by environmental factors. Dr. Kunkel has made extensive contributions to our understanding of the three major processes involved in DNA replication fidelity: nucleotide selectivity by DNA polymerases, exonucleolytic proofreading, and DNA mismatch repair. He is recognized as one of the world's leading experts on DNA polymerase structure, function, and mechanism. He has also made broad contributions to the field of molecular biology by developing some of the early methods for efficient generation of site-directed mutations.

Meet One of the World's Smallest Typewriters



The X Ray Crystal Structure of a DNA Polymerase Forming an A-T Base Pair

Lectures

Monday, September 15, 4:00pm

Deans Auditorium (PFEN)

"DNA Replication Fidelity"

When describing the structure of the DNA double helix, Watson and Crick wrote, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." Fifty years later, interest in the fidelity of these DNA copying mechanisms remains high because the balance between correct and incorrect DNA synthesis is relevant to a great deal of biology. High fidelity DNA synthesis is beneficial for maintaining genetic information over many generations and for avoiding mutations that can initiate and promote human diseases such as cancer and neurodegenerative diseases. Low fidelity DNA synthesis is beneficial for the evolution of species, for generating diversity leading to increased survival of viruses and microbes when subjected to changing environments, and for the development of a normal immune system. What was not yet appreciated fifty years ago was the large number and amazing diversity of transactions involving DNA synthesis that are required to faithfully replicate genomes and to stably maintain them in the face of constant challenges from cellular metabolism and the external environment. To perform these tasks, cells harbor multiple DNA polymerases, many of which have only been discovered in the past nine years and whose cellular functions are not fully understood. This polymerase diversity and the sequence complexity of genomes provide the potential to vary DNA synthesis error rates over a much wider range than was appreciated only a few years ago. This seminar will consider some of the major concepts and recent progress on DNA replication fidelity.

Tuesday, September 16, 4:00pm

Deans Auditorium (PFEN)

"Division of Labor at a Eukaryotic Replication Fork"

The two strands of the DNA double helix are oriented antiparalle to each other, yet DNA polymerases copy DNA in only one direction. Therefore, replication of duplex DNA is an intrinsically asymmetric process. Efficient and accurate replication of the nuclear genome in eukaryotes requires two DNA polymerases, delta and epsilon. However, the division of labor between these enzymes in replicating the leading and lagging strand templates has remained unclear for more than 20 years. To investigate this, we generated variants of *S. cerevisiae* DNA polymerases delta and epsilon with a substitution for a conserved amino acid located at the polymerase active site. We then examined the error specificity of these DNA polymerases *in vitro* and the patterns of spontaneous replicational mutagenesis observed *in vivo* when a mutational reporter gene was placed in two orientations adjacent to well characterized origins of replication. The results lead us to infer that the leading strand is primarily replicated by DNA polymerase epsilon, and that the lagging strand is primarily replicated by DNA polymerase delta. The approach used in these studies can be extended to see if this division of labor applies under other circumstances, e.g., at other locations in the genome or after replication fork stalling resulting from DNA damage.