THE UNIVERSITY OF TOLEDO
1872

Department of Chemistry

Colloquium Speaker

Organic Syntheses

Lecturer

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The University of Utah, UT

"Organic Synthesis Informs Epigenetics"

Less than 2% of the human genome codes for the amino acid sequence of proteins. Why is all the rest of the DNA there? Some of it participates in orchestrating replication, some in the protection of the ends (telomeres), and some sections upstream of transcription start sites (promoters) control whether or not a gene is expressed as protein. Epigenetics involves the study of chemical modifications to DNA that affect gene expression. Many of the aforementioned functions of DNA include guanine-rich sequences capable of folding into G-quadruplexes, four-stranded folds of DNA that differ dramatically from the classical base-pairing scheme of the Watson-Crick double helix. Furthermore, the G-rich sequences are sensitive to oxidative stress, converting to modified structures including 8-oxo-7,8-dihydroguanine (OG) and the hyperoxidized lesions spiroiminodihydantoin (Sp) and guanidinohydantoin (Gh). We propose that G-rich sequences respond to oxidative stress by selecting a secondary structure that can best accommodate the damaged base, and that 'shape-shifting' may be used as a signaling mechanism to affect transcription and repair. We test this hypothesis by synthesizing chemically modified heterocycles and incorporating them into DNA that can be studied either in vitro or in cellulo. The implications are that nucleotide identity beyond the exome may be important in gene expression and disease, and that the definition of epigenetic modifications should be expanded to include guanine oxidation.

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