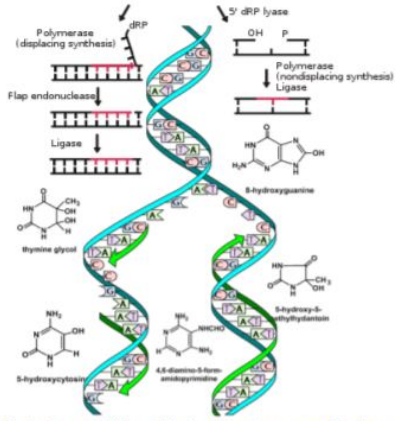
Genetic and Environmental Toxicology Association of Northern California (GETA) 2018 Spring Symposium

Monday, April 23rd, 1-5 PM

California EPA Building, Room 550
1001 I Street, Sacramento, CA 95812

DNA: Damage, Repair and Replication



Replication and APE1 graphics from https://commons.wikipedia.org

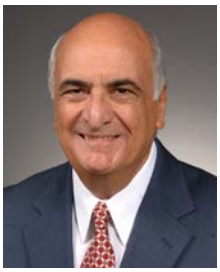
http://getanorcal.org/

12:00 - 1:00	Registration
1:00 - 1:15	Welcome
1:15 - 2:00	**Oxidative DNA damage: Mechanisms, measurement and biological consequences,** Dr. Miral Dizdaroglu, National Institute of Standards and Technology
2:00 – 2:45	**SOG1 (Suppressor of gamma response 1) links DNA damage detection and organ regeneration in plants,** Dr. Anne Britt, University of California, Davis
2:45 – 3:45	Coffee Break and Poster Session
3:45 – 4:30	**Packing, folding and simplifying DNA topology,** Dr. Mariel Vazquez, University of California, Davis
4:30 – 5:00	Wrap-up

Oral Presentation Abstracts

Oxidative DNA damage: Mechanisms, measurement and biological consequences

Dr. Miral Dizdaroglu
National Institute of Standards and Technology, Gaithersburg, MD



Biography

Dr. Dizdaroglu obtained his doctorate at the Technical University of Karlsruhe (now *Karlsruhe Institute of Technology*), Germany, and subsequently worked for 7 years at the Max-Planck-Institute for Radiation Chemistry in Mülheim a.d. Ruhr, Germany before moving to the US. He has been at the National Institute of Standards and Technology (NIST) for more 30 years. In 2006, Dr. Dizdaroglu was conferred upon the rank of NIST Fellow. To date, he has published 250 highly-cited, peer-reviewed papers. Dr. Dizdaroglu received numerous scientific awards including the Hillebrand Prize of the American Chemical Society, the Silver and Gold Medal Awards of the US Department of Commerce and the Samuel Wesley Stratton Award of NIST. He also received two Honorary Doctorates from the Nicolaus Copernicus University in Poland, and from the Dokuz Eylul University in Turkey.

Abstract

Oxidative DNA damage is caused in living organisms by endogenous and exogenous reactive species including free radicals and other DNA-damaging agents. DNA lesions resulting from this type of damage are mutagenic and/or cytotoxic and, if not repaired, can cause genetic instability that may lead to disease processes including carcinogenesis. Living organisms possess DNA repair mechanisms that include a variety of pathways to repair multiple DNA lesions. Mutations and polymorphisms also occur in DNA repair genes adversely affecting DNA repair systems. Cancer tissues develop greater DNA repair capacity than normal tissues, leading to therapy resistance. Thus, DNA repair proteins constitute targets for inhibitors to increase the effect of therapy. Numerous inhibitors have been developed and are being tested in clinical trials. Recent work discovered potent inhibitors of DNA glycosylases, which are involved in the first step of the base excision repair pathways. Environmental toxins also cause oxidative DNA damage in various ecosystems, endangering public health. Increasing levels of thus-formed DNA lesions have been observed in aquatic animals in polluted areas. Such DNA lesions may serve as biomarkers for identifying contaminant-induced DNA damage in animals from polluted and reference sites and, in addition, for monitoring the progress and potential success of remedial

actions in reducing observed toxic effects. This talk will present and discuss the mechanistic aspects of oxidative DNA damage, the measurement of DNA lesions and their repair, inhibition of DNA repair proteins and DNA damage by environmental toxins.

SOG1 (Suppressor of gamma response 1) links DNA damage detection and organ regeneration in plants

Dr. Anne Britt
Department of Plant Biology, University of California, Davis

Biography

Dr. Britt decided to become a biologist when she was 8, and decided to work on inheritance when at age 11- probably because of a picture of the structure of DNA that was published in "Life" magazine. In high school, she and her roommate decided to figure out how DNA replication occurred – why would the two halves of the molecule separate at all? They were disappointed to find that this occurred through the action of little black boxes called enzymes, which, at the time, seemed like cheating, not a real explanation. In college, Britt worked in Graham Walker's lab at MIT, choosing a project designed to determine whether mutagenesis was something that happened accidentally, or instead, perhaps, something the cell chose to do after experiencing DNA damage. She found that *umuC*, a gene *required* for UV-induced mutagenesis, was induced only after UV irradiation. After grad school at UC Berkeley, Britt worked on transposable elements in maize (maize genetics are both fun and elegant) and then returned to DNA damage response, repair, and mutagenesis in Arabidopsis in her own laboratory at UCD. Her laboratory currently focuses on genetic engineering (targeted mutagenesis and gene replacement), chromosome segregation, and DNA damage response, including programmed cell death, in Arabidopsis (a model plant) and several crop plants.

Abstract

DNA damage can trigger a programmed cell death (PCD) response, activating a cellular pathway for cellular suicide. In animals this is an important mechanism for the self-identification and self-destruction of potentially cancerous cells. In plants however, the formation of tumors is rarely-perhaps never-a threat to the viability of the organism, as plant development is inherently flexible, and tumors cannot metastasize (the cell wall prevents this, and plant cells are not

motile). However, DNA damage-induced PCD does occur in plants, but only in the handful of cells that form the stem cell niche required for the growth of the root and shoot tips. The significance of this cell-type specific programmed cell death has been unclear. We have found that it is the programmed destruction of the compromised stem cell niche that triggers its regeneration, enabling growth recovery. We propose the DNA damage-induced PCD is employed by plants as a developmental response in which plants ablate viable but mitotically incompetent stem cell niches, rebuilding them through transdifferentiation of surrounding cells. This role for PCD, which is limited to flowering plants, may have evolved to restore the growth of embryos after the accumulation of DNA damage during desiccation and rehydration of seeds.

Packing, folding and simplifying DNA topology

Dr. Mariel Vazquez
University of California, Davis

Biography

Mariel Vazquez is Professor of Mathematics, and of Microbiology & Molecular Genetics at UC Davis. She is a mathematical biologist whose research focuses on the applications of topological and discrete methods to the study of DNA. Her emphases include DNA packing on the topological changes affected on DNA by enzymes and the study of chromosomal rearrangements. Her contributions are characterized by the use of tools from pure mathematics (knot theory, low-dimensional topology, graph theory) to the study of important biological questions. Mariel obtained her PhD in Mathematics in 2005 from Florida State University. In 2018 she was selected to the inaugural class of fellows of the Association for Women in Mathematics. She is the recipient of the 2016 Blackwell-Tapia Prize, a 2014 CAMPOS scholarship at UC Davis, the 2014 Mohammed Dahleh Distinguished Lectureship at UC Santa Barbara, a 2012 U.S. Presidential Early Career Award for Scientists and Engineers (PECASE), and a 2011 NSF CAREER Award.

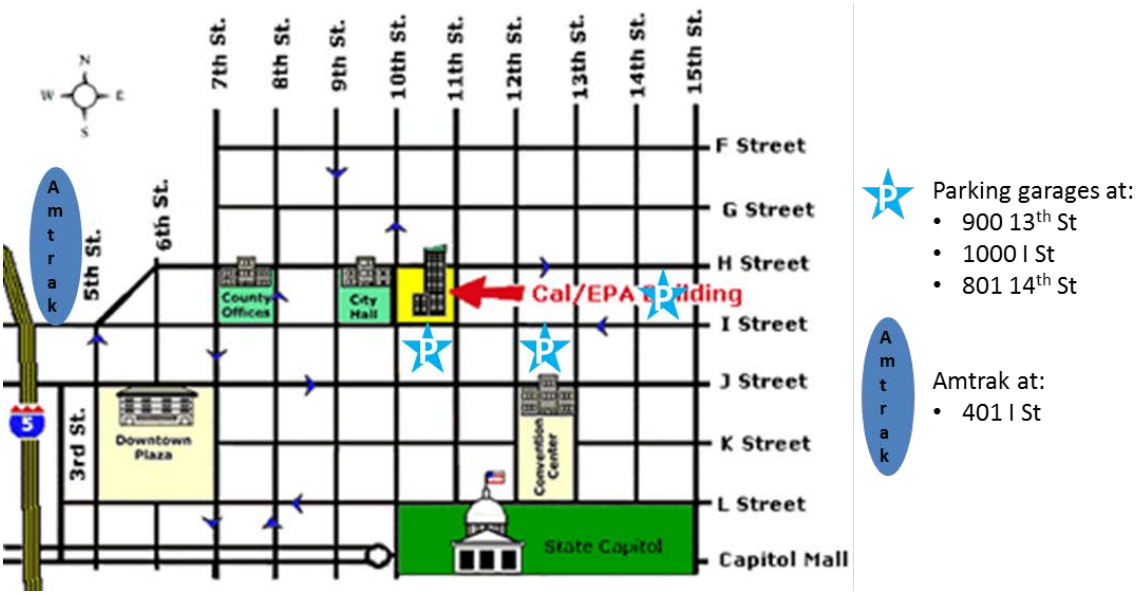
Abstract

Cellular processes such as DNA replication, recombination, and packing change the topology of DNA. Controlling these changes is key to preventing chromosomal instability. We use

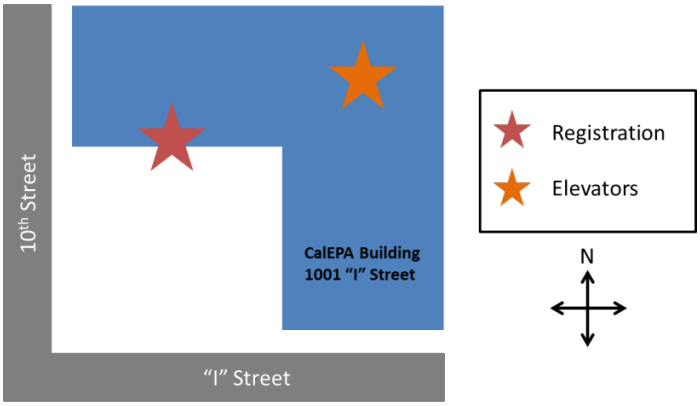
mathematical and computational methods to study these processes with a focus on DNA topology simplification mediated by enzymes such as recombinases and topoisomerases.
In *Escherichia coli* DNA replication yields two interlinked circular chromosomes. Returning the chromosomes to an unlinked monomeric state is essential to cell survival. This process is typically mediated by topo IV, a type II topoisomerase. In the absence of topo IV, site-specific recombinases XerC/D co-localize with translocase FtsK in the replication termination region to remove replication links. We investigate minimal pathways of unlinking replication links by local recombination when we relax the complexity assumption. We first determine analytically the number of minimal reconnection pathways for unlinking the 6-cat if we assume no increase in complexity at every step. Then we eliminate the assumption and embark on a numerical exploration of unlinking pathways. We introduce a Monte Carlo method to simulate local reconnection, provide a quantitative measure to distinguish among pathways and identify a most probable pathway. These results point to a universal property relevant to any local reconnection event between two sites along one or two circles.

Building Logistics

The CalEPA building is located at 1001 "I" Street, Sacramento, CA 95814. The entrance is at 10th and I streets. For more information, go to: https://calepa.ca.gov/headquarters-sacramento/location/



Register/check-in and obtain a badge from security in the main lobby of the building.



Board members/volunteers will escort conference attendees to Room 550 (5th floor) via East bank of elevators.