BIOGRAPHICAL SKETCH

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NAME: Tse-Dinh, Yuk-Ching

eRA COMMONS USER NAME (credential, e.g., agency login): yuk-ching

POSITION TITLE: Distinguished University Professor, Director of Biomolecular Sciences Institute

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hollins University, Virginia	B.A.	05/1977	Chemistry
Harvard University, Massachusetts	Ph.D.	05/1982	Biological Chemistry

A. Personal Statement

I began my research on topoisomerases as a graduate student at Harvard University under James C. Wang who discovered topoisomerase enzymes. The ubiquitous topoisomerase enzymes are not only essential for life, but are also important targets for antibacterial and anticancer therapy. After obtaining my PhD degree, as a PI at DuPont Central Research & Development, I continued with basic studies on the mechanism and regulation of topoisomerases. I joined the faculty of New York Medical College in 1988 and continued to make highly significant discoveries on topoisomerase mechanism and cellular functions, often by collaborating with other researchers at New York Medical College and elsewhere. I was hired in 2012 as the Founding Director for the Biomolecular Sciences Institute at FIU because of my record in trans-disciplinary research approach. My basic research efforts over the past 40 years have provided the foundation for research that can lead to discovery of new inhibitors of DNA topoisomerases and their translational applications. I was appointed in 2018 also as the Director of an FIU Emerging Preeminent Program, the Translational Molecular Discoveries (TMD) program, with the goals of engaging with internal and external partners in making new discoveries resulting in patents, increased funding for research and the integration of those discoveries into real life practices and treatments.

B. Positions and Honors

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, Department of Biochemistry & Mol Biology, New York Medical College
1994-2012 Professor, Department of Biochemistry & Molecular Biology, New York Medical College.
2007-2012 Ph.D. Program Director, Dept. Biochemistry & Molecular Biology, New York Medical College
2012- Professor, Department of Chemistry & Biochemistry, Florida International University
2012- Founding Director, Biomolecular Sciences Institute, Florida International University
2018- Founding Director, Translational Molecular Discoveries, Florida International University
2018- Distinguished University Professor, Florida International University

Other Experience and Professional Memberships

1991-1995 NIH Reviewer, regular member of NIH Physiological Chemistry Study Section (PC).
1995-1999 NIH Reviewers Reserve
1999- Member, American Society of Microbiology
2001- Managing Editor, Frontiers in Bioscience

2002	Temporary reviewer, NIH Microbial Physiology and Genetics-2 Study Section (MBC-2)
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, 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
2014	Grant Reviewer for French National Research Agency
2014	NIH Reviewer, HTS Review Panel (October)
2015	NIH Reviewer, R21/R33 Development of Novel Therapeutics for Select Pathogens (March), Special Emphasis Review Panel (July)
2016	NIH Reviewer, Special Emphasis Panel for SBIR/STTR Biological Chemistry, Biophysics. Drug Discovery (March, November), R21/R33 Development of Novel Therapeutics for Eukaryotic Pathogens (May)
2017	NIH Reviewer, Partnerships for Countermeasures against Select Pathogens (February); Special Emphasis Panel (July)
2018	Grant Reviewer for MRC, UK
2018	NIH Reviewer, SBIR/STTR Drug Discovery and Development (March); U19 for NIAID CETR (September, October)
2019	NIH Reviewer, NIAID R21 panel on non-coding RNA (March); SBIR/STTR Drug Discovery and Development (March)
2019	Grant Reviewer for MRC, UK and National Science Centre, Poland

Honors

1974	International Institute of Education Scholarship for College Study
1977	Phi beta kappa
1977	Lewis Howe Award for graduating senior from American Chemical Society, Blue Ridge Section
1977	Hollins Faculty Gold Medal Award for Academic Excellence
2013, 2018	FIU Top Scholar Award
2017	FIU College of Arts, Science and Education Service Award
2018	FIU College of Arts, Science and Education Research Award
2018	FIU Faculty Award for Research Excellence and Creative Activities

C. Contributions to Science

1. **Bacterial Topoisomerase I Mechanism** - As part of my PhD thesis research, I determined the chemical identity of the covalent 5'-phosphotyrosine linkage between cleaved DNA and topoisomerases. This work was described in a 1980 JBC Classic publication. The use of active site tyrosine as nucleophile for DNA cleavage by topoisomerases allows the energy of the phospohdiester bond to be conserved in the high energy phosphotyrosine bond for DNA religation. My research since then has identified other residues and domains required for type IA topoisomerase activity. My collaborations with X-ray crystallographists have produced key structures of topoisomerase I that overcome long-standing barriers in the elucidation of structure-function, including the covalent intermediate structure.

a. Tse YC, Kirkegaard K, Wang JC. Covalent bonds between protein and DNA. Formation of phosphotyrosine linkage between certain DNA topoisomerases and DNA. J Biol Chem. 1980; 255:5560-5. PMID: 6155377. **JBC Classic Paper**

b. Zhang Z, Cheng B, Tse-Dinh YC. Crystal structure of a covalent intermediate in DNA cleavage and rejoining by *Escherichia coli* DNA topoisomerase I. Proc Natl Acad Sci USA. 2011; 108:6939-6944. PMID: 21482796; PMCID: PMC3084087

c. Tan K, Zhou Q, Cheng B, Zhang Z, Joachimiak J, Tse-Dinh YC. Structural basis for suppression of hypernegative DNA supercoiling by *E. coli* topoisomerase I, Nucl Acids Res 2015; 43(22):11031-46. PMID: 26490962; PMCID: PMC4678816
d. Cao N, Tan K, Annamalai T, Joachimiak A, Tse-Dinh YC. Investigating mycobacterial topoisomerase I mechanism from the analysis of metal and DNA substrate interactions at the active site. Nucleic Acids Res. 2018; 46(14):7296-7308. PMID: 29905859; PMCID: PMC6101483

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2. **Supercoiling Sensitive Regulation of *topA* Transcription by Multiple Promoters** - I demonstrated that transcription of *E. coli* topoisomerase I (*topA)* gene is inhibited by loss of negative DNA supercoiling. This is an important component of the global homeostatic regulation of DNA supercoiling, so that the organism can maintain the DNA supercoiling in an optimal range by increasing DNA gyrase gene transcription when DNA is relaxed, and increasing topoisomerase I gene transcription when negative DNA supercoiling is excessive. Optimal level of DNA supercoiling is required for vital cellular processes including replication, transcription, recombination and repair. The requirement of topoisomerase I during different growth conditions was illustrated by the use of multiple sigma factors including sigma70, sigma32 and sigmaS to regulate *topA* transcription in response to change in growth conditions. The response of *topA* transcription to supercoiling partially suppresses the decrease in TopA relaxation activity from increased lysine acetylation in mutant lacking deacetylase activity.

a. Tse-Dinh YC. Regulation of the *Escherichia coli* DNA topoisomerase I gene by DNA supercoiling. Nucleic Acids Res. 1985; 13:4751-63. PMID: 2991845; PMCID: PMC321824
b. Tse-Dinh YC, Beran RK. Multiple promoters for transcription of the *Escherichia coli* DNA topoisomerase I gene and their regulation by DNA supercoiling. J Mol Biol. 1988; 202:735-42. PMID: 2845101
c. Tse-Dinh YC, Qi H, Menzel R. DNA supercoiling and bacterial adaptation: thermotolerance and thermoresistance. Trends Microbiol. 1997; 5:323-6. PMID: 9263411
d. Zhou Q, Zhou YN, Jin DJ, Tse-Dinh YC. Deacetylation of topoisomerase I is an important physiological function of CobB. Nucleic Acids Res. 2017; 45:5349-58. PMID: 28398568; PMCID: PMC5605244

3. **Topoisomerase I Function in Transcription and Stress Response** - I demonstrated the direct interaction between RNA polymerase and topoisomerase I for the important role of topoisomerase activity in transcription. Topoisomerase activity is required for suppressing R-loop accumulation during transcription elongation in all organisms. This function of topoisomerases is especially critical for cell survival upon stress challenge including DNA damage, oxidative stress and drug treatment. I demonstrated that *E. coli* and mycobacteria have evolved to use different topoisomerase I C-terminal domain motifs to interact with the beta' subunit of RNA polymerase for this important function.

a. Cheng B, Zhu CX, Ji C, Ahumada A, Tse-Dinh YC. Direct interaction between *Escherichia* coli RNA polymerase and the zinc ribbon domains of DNA topoisomerase I. J Biol Chem. 2003; 278:30705-10. PMID: 12788950
b. Yang J, Annamalai T, Cheng B, Banda S, Tyagi R, Tse-Dinh YC. Antimicrobial Susceptibility and SOS-dependent Increase in Mutation Frequency are Impacted by *E. coli* Topoisomerase I C-terminal Point Mutation. Antimicrob Agents Chemother. 2015; 59:6195-202. PMID: 26248366; PMCID: PMC4576087
c. Tiwari PB, Chapagain PP, Banda S, Darici Y, Üren A, Tse-Dinh YC. Characterization of molecular interactions between *Escherichia coli* RNA polymerase and topoisomerase I by molecular simulations. FEBS Lett. 2016; 590:2844-51. PMID: 27448274; PMCID: PMC5014613
d. Banda S, Cao N, Tse-Dinh YC. Distinct mechanism evolved for mycobacterial RNA polymerase and topoisomerase I protein-protein interaction. J Mol Biol 2017; 429:2931-42. PMID:28843989; PMCID: PMC5610943

4. **Genetic Validation of Topoisomerase I as Bactericidal Target** - Using a genetic approach, I validated bacterial topoisomerase I as a novel bactericidal target that is present in every bacterial pathogen. Mutations that mimic potential type IA topoisomerase poison inhibitors in prevention of DNA religation after DNA cleavage and formation of covalent topoisomerase-DNA complex were identified. Expression of these recombinant topoisomerase I with dominant lethal mutations was regulated by the BAD promoter and suppressed by glucose. Induction of the mutant topoisomerase I by arabinose results in rapid bacterial cell

death. The locations of the residues associated with this dominant lethal phenotype inform us on the regulation of DNA cleavage-religation equilibrium, and are potential binding sites for the desired bacterial topoisomerase I poison inhibitors.

a. Cheng B, Shukla S, Vasunilashorn S, Mukhopadhyay S, Tse-Dinh YC. Bacterial cell killing mediated by topoisomerase I DNA cleavage activity. J Biol Chem. 2005; 280:38489-95. PMID: 16159875; PMCID: PMC1351368
b. Sorokin EP, Cheng B, Rathi S, Aedo SJ, Abrenica MV, Tse-Dinh YC. Inhibition of Mg^{2+} binding and DNA religation by bacterial topoisomerase I via introduction of an additional positive charge into the active site region. Nucleic Acids Res. 2008;36:4788-96. PMID: 18653534; PMCID: PMC2504298
c. Cheng B, Annamalai T, Sorokin E, Abrenica M, Aedo S, Tse-Dinh YC. 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. 2009; 385:558-67. PMID: 19013470; PMCID: PMC2905861
d. Narula G, Annamalai T, Aedo S, Cheng B, Sorokin E, Wong A, Tse-Dinh YC. 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. 2011; 286:18673-80. PMID: 21478161; PMCID: PMC3099684

5. **Screening and Identification of Bacterial Topoisomerase I Inhibitors** - I have spear headed the ongoing interdisciplinary team efforts to identify bacterial topoisomerase I inhibitors that might be useful leads for development of novel antibiotics that can be used to treat multi-drug resistant bacteria. I collaborated with structural biologists to obtain the important structure of the covalent topoisomerase I-DNA cleavage complex intermediate. We are trying to obtain addition structures of enzyme-DNA and enzyme-DNA-inhibitor complexes. I have utilized cell based and enzyme based high throughput screening assays in collaboration with screening centers and natural product chemists to identify bacterial topoisomerase I poison inhibitors. I have been working with organic chemistry collaborators to use SAR to improve on the potency and selectivity of bacterial topoisomerase I inhibitors.

a. Cheng B, Liu IF, Tse-Dinh YC. Compounds with antibacterial activity that enhance DNA cleavage by bacterial DNA topoisomerase I. J Antimicrob Chemother. 2007; 59:640-5. PMID: 17317696.
b. Tse-Dinh YC. Bacterial topoisomerase I as a target for discovery of antibacterial compounds. Nucleic Acids Res. 2009; 37:731-7. PMID: 19042977; PMCID: PMC2647297.
c. 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;8:e60770. PMID: 23593306; PMCID: PMC3620467
d. Gupta R, Rodrigues Felix C, Akerman MP, Akerman KJ, Slabber CA, Wang W, Adams J, Shaw LN, Tse-Dinh YC, Munro OQ, Rohde KH. Evidence for Inhibition of Topoisomerase 1A by Gold(III) Macrocycles and Chelates Targeting *Mycobacterium tuberculosis* and *Mycobacterium abscessus*. Antimicrob Agents Chemother. 2018; 62(5). pii: e01696-17. PMID: 29483110; PMCID: PMC5923144

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/42197965/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

NIH/NIGMS R01GM054226 Tse-Dinh (PI) 04/01/96 – 6/30/21
"Control of DNA topology"
The long term goals of this study are to elucidate the reaction mechanism and physiological function of type IA DNA topoisomerases.
Role: PI

Broward Community Foundation Tse-Dinh (PI) 01/01/15 - 06/30/20
"Investigation of a Novel Treatment for Advanced Prostate Cancer"

This team project (with two co-Pis) develops a HTS assay for inhibitors of DNA repair activity in prostate cancer whole cell extract, and tests the hits for inhibition of prostate cancer cell growth to provide new treatment for castrate-resistant prostate cancer.
Role: PI

NIH/NIGMS T32GM132054 Tse-Dinh, Kos (Pis) 07/01/19 - 06/30/24
"Transdisciplinary Training in Biomolecular and Biomedical Sciences"
This is a predoctoral training grant for students to receive training and mentorship in biomolecular biomedical sciences from faculty mentors across different disciplines who are engaged in collaboration.
Role: PI/PD

NIH/NIEHS R32ES030523 Kim Tieu (PI) 06/01/19 – 05/31/27
"Toxicant-Induced Neurotoxicity Medicated by Glia-Neuron and Gene-Environment Interactions in Parkinson's Disease"
This project addresses the neurotoxicity mediated by glia-neuron interactions, gene-environment interactions and gastric bacteria that have been linked to Parkinson disease.
Role: Co-Investigator

Completed Research Support

Gifts of private donors Tse-Dinh (PI) 03/01/2015 – 02/28/2018
"Predictive biomarkers for glioblastoma progression and treatment"
This team project (with two co-PIs) investigates topoisomerase and DNA repair activities as predictive biomarkers for selection of optimized treatment of individual glioblastoma patient.
Role: PI

Global Alliance for TB Drug Development Tse-Dinh (PI) 07/01/16-06/30/17
"*Mycobacterium tuberculosis* topoisomerase I: Interaction with DNA and inhibitor"
This grant provides bridge support for the collaboration between the PI and Dr. Kemin Tan to obtain structures of *M. tuberculosis* topoisomerase I in complex with DNA, and endogenous protein toxin Rv1495. Genetic studies will identify residues on topoisomerase I interacting with the toxin Rv1495.
Role: PI

NIH/NIAID R01AI069313 Tse-Dinh (PI) 02/01/06 – 8/31/16
"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