Invited Lecture

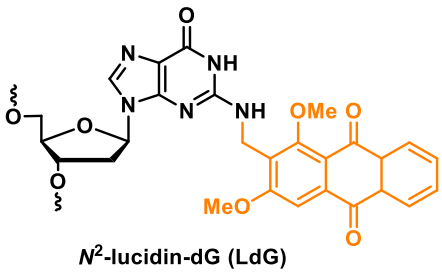
Inter-Disciplinary Explorations in Chemistry (I-DEC 2018)

Translesion synthesis across the lucidin- induced DNA damage

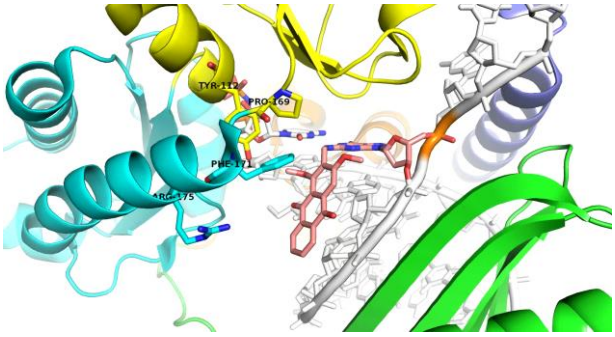
Pradeepkumar P.I.*
Department of Chemistry
Indian Institute of Technology Bombay
pradeep@chem.iitb.ac.in

Abstract:
Translesion DNA Synthesis (TLS), involves the tolerance of DNA damages with the help of TLS polymerases. To understand the structural and functional requirements of TLS polymerases, we have utilized a chemical biology approach. In this direction, we have developed a robust protocol to synthesize the N^2-lucidin-dG (LdG) damaged DNAs. Lucidin, a coloring agent, is a metabolite of a Lucidin-3-*O*-primeveroside, which is present in the roots of *Rubia tinctorum L*. (madder root). Lucidin reacts with N^2-amino group of dG and forms adducts. Lucidin is mutagenic and carcinogenic in rodents but has low carcinogenic risks in humans.

Primer extension studies revealed that TLS polymerases such as Pol IV (*E. Coli*) and polκ (human) are able to bypass this adduct in an error free manner with high efficiency. Crystal structures of these damaged DNAs in complex with Pol IV/pol polκ and incoming dCTP reveal the formation of a hydrophobic pocket in the active site of the enzymes to accommodate LdG and thereby facilitating TLS. Overall, our studies provide mechanistic insights into the low carcinogenicity of lucidin in humans.



N^2-lucidin-dG (LdG)



Active site of pol polκ with LdG

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Bio-Sketch of Speaker

Dr. Pradeepkumar P.I.
Professor

Department of Chemistry
Indian Institute of Technology Bombay
Powai, Mumbai-400076
+91-9969657267
pradeep@chem.iitb.ac.in

Pradeepkumar received his Ph.D in Bioorganic Chemistry in 2004 from the Uppsala University, Sweden. Subsequently, he spent 3 years at the University of Illinois at Urbana Champaign, USA as a post-doctoral fellow. In 2007, he joined the Department of Chemistry, IIT Bombay, where he is currently a Professor. He was also a Max Planck India Fellow at the Max Planck Institute of Biophysical Chemistry, Göttingen, Germany from 2008-2012. His laboratory is interested in various aspects of the chemical biology of nucleic acids: therapeutic siRNAs, G-quadruplex nucleic acids, damaged DNAs and DNA catalysis.