BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Tse-Dinh, Yuk-Ching	Professor of Chemistry and Biochemistry Director, Biomolecular Sciences Institute
eRA COMMONS USER NAME yuk-ching	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Hollins University, Virginia	B.A.	1977	Chemistry
Harvard University, Massachusetts	Ph.D.	1982	Biological chemistry

A. Personal Statement

I began my research on topoisomerases as a graduate student at Harvard University under James C. Wang who discovered *E. coli* topoisomerase I as the first example of DNA topoisomerase enzymes. The ubiquitous topoisomerase enzymes are not only essential for life processes, but are also important targets for antibacterial and anticancer therapy. I determined the chemical identity of the covalent 5'-phosphotyrosine linkage between cleaved DNA and bacterial topoisomerase I and gyrase described in a 1980 JBC Classic publication. As a PI at DuPont Central Research & Development, I continued with basic studies on the mechanism and regulation of *E. coli* topoisomerase. I demonstrated that transcription of the *E. coli topA* gene is enhanced by negative supercoiling of the DNA template as part of the homeostatic regulation of global supercoiling. At New York Medical College, I continue to make highly significant discoveries on all aspects of bacterial topoisomerase I, often by collaborating with other researchers. I showed that at least three different *E. coli* sigma factors direct the transcription of *topA* gene and topoisomerase I function is important for adaptation to stress challenge and survival. By isolating and using bacterial topoisomerase I mutants deficient in DNA religation as model system, I demonstrated the bactericidal consequence of accumulation of topoisomerase I covalent intermediate to provide support for bacterial topoisomerase I as a target for discovery of new antibiotics. I developed enzyme and cell based HTS assays for identification of bacterial topoisomerase I inhibitors. Working with Dr. Zhongtao Zhang, an X-ray crystallographist at New York Medical College, we successfully determined the critical topoisomerase I cleavage complex structure that is to be stabilized by inhibitors of religation. I brought this research program to FIU where I am utilizing interdisciplinary collaborations to make an impact for antibacterial drug discovery for treatment of drug resistant pathogens, including MDR and XDR TB. This drug discovery effort is built from the foundation of the basic research I have carried out on topoisomerases for over 32 years, and continues to be complemented by the ongoing investigation of the structure, mechanism and regulation of topoisomerases and DNA topology. As Director of the Biomolecular Sciences Institute at FIU, I am engaged in multiple collaborations with other FIU faculty to gain synergism in our research efforts. To access the complementary medicinal chemistry resources, I have established new partnerships with the Sanford Burnham Medical Research Institute and Torrey Pines Institute for Molecular Studies in Florida.

B. Positions

Positions and Employment

1982-1988 Principal Investigator, Molecular Biology, Central Research & Development, E. I. duPont.
1988-1990 Assistant Professor, Department of Biochemistry & Mol Biology, New York Medical College
1990-1994 Associate Professor, New York Medical College
1994-2012 Professor, Department of Biochemistry & Mol Biology, New York Medical College.
2007-2012 Ph.D. Program Director, Department of Biochemistry & Molecular Biology, New York Medical College
2012-present Professor, Department of Chemistry & Biochemistry, Florida International University
2012-present Founding Director, Biomolecular Sciences Institute

Other Experience and Professional Memberships

1991-1995 NIH Reviewer, regular member of NIH Physiological Chemistry Study Section (PC).
1995-1999 NIH Reviewers Reserve
1999-present Member, American Society of Microbiology
2001-present Managing Editor, Frontiers in Bioscience
2002 Temporary reviewer, NIH Microbial Physiology and Genetics-2 Study Section (MBC-2)
2003-present Member, American Society for Biochemistry and Molecular Biology
2003-2008 Editorial Board, Journal of Biological Chemistry
2004 NIH Reviewer, Special Review Section (April), Regular member for MBC-2 (June)
2004-2006 NIH Reviewer, regular member for Prokaryotic Cell and Molecular Biology Study Section (PCMB)
2008 NIH Reviewer, Cooperative Research Partnerships for Biodefense and Emerging Infectious Diseases (September)
2009 NIH Reviewer, Special Emphasis Review Panel (February)
Challenge grant reviewer (June)
2010 NIH Reviewer, Chair of Special Emphasis Review Panel (March)
2010 Grant Reviewer for Wellcome Trust (November)
2011 NIH Reviewer, HTS panel (November)
2012 NIH Reviewer, HTS panel (June), Biodefense (September)
2013 NIH Reviewer, U19 for NIAID CETR (July)
2013 Grant Reviewer for National Science Centre, Poland (September)
2014 Grant Reviewer for French National Research Agency (May)
2014 NIH Reviewer, Special Emphasis Review Panel (October)

C. Selected peer-reviewed publications (From 94 peer-reviewed publications)

1. Cheng B, Sorokin E, Tse-Dinh YC 2008. Mutation adjacent to the active site tyrosine can enhance DNA cleavage and cell killing by the TOPRIM Gly to Ser mutant of bacterial topoisomerase I. Nucleic Acids Res. 36,1017-25. PMC2241903
2. Sorokin, E, Cheng B, Rathi S, Aedo S, Abrenica MV, Tse-Dinh YC 2008. Inhibition of Mg^{2+} binding and DNA religation by bacterial topoisomerase I via introduction of additional positive charge into the active site region. Nucl Acids Res 36, 4788-96. PMC2504298
3. Cheng B, Annamalai T, Sorokin E, Abrenica M, Aedo S, Tse-Dinh YC 2009. Asp to Asn substitution at the first position of the DxD TOPRIM motif of recombinant bacterial topoisomerase I is extremely lethal to *E. coli.* J Mol Biol 385, 558-67. PMC2905861
4. Tse-Dinh YC 2009. Bacterial topoisomerase I as a target for discovery of antibacterial compounds. Invited peer reviewed Survey and Summary for Nucl Acids Res 37, 731-737. PMC2647297
5. Sutherland JH, Tse-Dinh YC 2010. Analysis of RuvABC and RecG involvement in the *Escherichia coli* response to the covalent topoisomerase-DNA complex. J Bacteriol 192, 4445-51. PMC2937393
6. Zhang Z, Cheng B, Tse-Dinh YC 2011. Crystal structure of a covalent intermediate in DNA cleavage and rejoining by *Escherichia coli* DNA topoisomerase I. Proc Natl Acad Sci USA 108, 6939-6944. PMC3084087
7. Narula G, Annamalai T, Aedo S, Cheng B, Sorokin E, Wong A, Tse-Dinh YC 2011. The strictly conserved Arg-321 residue in the active site of *Escherichia coli* topoisomerase I plays a critical role in DNA rejoining. J Biol Chem 286, 18673-18682. PMC3099684
8. Liu IF, Sutherland JH, Cheng B, Tse-Dinh YC 2011. Topoisomerase I function during *Escherichia coli* response to antibiotics and stress enhances cell killing from stabilization of its cleavage complex. J Antimicrob Chemother. 66, 1518-1524. PMC3112028
9. Narula G, Tse-Dinh YC 2012. Residues of E. coli topoisomerase I conserved for interaction with a specific cytosine base to facilitate DNA cleavage. Nucl Acids Res, 40, 9233-9243. PMC3467081
10. Aedo S, Tse-Dinh YC. Isolation and quantitation of topoisomerase complexes accumulated on E. coli chromosomal DNA. Antimicrob Agents Chemother 2012, Nov; 56(11):5458-64. PMC3486612
11. Bansal S, Singh M, Sinha D, Cheng B, Tse-Dinh YC, Tandon V. 3, 4 dimethoxyphenyl bis-benzimidazole, a novel DNA Topoisomerase Inhibitor that Preferentially Targets *E. coli* Topoisomerase I. J Antimicrob Chemother 2012 Dec; 67(12):2882-91
12. Cheng B, Cao S, Vasquez V, Annamalai T, Tamayo-Castillo G, Clardy J, Tse-Dinh YC. Identification of

Anziaic Acid, a Lichen depside from Hypotrachyna sp., as a New Topoisomerase Poison Inhibitor. PLOS ONE 2013, Apr 8;8(4):e60770. PMC3620467
13. Sissi C, Cheng B, Lombardo V, Tse-Dinh YC, Palumbo M. Metal ion and inter-domain interactions as functional networks in E. coli topoisomerase I. Gene. 2013 Jul 25;524(2):253-60. PMC3876943
14. Aedo S, Tse-Dinh YC. SbcCD-mediated processing of covalent gyrase-DNA complex in Escherichia coli. Antimicrob Agents Chemother. 2013 Oct;57(10):5116-9. PMC3811449
15. Lin H, Annamalai T, Bansod P, Tse-Dinh YC, Sun D. Synthesis and antibacterial evaluation of anziaic acid and analogues as topoisomerase I inhibitors. Med Chem Comm. 2013 Dec 1;4(12). PMC3867937

D. Research Support

Ongoing Research Support

R01 AI069313 Tse-Dinh (PI) 02/01/06 – 8/31/15
NIH/NIAID
Bacterial Cell killing by topoisomerase I mediated DNA lesion
This study aims to identify small molecules that may interact with *Yersinia pestis* topoisomerase I to result in DNA lesion and cell killing of gram negative bacteria, while studying the cell killing pathway and repair mechanism *E. coli* with genetic experiments.
Role: PI

R01 GM054226 Tse-Dinh (PI) 04/01/96 – 12/31/15
NIH/NIGMS
Control of DNA topology
The long term goals of this study are to elucidate the reaction mechanism and physiological function of bacterial type IA DNA topoisomerases.
Role: PI

Completed Research Support

Tres Cantos Open Lab Foundation Collaboration Project
Tse-Dinh (PI) 09/01/13 – 05/31/14
Identification of inhibitors of M. tuberculosis topoisomerase I for novel anti-TB therapy
A postdoctoral fellow from the PI's lab will conduct an enzyme based HTS assay at GSK Tes Cantos open Lab to identify inhitors of M. tuberculosis topoisomerase I
Role: PI

Global Alliance for TB Tse-Dinh (PI) 05/01/09-4/30/12
Development of enzyme based HTS assay for small molecules that can trap the DNA cleavage complex formed by Mycobacterium tuberculosis topoisomerase I.
Role: PI

R21 NS067592 Tse-Dinh (PI) 06/01/10 – 5/31/12
NIH Roadmap Initiative
HTS assay development targeting Yersinia pestis topoisomerase I
An enzyme based HTS assay for compounds that lead to accumulation of covalent complex by Y. Pestis topoisomerase I was developed.
Role: PI