BIOGRAPHICAL SKETCH

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NAME: Wei-Jen Tang

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POSITION TITLE: 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
National Taiwan University	B.S.	05/1982	Zoology
University of Texas, Austin	Ph.D.	05/1988	Biological Science (Mentor: William R. Folk)
University of Texas, Austin	Postdoctoral fellow	08/1988	Microbiology (Mentor: William R. Folk)
University of Texas Southwestern Medical School	Postdoctoral fellow	06/1991	Pharmacology (Mentor: Alfred G. Gilman)

A. Personal Statement

My research program focuses on elucidating the molecular basis of cellular signal transduction with the premise that a better understanding of protein-protein and protein-ligand interactions is key to deciphering the fundamental principles governing cellular signaling networks. We employ a variety of techniques, including X-ray crystallography, cryo-electron microscopy (cryoEM), proteomics, biochemistry, biophysics, cellular assays, and pharmacological tools, to study protein functions and regulations. I am recognized for my studies on the catalysis and regulation of mammalian adenylyl cyclase, toxins from anthrax and pertussis adenylyl cyclase, and protease families that degrade amyloid peptide, e.g., human insulin-degrading enzyme (IDE) and human presequence protease (PreP). I have also contributed significantly to drug discovery for anthrax toxins, including edema factor and lethal factor, and for IDE. For example, I led an effort to assemble a team of researchers from academia and industry to demonstrate the efficacy of the approved antiviral drug Adefovir in inhibiting anthrax edema factor and mitigating anthrax pathogenesis. This work paves the way for repurposing an existing anti-hepatitis B virus drug for biodefense against anthrax. Having grown up in Taiwan, I deeply appreciate the values of diversity and inclusion and am committed to mentoring students and early-stage investigators, particularly those who are underrepresented minorities in STEM. As the chair of the subcommittee within the cancer biology that deals with research community building, I am actively engaged in improving diversity and inclusion on and off campus.

a. Liang, W. G., Wijiya, J., Wei, H., Noble, A., Mo, S., Lee, D., Mancl, J. M., King, J. L., Pan, M., Liu, C., Koehler, C., Zhao, M., Potter, C. S., Carragher, B., Li, S., and **Tang, W. J.** (2022)

Structural basis for the mechanisms of human presequence protease conformational switch and substrate recognition. Nature Communications 13:1833.

b. Zheng, Z., Liang, W.G., Bailey, L.J., Tan, Y.Z., Wei, H., Wang, A., Farcasanu, M., Woods, V.A., McCord, L. A., Lee, D., Shang, W., Deprez-Poulain, R., Deprez, B., Liu, D.R., Koide, A., Koide, S., Kossiakoff, A.A., Li, S.*, Carragher*, B., Potter, C.S.*, and **Tang, W.-J.*,** (2018) Ensemble cryoEM elucidates the mechanism of insulin capture and degradation by human insulin degrading enzyme. ELife 7:e33572 (*co-corresponding authors).

c. Shen, Y., Joachimiak, A., Rosner, M.R., & **Tang, W.-J.** (2006) Structures of human insulin degrading enzyme reveal a new substrate recognition mechanism. Nature 443:870-874.

d. Drum, C.L., Yan, S.-Z., Bard, J., Shen, Y.-Q., Lu, D., Soelaiman, S., Grabarek, Z., Bohm, A., & **Tang, W.-J.** (2002) Structural basis for the activation of anthrax adenylyl cyclase exotoxin by calmodulin. Nature 415:396-402.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2007-now Professor, Ben-May Department for Cancer Research, University of Chicago
2001-07 Associate Professor, Ben-May Institute for Cancer Research, University of Chicago
1998-2001 Assistant Professor, Dept. of Neurobiol. Pharmacol. & Physiol., University of Chicago
1994-98 Assistant Professor, Dept. of Pharmacol. & Physiol. Sciences, University of Chicago
1993-94 Assistant Professor, Dept. of Pharmacology, UT Southwestern Medical School
1991-93 Instructor, Dept. of Pharmacology, UT Southwestern Medical School

Other Experience and Professional Memberships

2018-24 AHA Fellowship Basic Cell--proteins and crystallography review
2016-2022 NIH New Innovator Award review
2016 Review panel member for APS XSD chemical and materials science review
2014-present Society of Chinese Bioscientists in American Nomination committee
2012-14 Regular member of American Heart Association Signaling 4 study section
2009-2022 The advisory Board, Structure Biology Center, APS, Argonne National Lab
2007-2011 Regular member of NIH MSF-C study section
1998-present Ad Hoc NIH and NSF grant reviewing panels
1986-2013 American Association for the Advancement of Science
1992-present American Society for Biochemistry and Molecular Biology

Honors

1999-2002 American Heart Association Established Investigator
1987-1988 University Fellowship, University of Texas, Austin

C. Contributions to Science

1. Structural and functional analyses of human insulin degrading enzyme (IDE): Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are chronic diseases that affect millions of people in the US alone. Aberrant levels of insulin and improper responses to insulin and other hormones that control glucose levels are the primary causes of T2DM. Amyloid β (Aβ) peptide, the primary component in amyloid plaques, plays a central role in the progression of AD. IDE is a 110 kDa M16 Zn^{2+}-metalloproteases that utilizes an enclosed catalytic chamber to recognize and degrade peptide substrates into fragments. IDE is involved in the clearance of peptides diverse in structure and sequence, including three glucose-regulating hormones (insulin, amylin,

and glucagon), Aβ, and other bioactive peptides less than 80 amino acids in length. The involvement of IDE in clearing both insulin and Aβ links it to the progression of T2DM and AD. Using structural, biochemical, and biophysical analyses, we have constructed a working model of how human IDE utilize their catalytic chambers to recognize substrates shorter than 80 amino acids in a distinct manner. Furthermore, we have developed potent inhibitors of human IDE to explore the biological functions and therapeutic potential of these proteases. Together, our studies pave the way for exploring IDE-based therapies, offering promising avenues for the treatment of T2DM and AD.

a. Mancl, J. M., Liang, W. G., Bayhi, N. L., Wei, H., Carragher, B., Potter, C. S., and **Tang, W.-J.** (2025) Characterization and modulation of human insulin degrading enzyme conformational dynamics to control enzyme activity. *eLife (https://elifesciences.org/reviewed-preprints/105761)*.

b. Zheng, Z., Liang, W.G., Bailey, L.J., Tan, Y.Z., Wei, H., Wang, A., Farcasanu, M., Woods, V.A., McCord, L. A., Lee, D., Shang, W., Deprez-Poulain, R., Deprez, B., Liu, D.R., Koide, A., Koide, S., Kossiakoff, A.A., Li, S.*, Carragher*, B., Potter, C.S.*, and **Tang, W.-J.*,** (2018) Ensemble cryoEM elucidates the mechanism of insulin capture and degradation by human insulin degrading enzyme. ELife 7:e33572 (*co-corresponding authors).

c. McCord L.A., Liang, W.G., Dowdell, E., Kalas, V., Hoey, R.J., Koide, A., Koide, S., & **Tang, W.-J.** (2013) Conformational states and recognition of amyloidogenic peptides of human insulin-degrading enzyme. Proc. Natl. Acad. Sci. USA 110(34):13827-32.

d. Shen, Y., Joachimiak, A., Rosner, M.R., & **Tang, W.-J.** (2006) Structures of human insulin degrading enzyme reveal a new substrate recognition mechanism. Nature 443:870-874.

2. Structural and functional analysis of amyloid peptide degrading proteases: Aggregates of amyloid peptides are highly cytotoxic and are associated with human diseases such as Alzheimer's disease, Parkinson's disease, and AL and AA amyloidosis. The formation of toxic amyloid aggregates is driven by cross-β-sheet formation between amyloid peptides, with monomeric amyloid peptides playing a critical role in key steps of amyloid aggregation, including seeding formation and propagation of aggregation. In addition to the insulin-degrading enzyme, several proteases, including presequence protease (PreP, a metalloprotease from the M16C clan), angiotensin-1 converting enzyme (ACE, a metalloprotease from the M2 clan), and neprilysin (M13), are structurally distinct enzymes capable of degrading monomeric amyloid peptides such as amyloid β (Aβ). This degradation prevents the formation of toxic amyloid oligomers and fibrils. PreP is located in the mitochondrial matrix, where it degrades mitochondrial targeting sequences (presequences) to maintain mitochondrial proteostasis. Loss-of-function mutations in PreP are linked to human neurological disorders. ACE and neprilysin, on the other hand, are localized to the plasma membrane or extracellular space, where it degrades a variety of bioactive peptides. We have deciphered the key conformational states required for the catalytic cycle of PreP and applied integrative approaches to understand the structural basis of substrate recognition of PreP. Using cryoEM and molecular dynamics simulation, we have elucidated the structural basis of ACE dimerization and the open-closed transition. Furthermore, we have solved the open state structure of neprilysin homolog ZMP1 from *Mycobacterium tuberculosis* to address how the M13 family of metalloproteases, such as neprilysin, undergoes open-closed transitions for catalysis. These insights are crucial for understanding the mechanisms by which these proteases degrade amyloid peptides.

a. Mancl, J. M., Wu, X., Zhao, M., and **Tang, W.-J.** (2025) Dimerization and dynamics of angiotensin-I converting enzyme revealed by cryoEM and MD simulations. eLife to be published, *BioRXiv* https://doi.org/10.1101/2025.01.09.632263.

b. Liang, W. G., Wijiya, J., Wei, H., Noble, A., Mo, S., Lee, D., Mancl, J. M., King, J. L., Pan, M., Liu, C., Koehler, C., Zhao, M., Potter, C. S., Carragher, B., Li, S., and **Tang, W. J.** (2022)

Structural basis for the mechanisms of human presequence protease conformational switch and substrate recognition. Nature Communications 13:1833.

c. Liang, W.G., Mancl, J.M., Zhao, M., **Tang, W.-J.** (2021) Structural analysis of *Mycobacterium tuberculosis* M13 metalloprotease Zmp1 open states. Structure 29(7):709-720.

d. King, J.V., Liang, W.G., Scherpelz, K.P., Schilling, A.B., Meredith, S.C., and **Tang, W.-J.** (2014) Molecular basis of substrate recognition and degradation by human presequence protease. Structure 22:996-1007.

3. Structural and functional analyses of human chemokines: Chemokines are 8-14 kDa chemotactic cytokines that modulate inflammation and infection, affecting many chronic human diseases, making them potential therapeutic targets. CCL3 (also known as MIP-1α), CCL4 (also known as MIP-1β), and CCL5 (also known as RANTES) are proinflammatory chemokines linked to several human diseases, including atherosclerosis, AIDS, and cancer. These chemokines readily dimerize and subsequently form high molecular weight oligomers exceeding 500 kDa. Our structural studies reveal how these chemokines form rod-shaped, double helical oligomers and how oligomerization regulates their functions at the ligand level. Furthermore, our structural analysis demonstrates how insulin-degrading enzyme uses charge and size complementarity to selectively degrade and inactivate CCL3 and CCL4, but not CCL5. Glycosaminoglycans (GAGs) are complex polysaccharides that can be free or attached to proteoglycans at the glycocalyx layer of the cell surface or in the extracellular matrix. The binding of chemokines to extracellular GAGs is crucial for their function. Our structures of GAG-bound CCL3 and CCL5 provide the structural basis of how GAGs bind these chemokines, which allows for further exploration of how GAG interactions regulate chemokine functions. These insights into the structural and functional properties of chemokines and their interactions with GAGs could pave the way for developing novel therapeutic strategies for treating a range of human diseases associated with inflammation and infection.

a. Liang WG, Triandafillou CG, Huang T-Y, Zulueta MML, Banerjee S, Dinner AR, Hung S-C, & **Tang W.-J**. (2016) Structural basis for oligomerization and glycosaminoglycan-binding of CCL5 and CCL3. Proc Natl Acad Sci USA 113:5000-5005.

b. Liang, W.G., Ren, M., Zhao, F., and **Tang, W.-J.** (2015) Structures of human CCL18, CCL3, and CCL4 reveal molecular determinants for quaternary structures and sensitivity to insulin degrading enzyme. J. Mol Biol 427:1345-1358.

c. Ren, M., Guo, Q., Guo, L., Lenz, M., Qian, F., Koenen, R.R., Xu, H., Schilling, A.B., Weber, C., Ye, R.D., Dinner, A.R., and **Tang, W.-J.** (2010) Polymerization of MIP-1 chemokine (CCL-3 and CCL-4) and clearance of MIP-1 by insulin degrading enzyme. EMBO J. 29:3952-3966.

4. Structural and functional analyses of bacterial adenylyl cyclase toxins: I have studied the molecular basis of how bacterial adenylyl cyclase toxins, enzymes that convert ATP to cyclic AMP, disrupt cellular signal transduction to benefit bacterial pathogenesis. My research has focused on edema factor (EF) from *Bacillus anthracis* (the bacteria causing anthrax), CyaA from *Bordetella pertussis* (the bacteria causing whooping cough), and ExoY from *Pseudomonas aeruginosa* (the bacteria causing nosocomial infections). Anthrax bacteriasecrete three major toxins: edema factor (EF), lethal factor (LF), and protective antigen (PA). EF is a calmodulin (CaM)-activated adenylyl cyclase. We have determined the structures of EF and the EF-CaM complex to elucidate the molecular basis of how CaM binds and activates EF. This work highlights the diverse modes of CaM binding and its mechanism of action to modulate their effectors. We also solved the structure of calmodulin-bound CyaA, elucidating how CyaA binds calmodulin distinct from EF. Unlike EF and CyaA, ExoY binds and is activated by actin. We demonstrated that ExoY binds to actin polymers and induces actin bundling. In collaboration with researchers from academia and industry, we also demonstrated the efficacy of the approved antiviral drug, adefovir, in inhibiting EF activity and anthrax pathogenesis. This finding allows for

the repurposing of the existing anti-hepatitis B virus drug to treat anthrax infections. Overall, my efforts further our understanding of bacterial adenylyl cyclase toxins and support the development of effective countermeasures against related bacterial diseases.

a. Mancl, J.M., Suarez, C., Liang, W.G., Kovar, D.R., **Tang, W.-J.** (2020) *Pseudomonas aeruginosa* exoenzyme Y directly bundles actin filaments. J Biol Chem 295:3506-3517.

b. Guo, Q., Shen, Y., Lee, Y.-S., Gibbs, C.S., Mrksich, M., and **Tang, W.-J.** (2005) Structural basis for the interaction of adenylyl cyclase toxin of *Bordetella pertussis* with calmodulin. EMBO J. 24:3190-3201.

c. Shen, Y.-Q., Zhukovskaya, N.L., Zimmer, M.I., Soelaiman, S., Wang, C.R., Gibbs, C.S., & **Tang, W.-J.** (2004) Selective inhibition of anthrax edema factor by adefovir, a drug for chronic hepatitis B virus infection. Proc. Natl. Acad. Sci. U.S.A. 101:3242-3247.

d. Drum, C.L., Yan, S.-Z., Bard, J., Shen, Y.-Q., Lu, D., Soelaiman, S., Grabarek, Z., Bohm, A., & **Tang, W.-J.** (2002) Structural basis for the activation of anthrax adenylyl cyclase exotoxin by calmodulin. Nature 415:396-402. (Highlighted in N&V Nature 415: 373, 2002; N &V Nature Structure Biology 9:156, 2002; Minireview Cell 108:739, 2002)

5. Regulation and catalysis of mammalian adenylyl cyclases: Cyclic AMP (cAMP) is a prototypic intracellular second messenger that controls a diverse array of physiological events in response to the stimulation of numerous hormones and neurotransmitters. My early publications focused on establishing the molecular basis for the regulation and catalysis of mammalian membrane-bound adenylyl cyclase (mAC), an enzyme that raises intracellular cAMP levels in response to extracellular stimuli. Upon activation by G protein-coupled receptors (GPCRs), hormone-regulated heterotrimeric G proteins dissociate into α and βγ subunits. At the time, the prevailing dogma held that only the α subunit of the G protein regulated mAC activity, not the βγ subunit. I found that G protein βγ subunit could effectively suppress the activity of type 1 adenylyl cyclase while directly activate the Gsα-activated type 2 adenylyl cyclase. My finding established the direct roles of the G protein βγ subunit in modulating the activity of downstream effectors. Mammalian membrane-bound adenylyl cyclase consists of two transmembrane domains, each followed by a conserved cytoplasmic domain. By combining protein-engineering and genetic approaches, I constructed a Gsα-activated soluble adenylyl cyclase from the two conserved cytoplasmic domains of adenylyl cyclase. Our research elucidated the molecular basis of how mammalian adenylyl cyclases are regulated by G proteins, calmodulin, and pharmacological agents such as forskolin. Collectively, these findings advanced our understanding of the diverse mechanisms regulating mammalian adenylyl cyclase, contributing to the broader knowledge of intracellular signaling pathways and their physiological implications.

a. Yan, S.-Z., Huang, Z.-H., Rao, V.D., Hurley, J.H., & **Tang, W.-J.** (1997) Three discrete regions of mammalian adenylyl cyclase form a site for Gsα activation. J. Biol. Chem. 272:18849-18854.

b. Yan, S.-Z., Hahn, D., Huang, Z.-H., & **Tang, W.-J.** (1996) Two cytoplasmic domains of mammalian adenylyl cyclase form a Gsα and forskolin-activated enzyme in vitro. J. Biol. Chem. 271:10941-10945.

c. **Tang, W.-J.** & Gilman, A.G. (1995) Forskolin and Gsα sensitive soluble adenylyl cyclase. Science 268:1769-1772.

d. **Tang, W.-J.** & Gilman, A.G. (1991) Type-specific regulation of adenylyl cyclase by G protein βγ subunits. Science 254:1500-1503.

Complete List of Published Work in MyBibliography.