Stanford

Tom Wandless

Professor of Chemical and Systems Biology and, by courtesy, of Chemistry

CONTACT INFORMATION

- **Alternate Contact**

  Tom Wandless

  Email wandless@stanford.edu

  Tel 650-723-4005

Bio

ACADEMIC APPOINTMENTS

- Professor, Chemical and Systems Biology
- Professor (By courtesy), Chemistry
- Member, Bio-X
- Member, Stanford Cancer Institute
- Faculty Fellow, Stanford ChEM-H

HONORS AND AWARDS

- Excellence in Teaching Award, Stanford School of Medicine (2014)
- Senior Scholar Award in Aging, Ellison Medical Foundation (2010-2014)
- Nobel Laureate Signature Award for Graduate Education, American Chemical Society (2009)
- CAREER Award, NSF (2000-2004)
- Alfred P. Sloan Research Fellow, Sloan Foundation (2000)
- Camille Dreyfus Teacher-Scholar, Dreyfus Foundation (2000)
- Dean's Award for Distinguished Teaching, Stanford University (1999)
- Beckman Foundation Young Investigator, Arnold & Mabel Beckman Foundation (1998-2000)
- Phi Beta Kappa Undergraduate Teaching Prize, Stanford Phi Beta Kappa (1998)

PROFESSIONAL EDUCATION

- Ph.D., Harvard University , Chemistry (1993)
- B.S., Trinity University , Biochemistry (1988)

LINKS

- Wandless Lab Homepage: http://wandless.stanford.edu

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Overview – The lab concentrates on the invention of molecules and techniques that enable better studies of biological processes. In short, we invent tools for biology and we are motivated by approaches that enable entirely new experiments with unprecedented control. These new techniques may also provide a window into mechanisms that cells use to maintain protein homeostasis. Protein quality control is a particular interest at present.

New Approaches for Conditional Control of Protein Function – We have developed an experimental system in which the stability of a specific protein depends on the presence or absence of a cell-permeable molecule. We started with a well-studied protein-ligand pair: the FKBP12 protein and a high-affinity ligand we synthesized called Shield-1. We screened a library of FKBP sequences to identify mutants that are unstable in the absence of Shield-1 and are stabilized by Shield-1. Further characterization of these mutants revealed that the most destabilizing mutants caused a 50-fold to 100-fold reduction in the expression levels of the proteins to which they were fused. Importantly, this instability is transmitted to any fused partner protein, allowing us to regulate the stability of any protein-of-interest using Shield-1.

These reagents are called destabilizing domains (DDs), and we have developed a broad portfolio of these reagents based on several distinct protein-ligand combinations. Most of these reagents are available through Addgene. The systems work well in cultured mammalian cells, a variety of model organisms (e.g., flies, worms, frogs) and in living mice and rats. This technique allows rapid and reversible elimination of a specific protein in a variety of biological contexts. We have also engineered a DD system that functions in the opposite sense. The fusion protein is stable in the absence of the ligand, and administration of the ligand causes the fusion protein to be rapidly degraded. Similarly, we have engineered a conditional stability system where light is used to regulate protein stability. Most of these reagents have been reviewed recently (Rakhit et al., Chemistry & Biology 2014, 21, 1238).

Protein Quality Control in Cells – The DDs can be thought of as model substrates that have the potential to help us understand how cells detect and deal with misfolded or unfolded proteins. The ability to conditionally regulate the folding state of these domains using high-affinity ligands allows us to correlate specific biophysical properties with biological stability. One focus of the lab is understanding how these technologies work in cells. Using purified proteins we have shown that the DD proteins are either unfolded or significantly populate the unfolded state in the absence of the stabilizing ligand (Egeler et al., JBC 2011, 286, 31328). We have also used a focused RNAi strategy to identify proteins involved in the cellular response to the unfolded DDs (Chu et al., JBC 2013, 288, 34575).

More recently, we are using the DDs as conditionally folded proteins to create an acute unfolded protein stress by withdrawing the stabilizing ligand from the cell culture media. This approach allowed us to identify a novel coordinated transcriptional response that mammalian cells trigger when unfolded protein appears (Miyazaki et al., eLIFE 2015). Interestingly, there is little overlap between this new cellular response and the heat shock response, which conventional wisdom holds as the "cytosolic unfolded protein response". Additionally, creating unfolded DD in either the cytosol or nucleus elicits distinct responses, suggesting that mammalian cells maintain different protein quality control surveillance environments in these compartments. Understanding the molecular mechanisms behind these new cellular responses as well as how they help to maintain protein homeostasis is a major focus of the lab.

Teaching

COURSES

2018-19

- Chemistry of Biological Processes: CSB 220 (Spr)

2016-17

- Chemistry of Biological Processes: CSB 220 (Spr)

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Zachary Harvey, Alex Johnson, Jonathan Mares, Thomas Privalsky

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biophysics (Phd Program)
- Chemical and Systems Biology (Phd Program)

Publications

PUBLICATIONS

- **A Novel Destabilizing Domain Based on a Small-Molecule Dependent Fluorophore** *ACS CHEMICAL BIOLOGY*
  Navarro, R., Chen, L., Rakhit, R., Wandless, T. J.
  2016; 11 (8): 2101-2104
- **A method to rapidly create protein aggregates in living cells** *NATURE COMMUNICATIONS*
  Miyazaki, Y., Mizumoto, K., Dey, G., Kudo, T., Perrino, J., Chen, L., Meyer, T., Wandless, T. J.
  2016; 7
- **Distinct transcriptional responses elicited by unfolded nuclear or cytoplasmic protein in mammalian cells** *ELIFE*
  Miyazaki, Y., Chen, L., Chu, B. W., Swigut, T., Wandless, T. J.
  2015; 4
- **General method for regulating protein stability with light.** *ACS chemical biology*
  Bonger, K. M., Rakhit, R., Payumo, A. Y., Chen, J. K., Wandless, T. J.
  2014; 9 (1): 111-115
- **Inducible control of gene expression with destabilized Cre** *NATURE METHODS*
  Sando, R., Baumgaertel, K., Pieraut, S., Torabi-Rander, N., Wandless, T. J., Mayford, M., Maximov, A.
  2013; 10 (11)
- **Visualizing cellular interactions with a generalized proximity reporter.** *Proceedings of the National Academy of Sciences of the United States of America*
  Sellmyer, M. A., Bronsart, L., Imoto, H., Contag, C. H., Wandless, T. J., Prescher, J. A.
  2013; 110 (21): 8567-8572
- **Using light to shape chemical gradients for parallel and automated analysis of chemotaxis.** *Molecular systems biology*
  Collins, S. R., Yang, H. W., Bonger, K. M., Guignet, E. G., Wandless, T. J., Meyer, T.
  2015; 11 (4): 804-?
- **Chemical Biology Strategies for Posttranslational Control of Protein Function** *CHEMISTRY & BIOLOGY*
  Rakhit, R., Navarro, R., Wandless, T. J.
  2014; 21 (9): 1238-1252
- **The E3 ubiquitin ligase UBE3C enhances proteasome processivity by ubiquitinating partially proteolyzed substrates.** *journal of biological chemistry*
  Chu, B. W., Kovary, K. M., Guillaume, J., Chen, L., Teruel, M. N., Wandless, T. J.
  2013; 288 (48): 34575-34587
- **FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension.** *journal of clinical investigation*
  Spiekerkoetter, E., Tian, X., Cai, J., Hopper, R. K., Sudheendra, D., Li, C. G., El-Bizri, N., Sawada, H., Haghighat, R., Chan, R., Haghighat, L., de Jesus Perez, V., Wang, et al
  2013; 123 (8): 3600-3613
- **Par-4 Downregulation Promotes Breast Cancer Recurrence by Preventing Multinucleation following Targeted Therapy** *CANCER CELL*
  Alvarez, J. V., Pan, T., Ruth, J., Feng, Y., Zhou, A., Pant, D., Grimley, J. S., Wandless, T. J., DeMichele, A., Chodosh, L. A.
  2013; 24 (1): 30-44

- **Rapid and tunable control of protein stability in Caenorhabditis elegans using a small molecule.** *PloS one*
  Cho, U., Zimmerman, S. M., Chen, L., Owen, E., Kim, J. V., Kim, S. K., Wandless, T. J.
  2013; 8 (8)
- **Rapid and Tunable Control of Protein Stability in Caenorhabditis elegans Using a Small Molecule.** *PloS one*
  Cho, U., Zimmerman, S. M., Chen, L., Owen, E., Kim, J. V., Kim, S. K., Wandless, T. J.
  2013; 8 (8)
- **Networks of Polarized Actin Filaments in the Axon Initial Segment Provide a Mechanism for Sorting Axonal and Dendritic Proteins** *CELL REPORTS*
  Watanabe, K., Al-Bassam, S., Miyazaki, Y., Wandless, T. J., Webster, P., Arnold, D. B.
  2012; 2 (6): 1546-1553
- **Intracellular Context Affects Levels of a Chemically Dependent Destabilizing Domain** *PLOS ONE*
  Sellmyer, M. A., Chen, L., Egeler, E. L., Rakhit, R., Wandless, T. J.
  2012; 7 (9)
- **Differential Trafficking of Transport Vesicles Contributes to the Localization of Dendritic Proteins** *CELL REPORTS*
  Al-Bassam, S., Xu, M., Wandless, T. J., Arnold, D. B.
  2012; 2 (1): 89-100
- **Destabilizing Domains Derived from the Human Estrogen Receptor** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Miyazaki, Y., Imoto, H., Chen, L., Wandless, T. J.
  2012; 134 (9): 3942-3945
- **Imaging the Impact of Chemically Inducible Proteins on Cellular Dynamics In Vivo** *PLOS ONE*
  Leong, H. S., Lizardo, M. M., Ablack, A., McPherson, V. A., Wandless, T. J., Chambers, A. F., Lewis, J. D.
  2012; 7 (1)
- **Ligand-switchable Substrates for a Ubiquitin-Proteasome System** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Egeler, E. L., Urner, L. M., Rakhit, R., Liu, C. W., Wandless, T. J.
  2011; 286 (36): 31328-31336
- **Evaluation of FKBP and DHFR based destabilizing domains in Saccharomyces cerevisiae** *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*
  Rakhit, R., Edwards, S. R., Iwamoto, M., Wandless, T. J.
  2011; 21 (17): 4965-4968
- **Small-molecule displacement of a cryptic degron causes conditional protein degradation** *NATURE CHEMICAL BIOLOGY*
  Bonger, K. M., Chen, L., Liu, C. W., Wandless, T. J.
  2011; 7 (8): 531-537
- **Chemical Control of FGF-2 Release for Promoting Calvarial Healing with Adipose Stem Cells** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Kwan, M. D., Sellmyer, M. A., Quarto, N., Ho, A. M., Wandless, T. J., Longaker, M. T.
  2011; 286 (13): 11307-11313
- **Asparagine repeat function in a Plasmodium falciparum protein assessed via a regulatable fluorescent affinity tag** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Muralidharan, V., Oksman, A., Iwamoto, M., Wandless, T. J., Goldberg, D. E.
  2011; 108 (11): 4411-4416
- **A General Chemical Method to Regulate Protein Stability in the Mammalian Central Nervous System** *CHEMISTRY & BIOLOGY*
  Iwamoto, M., Bjorklund, T., Lundberg, C., Kirik, D., Wandless, T. J.
  2010; 17 (9): 981-988
- **A Plant-Like Kinase in Plasmodium falciparum Regulates Parasite Egress from Erythrocytes** *SCIENCE*
  Dvorin, J. D., Martyn, D. C., Patel, S. D., Grimley, J. S., Collins, C. R., Hopp, C. S., Bright, A. T., Westenberger, S., Winzeler, E., Blackman, M. J., Baker, D. A., Wandless, T. J., Duraisingh, et al
  2010; 328 (5980): 910-912
- **Dicistronic regulation of fluorescent proteins in the budding yeast Saccharomyces cerevisiae** *YEAST*
  Edwards, S. R., Wandless, T. J.

2010; 27 (4): 229-236

- **A general method for conditional regulation of protein stability in living animals.** *Cold Spring Harbor protocols*
  Sellmyer, M. A., Thorne, S. H., Banaszynski, L. A., Contag, C. H., Wandless, T. J.
  2009; 2009 (3): pdb prot5173-?
- **Regulating protein stability in mammalian cells using small molecules.** *Cold Spring Harbor protocols*
  Hagan, E. L., Banaszynski, L. A., Chen, L., Maynard-Smith, L. A., Wandless, T. J.
  2009; 2009 (3): pdb prot5172-?
- **The proteasome makes sense of mixed signals** *NATURE CHEMICAL BIOLOGY*
  Wandless, T. J.
  2009; 5 (1): 3-4
- **Recent progress with FKBP-derived destabilizing domains** *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*
  Chu, B. W., Banaszynski, L. A., Chen, L., Wandless, T. J.
  2008; 18 (22): 5941-5944
- **Chemical control of protein stability and function in living mice** *NATURE MEDICINE*
  Banaszynski, L. A., Sellmyer, M. A., Contag, C. H., Wandless, T. J., Thorne, S. H.
  2008; 14 (10): 1123-1127
- **Synthesis and analysis of stabilizing ligands for FKBP-derived destabilizing domains** *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*
  Grimley, J. S., Chen, D. A., Banaszynski, L. A., Wandless, T. J.
  2008; 18 (2): 759-761
- **Rapid control of protein level in the apicomplexan Toxoplasma gondii** *NATURE METHODS*
  Herm-Goetz, A., Agop-Nersesian, C., Muenter, S., Grimley, J. S., Wandless, T. J., Frischknecht, F., Meissner, M.
  2007; 4 (12): 1003-U8
- **A directed approach for engineering conditional protein stability using biologically silent small molecules** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Maynard-Smith, L. A., Chen, L., Banaszynski, L. A., Ooi, A. G., Wandless, T. J.
  2007; 282 (34): 24866-24872
- **Rescue of degradation-prone mutants of the FK506-rapamycin binding (FRB) protein with chemical ligands** *CHEMBIOCHEM*
  Stankunas, K., Bayle, J. H., Havranek, J. J., Wandless, T. J., Baker, D., Crabtree, G. R., Gestwicki, J. E.
  2007; 8 (10): 1162-1169
- **Engineering small molecule specificity in nearly identical cellular environments** *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*
  Sellmyer, M. A., Stankunas, K., Briesewitz, R., Crabtree, G. R., Wandless, T. J.
  2007; 17 (10): 2703-2705
- **The rapamycin-binding domain of the protein kinase mammalian target of rapamycin is a destabilizing domain** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Edwards, S. R., Wandless, T. J.
  2007; 282 (18): 13395-13401
- **SIK1 is a class IIHDAC kinase that promotes survival of skeletal myocytes** *NATURE MEDICINE*
  Berdeaux, R., Goebel, N., Banaszynski, L., Takemori, H., Wandless, T., Shelton, G. D., Montminy, M.
  2007; 13 (5): 597-603
- **The enantioselective synthesis of phomopsin b** *ANGEWANDTE CHEMIE-INTERNATIONAL EDITION*
  Grimley, J. S., Sawayama, A. M., Tanaka, H., Stohlmeyer, M. M., Woiwode, T. E., Wandless, T. J.
  2007; 46 (43): 8157-8159
- **PI(3,4,5)P-3 and PI(4,5)P-2 lipids target proteins with polybasic clusters to the plasma membrane** *SCIENCE*
  Heo, W. D., Inoue, T., Park, W. S., Kim, M. L., Park, B. O., Wandless, T. J., Meyer, T.
  2006; 314 (5804): 1458-1461
- **A rapid, reversible, and tunable method to regulate protein function in living cells using synthetic small molecules** *CELL*
  Banaszynski, L. A., Chen, L., Maynard-Smith, L. A., Ooi, A. G., Wandless, T. J.

2006; 126 (5): 995-1004

- **Rapamycin analogs with differential binding specificity permit orthogonal control of protein activity** *CHEMISTRY & BIOLOGY*
  Bayle, J. H., Grimley, J. S., Stankunas, K., Gestwicki, J. E., Wandless, T. J., Crabtree, G. R.
  2006; 13 (1): 99-107
- **Conditional control of protein function** *CHEMISTRY & BIOLOGY*
  Banaszynski, L. A., Wandless, T. J.
  2006; 13 (1): 11-21
- **A cell-permeable, activity-based probe for protein and lipid kinases** *JOURNAL OF BIOLOGICAL CHEMISTRY*
  Yee, M., Fas, S. C., Stohlmeyer, M. M., Wandless, T. J., Cimprich, K. A.
  2005; 280 (32): 29053-29059
- **An inducible translocation strategy to rapidly activate and inhibit small GTPase signaling pathways** *NATURE METHODS*
  Inoue, T., Do Heo, W., Grimley, J. S., Wandless, T. J., Meyer, T.
  2005; 2 (6): 415-418
- **Characterization of the FKBP.rapamycin.FRB ternary complex.** *Journal of the American Chemical Society*
  Banaszynski, L. A., Liu, C. W., Wandless, T. J.
  2005; 127 (13): 4715-4721
- **Characterization of the FKBP center dot Rapamycin center dot FRB ternary complex** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Banaszynski, L. A., Liu, C. W., Wandless, T. J.
  2005; 127 (13): 4715-4721
- **Total synthesis of ustiloxin D and considerations on the origin of selectivity of the asymmetric allylic alkylation** *JOURNAL OF ORGANIC CHEMISTRY*
  Sawayama, A. M., Tanaka, H., Wandless, T. J.
  2004; 69 (25): 8810-8820
- **Quantitative analyses of bifunctional molecules** *BIOCHEMISTRY*
  Braun, P. D., Wandless, T. J.
  2004; 43 (18): 5406-5413
- **Conditional protein alleles using knockin mice and a chemical inducer of dimerization** *MOLECULAR CELL*
  Stankunas, K., Bayle, J. H., Gestwicki, J. E., Lin, Y. M., Wandless, T. J., Crabtree, G. R.
  2003; 12 (6): 1615-1624
- **A bifunctional molecule that displays context-dependent cellular activity** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Braun, P. D., Barglow, K. T., Lin, Y. M., Akompong, T., Briesewitz, R., Ray, G. T., Haldar, K., Wandless, T. J.
  2003; 125 (25): 7575-7580
- **Enantioselective total synthesis of ustiloxin D** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Tanaka, H., Sawayama, A. M., Wandless, T. J.
  2003; 125 (23): 6864-6865
- **Calcineurin inhibitors and the generalization of the presenting protein strategy** *ADVANCES IN PROTEIN CHEMISTRY, VOL 56*
  Vogel, K. W., Briesewitz, R., Wandless, T. J., Crabtree, G. R.
  2001; 56: 253-?
- **Synthesis of flavonol derivatives as probes of biological processes** *TETRAHEDRON LETTERS*
  Tanaka, H., Stohlmeyer, M. M., Wandless, T. J., Taylor, L. P.
  2000; 41 (50): 9735-9739
- **Mechanistic studies of affinity modulation** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Rosen, M. K., Amos, C. D., Wandless, T. J.
  2000; 122 (48): 11979-11982
- **A confederacy of bunches: Fundamentals and applications of a self-associating protein** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Wandless, T. J.

2000; 97 (13): 6921-6923

- **Efficient synthesis of beta,gamma-dehydrovaline** *JOURNAL OF ORGANIC CHEMISTRY*
  Woiwode, T. F., Wandless, T. J.
  1999; 64 (20): 7670-7674

- **A stereospecific elimination to form dehydroamino acids: Synthesis of the phomopsin tripeptide side chain** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Stohlmeyer, M. M., Tanaka, H., Wandless, T. J.
  1999; 121 (25): 6100-6101

- **Affinity modulation of small-molecule ligands by borrowing endogenous protein surfaces** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Briesewitz, R., Ray, G. T., Wandless, T. J., Crabtree, G. R.
  1999; 96 (5): 1953-1958

- **A simple and efficient method for the preparation of hindered alkyl-aryl ethers** *JOURNAL OF ORGANIC CHEMISTRY*
  Woiwode, T. F., Rose, C., Wandless, T. J.
  1998; 63 (25): 9594-9596

- **INHIBITION OF T-CELL SIGNALING BY IMMUNOPHILIN LIGAND COMPLEXES CORRELATES WITH LOSS OF CALCINEURIN PHOSPHATASE-ACTIVITY** *BIOCHEMISTRY*
  Liu, J., Albers, M. W., Wandless, T. J., Luan, S., Alberg, D. G., Belshaw, P. J., Cohen, P., Mackintosh, C., Klee, C. B., Schreiber, S. L.
  1992; 31 (16): 3896-3901

- **MOLECULAR RECOGNITION OF IMMUNOPHILINS AND IMMUNOPHILIN-LIGAND COMPLEXES** *SYMP ON NEW DIRECTIONS IN ORGANIC SYNTHESIS, IN HONOR OF HARRY H WASSERMAN*
  Schreiber, S. L., Liu, J., Albers, M. W., Rosen, M. K., Standaert, R. F., Wandless, T. J., Somers, P. K.
  PERGAMON-ELSEVIER SCIENCE LTD.1992: 2545–58

- **IMMUNOPHILIN-LIGAND COMPLEXES AS PROBES OF INTRACELLULAR SIGNALING PATHWAYS** *TRANSPLANTATION PROCEEDINGS*
  Schreiber, S. L., Liu, J., Albers, M. W., Karmacharya, R., Koh, E., Martin, P. K., Rosen, M. K., Standaert, R. F., Wandless, T. J.
  1991; 23 (6): 2839-2844

- **SYNTHESIS AND ANALYSIS OF 506BD, A HIGH-AFFINITY LIGAND FOR THE IMMUNOPHILIN FKBP** *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*
  Somers, P. K., Wandless, T. J., Schreiber, S. L.
  1991; 113 (21): 8045-8056

- **SOLUTION STRUCTURE OF FKBP, A ROTAMASE ENZYME AND RECEPTOR FOR FK506 AND RAPAMYCIN** *SCIENCE*
  Michnick, S. W., Rosen, M. K., Wandless, T. J., Karplus, M., Schreiber, S. L.
  1991; 252 (5007): 836-839

- **PROBING IMMUNOSUPPRESSANT ACTION WITH A NONNATURAL IMMUNOPHILIN LIGAND** *SCIENCE*
  Bierer, B. E., Somers, P. K., Wandless, T. J., Burakoff, S. J., Schreiber, S. L.
  1990; 250 (4980): 556-559