BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Liang Tong

eRA COMMONS USER NAME (credential, e.g., agency login): LIANGTONG

POSITION TITLE: William R. Kenan, Jr. Professor

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
Peking University, Beijing, China	B. Sc.	07/1983	Chemistry
University of California, Berkeley, California	Ph. D.	07/1989	Structural Biology
Purdue University, West Lafayette, Indiana	Post-doc	07/1992	Structural Biology

A. Personal Statement

Research: I have made major contributions to understanding the molecular mechanisms of biological systems, especially RNA processing and quality control and metabolic enzymes. We started working on pre-mRNA 3'-end processing in 2004 as a collaboration with Dr. James Manley, an expert in this area in our Department. I then expanded to related areas, such as RNA degradation by 5'-3' exonucleases and RNA polymerase II (Pol II) transcription termination, which unexpectedly led us to the discovery of the mRNA 5'-end capping quality surveillance mechanism from our studies on the Rat1-Rai1 complex. This has opened up a new area of research in RNA biology. More recently, we have also made substantial progress in the studies on Integrator, a critical machinery for widespread Pol II transcription attenuation and snRNA 3'-end processing, revealing a cellular metabolite (IP_6) that has an important role in its function. We have published extensively on these topics over the years, and some of the publications include *Nature*, 2006; *Nature*, 2009; *Nature*, 2010; *Nature*, 2010; *Science*, 2013; *Cell*, 2017; *Science*, 2020; *Mol. Cell*, 2023; *Mol. Cell*, 2024.

In addition, I established a structure-based drug design laboratory in a pharmaceutical company before starting my position at Columbia, and I remain strongly interested in studying proteins involved in human diseases and understanding protein-ligand interactions. At Columbia, we started working on acetyl-CoA carboxylase (ACC) in 2002, which was an attractive drug discovery target for diabetes and other metabolic diseases. This evolved into studies on other members of the biotin-dependent carboxylase family as well as other metabolic enzymes. Many of these enzymes are large assemblies (500-750 kDa) and we had to overcome serious challenges for their structure determination by X-ray crystallography, before the resolution revolution in electron microscopy. The structures reveal the molecular mechanism for their catalysis and overall architecture, as well as their regulation by small molecules. We have also published extensively on these topics, and some of the publications include *Cell*, 2003; *Science*, 2003; *Nature*, 2007; *Nature*, 2010; *Nature*, 2012; *Cell*, 2014; *Nature*, 2015; *Nature*, 2015; *Nature*, 2015; *Nature*, 2019.

Finally, I also have strong training in the theory and practice of protein crystallography, and have developed new methodologies and computer software (GLRF, Replace and COMO) that has been distributed to many laboratories around the world.

I have more than 330 publications, with an *h* index of 96.

Mentoring: One of the important considerations when I left industry in 1997 and established my lab at Columbia was the opportunity to train Ph.D. students and post-docs. During the past 28 years, 19 students have received their Ph.D. degree, and 32 post-docs have received their training in my lab. These former Ph.D. students and post-docs now have jobs in academia (faculty, research scientist) and industry (biotech, pharmaceutical, law). Currently, three Ph.D. student and five post-docs are receiving training in my lab. I put in significant time and effort working with the students and post-docs, to discuss their research projects, to teach

them structural biology and to help with their career development. The strong publication record from my lab over the past years is a reflection of their training and achievement.

Ongoing and recently completed projects that I would like to highlight include:

R35 GM118093
Tong (PI)
05/01/16-04/30/26 (ongoing)
Structural and functional studies of mRNA processing, stability and quality control

R01 NS135070
Tong (co-PI with Eric Wagner and Chris Proschel, University of Rochester)
09/20/23-07/31/2028 (ongoing)
Probing the role of Integrator in neuronal function

Kintor Pharmaceuticals
Tong (PI)
01/01/16-12/31/24 (recently completed)
Structures of human androgen receptor ligand binding domain (AR)-VHL in complex with inhibitors

Citations:

1. Y. Sun,* Y. Zhang,* W.S. Aik, X.-C. Yang, W.F. Marzluff, T. Walz[$], Z. Dominski[$] & **L. Tong**.[$] (**2020**). Structure of an active human histone pre-mRNA 3′-end processing machinery. ***Science***, 367, 700-703. (*–*equal first authors,* [$]*–co-corresponding authors*) PMCID: PMC7008720.
2. Y. Tao,* A. Budhipramono,* J. Huang,* M. Fang, S. Xie, J. Kim, V. Khivansara, Z. Dominski, L. Tong,[$] J.K. De Brabander[$] & D. Nijhawan.[$] (**2024**). Anticancer benzoxaboroles inhibit pre-mRNA processing by direct inhibition of CPSF3. ***Cell Chem. Biol***. **31**, 139-149. (Epub 11/14/23) (*–*equal first authors,* [$]*–co-corresponding authors*) PMCID: PMC10841686.
3. E.J. Wagner,[$] L. Tong[$] & K. Adelman.[$] (**2023**). Integrator is a global promoter-proximal termination complex. ***Mol. Cell***, **83**, 416-427. ([$]*–co-corresponding authors*) PMCID: PMC10866050.
4. M.-H. Lin,* M.K. Jensen,* N.D. Elrod, H.-F. Chu, M. Haseley, A.C. Beam, K.-L. Huang, W. Chiang, W.K. Russell, K. Williams, C. Proschel, E.J. Wagner[$] & L. Tong.[$] (**2024**). Cytoplasmic binding partners of the Integrator endonuclease INTS11 and its paralog CPSF73 are required for their nuclear function. ***Mol. Cell***, **84**, 2900-2917. (*–*equal first authors,* [$]*–co-corresponding authors*) PMCID: PMC11316654.

B. Positions, Scientific Appointments, and Honors

Positions

2015-present William R. Kenan, Jr. Professor of Biological Sciences, Columbia University, NY
2013-2019 Chair, Department of Biological Sciences, Columbia University, NY
2004-2015 Professor of Biological Sciences, Columbia University, NY
1997-2004 Associate Professor of Biological Sciences, Columbia University, NY
1996-1997 Principal Scientist. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT
1992-1995 Senior Scientist. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT

2019-2022 Honorary Research Professor, Durban University of Technology, Durban, South Africa
2015-2017 Honorary Professor, Nanjing Tech University, Nanjing, China

Scientific Appointments (past 3 years)

2020-present Independent non-executive director, Kintor Pharmaceuticals, Suzhou, China
2016-2024 Consultant, Nimbus Therapeutics, Cambridge, MA
2020-2024 Overseas Evaluation Expert, Chinese Academy of Sciences
2023-2023 Consultant, Syngenta Crop Protection AG, Basel, Switzerland

2021-2022 Consultant, Boragen Inc., Durham, NC
2021-2022 Consultant, RADD Pharmaceuticals, Inc., Westport, CT

Selected Service
Member, Columbia University Standing Committee on the Conduct of Research, 2022-present
co-Editor, Third Edition of Volume F of International Tables of Crystallography, 2018-present
Chair, Singapore Ministry of Education Academic Research Fund Tier 2 Expert Panel 3, 2015-2025
Member, International Review Committee of Ocean University of China Marine Science Program, 2024
Member, International Review Committee of ShanghaiTech University SIAIS and iHuman, 2024
Member, NIH ZRG1 F07A-F (20) panel, Fellowships: Infectious Diseases and Immunology, 2022
Member, International Review Committee of ShanghaiTech University School of Life Science and Technology, 2019
Chair, Department of Biological Sciences, Columbia University, 2013-2019

Manuscript Reviews for *Nature, Science, NSMB, NSB, Nature Chemical Biology, Molecular Cell, Science Advances, PNAS, Nature Communications, Nucleic Acids Research, RNA, Structure, Journal of Molecular Biology, Journal of Biological Chemistry, Biochemistry*, *Acta Crystallographica*, and others.

Honors
2021 American Crystallographic Association (ACA) Fellow
2009 American Association for the Advancement of Science (AAAS) Fellow
1997 The first Boehringer Ingelheim Worldwide Research and Development Award
1996 The Vice President's Golden Achievement Award, Boehringer Ingelheim Pharmaceuticals, Inc.
1989 Phi Beta Kappa

C. Contributions to Science

1. Eukaryotic pre-mRNAs undergo extensive co-transcriptional processing, including cleavage and polyadenylation at the 3'-end. A large protein machinery has been identified, but the molecular mechanism for its function is still poorly understood. We showed that CPSF73 is the long-sought endoribonuclease for the cleavage step of 3'-end processing, that the cleavage stimulation factor (CstF) may be dimeric in the machinery, and how the AAUAAA polyadenylation signal is recognized. We have also produced the first structural information on the distinct 3'-end processing machinery (U7 snRNP) for replication-dependent histone pre-mRNAs, which are cleaved but not polyadenylated. Over the past five years, we have demonstrated that CPSF73 is both an endo and an exo nuclease in the U7 snRNP, revealed how the 3'-end processing factor Fip1 is recruited to the machinery through CPSF30, begun to understand the molecular basis for the recognition of other polyadenylation signals, and defined the molecular basis for the function of a new class of small-molecule inhibitors of human CPSF73, which is a potential anti-cancer drug discovery target. Collaborators: James Manley (in our Department), William Marzluff and Zbigniew Dominski (University of North Carolina, Chapel Hill), Yongsheng Shi (University of California, Irvine), and Jef De Brabander and Deepak Nijhawan (University of Texas Southwestern Medical Center, Dallas).
    a. X.-C. Yang,* Y. Sun,* W.S. Aik, W.F. Marzluff, L. Tong[$] & Z. Dominski.[$] (**2020**). Studies with recombinant U7 snRNP demonstrate that CPSF73 is both an endonuclease and a 5′-3′ exonuclease. ***RNA***, **26**, 1345-1359. (*–*equal first authors,* [$]*–co-corresponding authors*). PMCID: PMC7491329.
    b. K. Hamilton & L. Tong. (**2020**). Molecular mechanism for the interaction between human CPSF30 and hFip1. ***Genes Develop.*** **34**, 1753-1761. PMCID: PMC7706699.
    c. P.A. Gutierrez, J. Wei, Y. Sun & L. Tong. (**2022**). Molecular basis for the recognition of the AUUAAA polyadenylation signal by mPSF. ***RNA***, **28**, 1534-1541. PMCID: PMC9745836.
    d. Y. Tao,* A. Budhipramono,* J. Huang,* M. Fang, S. Xie, J. Kim, V. Khivansara, Z. Dominski, L. Tong,[$] J.K. De Brabander[$] & D. Nijhawan.[$] (**2024**). Anticancer benzoxaboroles inhibit pre-mRNA processing by direct inhibition of CPSF3. ***Cell Chem. Biol***. **31**, 139-149. (Epub 11/14/23) (*–*equal first authors,* [$]*–co-corresponding authors*) PMCID: PMC10841686.

2. Integrator was originally identified as the machinery for snRNA 3'-end processing. Recent studies in many labs have shown it to be a transcription attenuator for a large collection of mRNAs. Over the past five years, we have identified a cellular metabolite (IP_6) that binds the Integrator cleavage module and is required for Integrator function, and discovered a protein partner for INTS11 that is required to stabilize this nuclease in the cytoplasm before it is transported into the nucleus and incorporated into Integrator. Collaborators: Eric Wagner and Chris Proschel (University of Rochester).
    a. M.-H. Lin,* M.K. Jensen,* N.D. Elrod, K.-L. Huang, K.A. Welle, E.J. Wagner[$] & L. Tong.[$] (**2022**). Inositol hexakisphosphate is required for Integrator function. ***Nature Commun***. **13**, 5742. (**–equal first authors, [$]–co-corresponding authors*) PMCID: PMC9525679.
    b. E.J. Wagner,[$] L. Tong[$] & K. Adelman.[$] (**2023**). Integrator is a global promoter-proximal termination complex. ***Mol. Cell***, **83**, 416-427. (*[$]–co-corresponding authors*) PMCID: PMC10866050.
    c. M.-H. Lin,* M.K. Jensen,* N.D. Elrod, H.-F. Chu, M. Haseley, A.C. Beam, K.-L. Huang, W. Chiang, W.K. Russell, K. Williams, C. Proschel, E.J. Wagner[$] & L. Tong.[$] (**2024**). Cytoplasmic binding partners of the Integrator endonuclease INTS11 and its paralog CPSF73 are required for their nuclear function. ***Mol. Cell***, **84**, 2900-2917. (**–equal first authors, [$]–co-corresponding authors*) PMCID: PMC11316654.

3. Our structure of the 5'-3' exoribonuclease Rat1 in complex with its binding partner Rai1 revealed that Rai1 contains an active site. In collaboration with Drs. Megerditch Kiledjian (Rutgers University) and James Manley (in our Department), we showed that Rai1 possesses RNA 5'-end pyrophosphohydrolase (PPH) activity and can also remove unmethylated caps. We hypothesized that Rai1 may be a central player in a novel mRNA 5'-end capping quality surveillance mechanism, and functional studies in Dr. Kiledjian's laboratory have demonstrated the existence of this mechanism in yeast and mammalian cells. We also discovered that the mammalian homolog of Rai1 (Dom3Z, which we have renamed as DXO) has distributive 5'-3' exoribonuclease activities. These studies overturn the belief that mRNA capping always proceeds to completion and therefore no quality surveillance is necessary, and have opened up a new area of research. We have since shown that the DXO/Rai1 enzymes can also remove other non-canonical caps on RNAs, such as NAD (deNADding), FAD (deFADding), and dephospho-CoA (deCoAping). Moreover, we have found that Nudix family protein Nudt12 also has deNADding activity. Over the past five years, we have shown that exoribonucleases in human, yeast and bacteria also have deFADding activity, and revealed the molecular basis how another protein factor, Rtt103, associates with the Rat1-Rai1 complex in yeast. A segment of Rtt103 is bound to Rai1, which may help to recruit Rat1-Rai1 to RNA polymerase II.
    a. S. Sharma,* J. Yang,* S.K. Doamekpor, E. Grudzien-Nogalska, L. Tong & M. Kiledjian. (**2022**). Identification of a novel deFADding activity in human, yeast and bacterial 5′ to 3′ exoribonucleases. ***Nucl. Acids Res***. **50**, 8807-8817. (**–equal first authors*) PMCID: PMC9410882.
    b. S.K. Doamekpor,* S. Sharma,* M. Kiledjian[$] & L. Tong.[$] (**2022**). Recent insights into noncanonical 5′ capping and decapping of RNA. ***J. Biol. Chem.*** **298**, 102171. (**–equal first authors, [$]–co-corresponding authors*) PMCID: PMC9283932.
    c. H.-F. Chu & L. Tong. (**2025**). Molecular basis for the interaction between *Saccharomyces cerevisiae* Rtt103 and the Rat1-Rai1 complex. ***Nature Commun***. **16**, 3266. PMCID: PMC11972402.

4. Acyl-CoA carboxylases have central roles in metabolism and defective mutations in several of these enzymes are linked to serious diseases, especially in infants. We have determined the crystal structures of the 500 kDa holoenzyme of acetyl-CoA carboxylase (ACC), the 750 kDa holoenzymes of propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase (MCC) and a novel long-chain acyl-CoA carboxylase (LCC), and the 500 kDa holoenzyme of *Listeria monocytogenes* pyruvate carboxylase (LmPC) bound to the bacterial second messenger cyclic-di-AMP. The structures provide a basis for understanding the catalysis by these enzymes, the disease-causing mutations, and the allosteric regulation of LmPC. We also produced the first structures of several other metabolic enzymes, including carnitine acetyltransferase, the heterotrimer core of SNF1, which is the yeast homolog of AMP-activated protein kinase (AMPK), and human ATP-citrate lyase (ACLY) in complex with an inhibitor. This has been a long-term project in my laboratory at Columbia. The work on LmPC was a collaboration with Dr. Joshua Woodward (University of Washington) and that on ACLY was a collaboration with scientists at Nimbus Therapeutics (Cambridge, MA).
    a. K. Sureka,* P.H. Choi,* M. Precit, M. Delince, D.A. Pensinger, T.N. Huynh, A.R. Jurado, Y.A. Goo, M. Sadilek, A.T. Iavarone, J.-D. Sauer, L. Tong[$] & J.J. Woodward.[$] (**2014**). The cyclic dinucleotide

c-di-AMP is an allosteric regulator of metabolic enzyme function. ***Cell***, **158**, 1389-1401. (**–equal first authors, $–co-corresponding authors*) PMCID: 4166403.

b. T.H. Tran, Y.-S. Hsiao, J. Jo, C.-Y. Chou, L. Dietrich, T. Walz & L. Tong. (**2015**). Structure and function of a single-chain, multi-domain long-chain acyl-CoA carboxylase. ***Nature***, **518**, 120-124. PMCID: PMC4319993.

c. J. Wei & L. Tong. (**2015**). Crystal structure of the 500-kDa yeast acetyl-CoA carboxylase holoenzyme dimer. ***Nature***, **526**, 723-727. PMCID: PMC4838907.

d. J. Wei, S. Leit, J. Kuai, E. Therrien, S. Rafi, H.J. Harwood Jr, B. DeLaBarre & L. Tong. (**2019**). An allosteric mechanism for potent inhibition of human ATP-citrate lyase. ***Nature***, **568**, 566-570.

5. I have also made important contributions to several other areas of modern biology. While at Boehringer Ingelheim Pharmaceuticals, I determined the structure of p38 MAP kinase in complex with a highly selective inhibitor, revealing for the first time how one can achieve strong selectivity with compounds that target the ATP binding site of protein kinases. With another series of compounds, we revealed a major conformational change in the active site region of the kinase that was necessary for inhibitor binding. I coined the term 'DFG-out conformation' for this new structure, which has been adopted by the field. During my first years at Columbia, we studied the molecular mechanism of signal transduction by the Toll-like receptors (in a collaboration with James Manley), which have important functions in innate immunity. We determined the first structure of the Toll/interleukin-1 receptor (TIR) domain, and I coined the term 'BB loop' as the name of a loop with important roles in protein-protein interaction for signaling. This term has also been adopted by scientists in the field. We discovered serendipitously the protocol of *in situ* partial proteolysis for crystallization, and this protocol is now in common use in the field. In addition, I have developed new methodologies (locked translation function, combined molecular replacement) and computer software for protein crystallography (locked rotation function (GLRF), Replace and COMO), which has been distributed to many laboratories around the world.

   a. C. Pargellis,* L. Tong,* L. Churchill, P.F. Cirillo, T. Gilmore, A.G. Graham, P.M. Grob, E.R. Hickey, N. Moss, S. Pav & J. Regan. (**2002**). Inhibition of p38 MAP kinase by utilizing a novel allosteric binding site. ***Nature Struct. Biol.*** **9**, 268-272. (**–co-corresponding authors*)

   b. Y. Xu, X. Tao, B. Shen, T. Horng, R. Medzhitov, J.L. Manley & L. Tong. (**2000**). Structural basis for signal transduction by the Toll/Interleukin-1 receptor (TIR) domains. ***Nature,*** **408**, 111-115.

   c. C.R. Mandel, D. Gebauer, H. Zhang & L. Tong. (**2006**). A serendipitous discovery that *in situ* partial proteolysis is essential for the crystallization of yeast CPSF-100 (Ydh1p). ***Acta Cryst.*** **F62**, 1041-1045.

   d. L. Tong & M.G. Rossmann. (**1990**). The locked rotation function. ***Acta Cryst***. **A46**, 783-792.

Complete List of Published Work: (332 total, 282 research papers, 50 reviews/book chapters)
http://www.ncbi.nlm.nih.gov/sites/myncbi/liang.tong.1/bibliography/41159164/public/?sort=date&direction=ascending