BIOGRAPHICAL SKETCH

NAME: Wang, Shaomeng

POSITION TITLE: Warner-Lambert/Parke Davis Professor in Medicine; Professor of Medicine, Pharmacology and Medicinal Chemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University	BS	07/1986	Chemistry
Case Western Reserve University	PhD	10/1992	Chemistry
National Cancer Institute, NIH	Fellow	07/1996	Drug Design

A. Personal Statement

I have been working on the discovery and development of novel small-molecules therapeutics for more than 20 years. One area of my research has been focused on targeting protein-protein interactions which regulate apoptosis, including the PPIs between the anti-death Bcl-2 and pro-death Bcl-2 members, the MDM2-p53 PPI, and the PPI of IAP proteins with Smac. My research in targeting apoptosis has resulted in the discovery and advancement of 8 compounds into Phase I/II/III clinical development targeting Bcl-2/Bcl-xL, MDM2 and IAP proteins. In more recent years, I have expanded my research program to target a number of PPIs, which regulate epigenetics, including histone readers, writers and erasers, and have advanced several classes of compounds into advanced preclinical development. To accomplish our goals of discovering highly optimized compounds suitable for clinical development and rapidly advancing them into clinical development, I have established extensive collaborations with basic scientists, translational scientists and clinical investigators at UMCCC and in other institutions. I have co-founded five UM start-up companies to help us to bring our drugs into clinical development and marketplace. I have published 300+ peer-reviewed papers and an inventor of 60+ issued US patents and hundreds of international patents. I was elected as Fellow of the National Academy of Inventors in 2014 and as Fellow of the American Association for the Advancement of Science (AAAS) in 2019, was induced into Hall of Fame of the Division of Medicinal Chemistry of American Chemical Society in 2020. I was the 2014 University of Michigan Distinguished Innovator.
(H-index =94 with total citations = 30,801 by Google Scholar).

B. Positions and Employment

1992-1996 Postdoctoral fellow, National Cancer Institute, NIH, Bethesda, MD, USA
1996-2000 Assistant Professor, Georgetown University Medical Center, DC. USA
2000-2001 Associate Professor, Georgetown University Medical Center, DC. USA
2001-2006 Associate professor with tenure, Departments of Internal Medicine, Pharmacology and Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan.
2004-2019: Co-Director, Experimental Therapeutics program, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA
2006-present Professor with tenure, Departments of Internal Medicine, Pharmacology and Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan.
2007-present Warner-Lambert/Parke Davis Professor in Medicine, University of Michigan Medical School, Ann Arbor, Michigan
2007-present: Director, Cancer Drug Discovery program, University of Michigan, USA.
2015-present: Director, Michigan Center for Therapeutic Innovation
2012-2020: Editor-in-Chief, Journal of Medicinal Chemistry, American Chemical Society.

Recent Awards: The Division of Medicinal Chemistry Award of the American Chemical Society (2020). Hall of Fame of the Division of Medicinal Chemistry, the American Chemical Society (2020).

Fellow of the American Association for the Advancement of Science (AAAS, 2019).
University of Michigan Medical School Innovation and Commercialization Award (2017).
University of Michigan, Distinguished Innovator Award (2014).
Elected Fellow of the National Academy of Inventors (2014).
University of Maryland Grollman Lectureship (2013).

Contribution to Science

(1). Discovery of development of small-molecule antagonists of inhibitors of apoptosis proteins (IAPs) or Smac mimetics for the treatment of human cancer

Smac protein was discovered in 2001 as an endogenous cellular antagonist of inhibitors of apoptosis proteins (IAPs), which function as key apoptosis blockades. We proposed that small-molecules designed to mimic the interaction of Smac with IAPs may have a therapeutic potential for the treatment of human cancer and other diseases. Employing a powerful structure-based design approach, our lab was among the first to report the design of conformationally constrained Smac mimetics in 2004. Further extensive optimization has ultimately led to the discovery of SM-406 as a potent and orally active Smac mimetic as our clinical development candidate. SM-406 (renamed as Debiopharm 1143/xevinapant by our development partner) is currently in Phase III registration trial for the treatment of human cancer. Debiopharm has recently licensed xevinapant to Merck KGaA for further development and commercialization. Our lab has also designed bivalent Smac mimetics to mimic the natural dimeric form of Smac proteins and has advanced SM-1387 (renamed as APG-1387) into clinical development by our development partner Ascentage Pharma Group.

i) Sun H, Nikolovska-Coleska Z, Yang CY, Xu L, Liu M, Tomita Y, Pan H, Yoshioka Y, Krajewski K, Roller PP, ***Wang S****. Structure-based design of potent, conformationally constrained Smac mimetics. J Am Chem Soc. 2004 Dec 29;126(51):16686-7. PMID:15612682

ii) Sun H, Nikolovska-Coleska Z, Lu J, Meagher JL, Yang CY, Qiu S, Tomita Y, Ueda Y, Jiang S, Krajewski K, Roller PP, Stuckey JA, ***Wang S****. Design, synthesis, and characterization of a potent, nonpeptide, cellpermeable, bivalent Smac mimetic that concurrently targets both the BIR2 and BIR3 domains in XIAP. J Am Chem Soc. 2007 Dec 12;129(49):15279-94. PMID:17999504.

iii) Lu J, Bai L, Sun H, Nikolovska-Coleska Z, McEachern D, Qiu S, Miller RS, Yi H, Shangary S, Sun Y, Meagher JL, Stuckey JA, ***Wang S****. SM-164: a novel, bivalent Smac mimetic that induces apoptosis and tumor regression by concurrent removal of the blockade of cIAP-1/2 and XIAP. Cancer Res. 2008 Nov 15;68(22):9384-93. doi: 10.1158/0008-5472.CAN-08-2655.

iv) Cai Q, Sun H, Peng Y, Lu J, Nikolovska-Coleska Z, McEachern D, Liu L, Qiu S, Yang CY, Miller R, Yi H, Zhang T, Sun D, Kang S, Guo M, Leopold L, Yang D, **Wang S***. A potent and orally active antagonist (SM406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer *Sheng R, Sun H, Liu L, Lu J, McEachern D, Wang G, Wen J, Min P, Du Z, Lu H, Kang S, Guo M, Yang D, **Wang S***. A potent bivalent Smac mimetic (SM-1200) achieving rapid, complete, and durable tumor regression in mice. J Med Chem. 2013 May 23;56(10):3969-79. PMID:23651223*

(2). Discovery of development of small-molecule inhibitors and degraders to block the MDM2-p53 protein-protein interaction for cancer treatment

Our research has resulted in the discovery of MI-773 (renamed SAR405838 by our development partner) as a highly potent, selective and orally active MDM2 inhibitor for clinical development. We have also advanced a 2nd clinical candidate (AA-115, renamed as APG-115 by our development partner, Ascentage Pharma), now in Phase I clinical development.

i). Ding K, Lu Y, Nikolovska-Coleska Z, Qiu S, Ding Y, Gao W, Stuckey J, Krajewski K, Roller PP, Tomita Y, Parrish DA, Deschamps JR, ***Wang S****. Structure-based design of potent non-peptide MDM2 inhibitors. J Am Chem Soc. 2005 Jul 27;127(29):10130-1. PMID: 16028899.

ii). Shangary S, Qin D, McEachern D, Liu M, Miller RS, Qiu S, Nikolovska-Coleska Z, Ding K, Wang G, Chen J, Bernard D, Zhang J, Lu Y, Gu Q, Shah RB, Pienta KJ, Ling X, Kang S, Guo M, Sun Y, Yang D, Wang S. Temporal activation of p53 by a specific MDM2 inhibitor is selectively toxic to tumors and leads to complete tumor growth inhibition. Proc Natl Acad Sci U S A. 2008 Mar 11;105(10):3933-8. PMID:8316739

iii). Zhao Y, Liu L, Sun W, Lu J, McEachern D, Li X, Yu S, Bernard D, Ochsenbein P, Ferey V, Carry JC, Deschamps JR, Sun D, ***Wang S****. Diastereomeric spirooxindoles as highly potent and efficacious MDM2 inhibitors. J Am Chem Soc. 2013 May 15;135(19):7223-34. PMID:23641733

iv). **Wang S***, Sun W, Zhao Y, McEachern D, Meaux I, Barrière C, Stuckey JA, Meagher JL, Bai L, Liu L, Hoffman-Luca CG, Lu J, Shangary S, Yu S, Bernard D, Aguilar A, Dos-Santos O, Besret L, Guerif S, Pannier P, Gorge-Bernat D, Debussche L. SAR405838: an optimized inhibitor of MDM2-p53 interaction that induces complete and durable tumor regression. Cancer Res. 2014 Oct 15;74(20):5855-65.

v). Aguilar A, Lu J, Liu L, Du D, Bernard D, McEachern D, Przybranowski S, Li X, Luo R, Wen B, Sun D, Wang H, Wen J, Wang G, Zhai Y, Guo M, Yang D, **Wang S***. Discovery of 4-((3'R,4'S,5'R)-6″-Chloro-4'-(3-chloro-2-fluorophenyl)-1'-ethyl-2″-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3″-indoline]-5'-carboxamido)bicyclo[2.2.2]octane-1-carboxylic Acid (AA-115/APG-115): A Potent and Orally Active Murine Double Minute 2 (MDM2) Inhibitor in Clinical Development. J Med Chem. 2017 Apr 13;60(7):2819-2839. doi: 10.1021/acs.jmedchem.6b01665. Epub 2017 Mar 24. PMID: 28339198

(3). Discovery of development of small-molecule inhibitors to block the anti-death and pro-death Bcl-2 protein-protein interactions for the treatment of human cancer

Using a structure-based de novo design approach, we have designed and optimized highly potent and selective small-molecule inhibitors of Bcl-2, and/or Bcl-xL. We have advanced BM-1252, a highly potent Bcl-2 and Bcl-xL dual inhibitor (renamed APG-1252 by our development partner) into Phase I clinical development. BM-1252 is probably the most potent and efficacious Bcl-2 and Bcl-xL inhibitor discovered to date. Using a prodrug strategy, we have also dramatically reduced the platelet toxicity, as seen with other Bcl-xL inhibitors such as ABT-737 and ABT-263. We have also advanced BM-2575, a highly potent and selective Bcl-2 inhibitor into IND-enabling studies.

i). Wang G, Nikolovska-Coleska Z, Yang CY, Wang R, Tang G, Guo J, Shangary S, Qiu S, Gao W, Yang D, Meagher J, Stuckey J, Krajewski K, Jiang S, Roller PP, Abaan HO, Tomita Y, **Wang S***. Structure-based design of potent small-molecule inhibitors of anti-apoptotic Bcl-2 proteins. J Med Chem. 2006 Oct 19;49(21):6139-42. PMID:17034116

ii). Zhou H, Chen J, Meagher JL, Yang CY, Aguilar A, Liu L, Bai L, Cong X, Cai Q, Fang X, Stuckey JA, Wang S. Design of Bcl-2 and Bcl-xL inhibitors with subnanomolar binding affinities based upon a new scaffold. J Med Chem. 2012 May 24;55(10):4664-82. PMID: 22448988

iii). Chen J, Zhou H, Aguilar A, Liu L, Bai L, McEachern D, Yang CY, Meagher JL, Stuckey JA, Wang S. Structure-based discovery of BM-957 as a potent small-molecule inhibitor of Bcl-2 and Bcl-xL capable of achieving complete tumor regression. J Med Chem. 2012 Oct 11;55(19):8502-14. PMID:23030453

iv). Aguilar A, Zhou H, Chen J, Liu L, Bai L, McEachern D, Yang CY, Meagher J, Stuckey J, **Wang S***. A potent and highly efficacious Bcl-2/Bcl-xL inhibitor. *J Med Chem*. 2013;56(7):3048-67. PMCID: PMC3806060.

(4). Discovery of development of small-molecule inhibitors to block the WDR5-MLL1 protein-protein interaction for the treatment of acute leukemia carrying MLL1 fusion protein

MLL1 (mixed lineage leukemia 1) is a histone methyltransferase (H3K4) and is frequently misregulated in acute human leukemia. We have hypothesized that targeting MLL1 is a potentially promising approach for the treatment of acute leukemia carrying MLL1 translocations. In close collaboration with Dr. Yali Dou's laboratory, we are the first to report the design and discovery of a class of highly potent and cell-permeable peptidomimetics to target the WDR5-MLL1 PPI and have performed critical proof-of-concept studies. Our research has laid the foundation for the development of a new class of therapy for the treatment of acute leukemia.

i). Karatas H, Townsend EC, Cao F, Chen Y, Bernard D, Liu L, Lei M, Dou Y, **Wang S***. High-affinity, smallmolecule peptidomimetic inhibitors of MLL1/WDR5 protein-protein interaction. *J Am Chem Soc*. 2013;135(2):669-82.

ii). Cao F, Townsend EC, Karatas H, Xu J, Li L, Lee S, Liu L, Chen Y, Ouillette P, Zhu J, Hess JL, Atadja P, Lei M, Qin ZS, Malek S, **Wang S***, Dou Y. Targeting MLL1 H3K4 methyltransferase activity in mixedlineage leukemia. *Mol Cell*. 2014;53(2):247-61. PMCID: PMC3965208.

iii). Karatas H, Li Y, Liu L, Ji J, Lee S, Chen Y, Yang J, Huang L, Bernard D, Xu J, Townsend EC, Cao F, Ran X, Li X, Wen B, Sun D, Stuckey JA, Lei M, Dou Y, **Wang S***. Discovery of a Highly Potent, Cell-Permeable Macrocyclic Peptidomimetic (MM-589) Targeting the WD Repeat Domain 5 Protein (WDR5)-Mixed Lineage

Leukemia (MLL) Protein-Protein Interaction. J Med Chem. 2017 Jun 22;60(12):4818-4839. doi: 10.1021/acs.jmedchem.6b01796. Epub 2017 Jun 12.

(5). Discovery and Development of Small-Molecule PROTAC Degraders

In recent years, our laboratory has discovered small-molecule degraders designed based upon the PROTAC concept. In particular, we have discovered small-molecule PROTAC degraders against the BET proteins, MDM2 protein, androgen receptor (AR), estrogen receptor (ER) and STAT3, among others.

i) Zhou B, Hu J, Xu F, Chen Z, Bai L, Fernandez-Salas E, Lin M, Liu L, Yang CY, Zhao Y, McEachern D, Przybranowski S, Wen B, Sun D, **Wang S***. Discovery of a Small-Molecule Degrader of Bromodomain and Extra-Terminal (BET) Proteins with Picomolar Cellular Potencies and Capable of Achieving Tumor Regression. J Med Chem. 2017 Mar 24. doi: 10.1021/acs.jmedchem.6b01816. [Epub ahead of print] PMID: 28339196

ii) Bai L, Zhou B, Yang CY, Ji J, McEachern D, Przybranowski S, Jiang H, Hu J, Xu F, Zhao Y, Liu L, Fernandez-Salas E, Xu J, Dou Y, Wen B, Sun D, Meagher J, Stuckey J, Hayes DF, Li S, Ellis MJ, **Wang S***. Targeted Degradation of BET Proteins in Triple-Negative Breast Cancer. Cancer Res. 2017 May 1;77(9):2476-2487. doi: 10.1158/0008-5472.CAN-16-2622. Epub 2017 Feb 16. PMID: 28209615

iii) Li Y, Yang J, Aguilar A, McEachern D, Przybranowski S, Liu L, Yang CY, Wang M, Han X, **Wang S***. Discovery of MD-224 as a First-in-Class, Highly Potent, and Efficacious Proteolysis Targeting Chimera Murine Double Minute 2 Degrader Capable of Achieving Complete and Durable Tumor Regression. J Med Chem. 2019 Jan 24;62(2):448-466. doi: 10.1021/acs.jmedchem.8b00909. Epub 2018 Dec 10.

iv) Han X, Wang C, Qin C, Xiang W, Fernandez-Salas E, Yang CY, Wang M, Zhao L, Xu T, Chinnaswamy K, Delproposto J, Stuckey J, **Wang S***. Discovery of ARD-69 as a Highly Potent Proteolysis Targeting Chimera (PROTAC) Degrader of Androgen Receptor (AR) for the Treatment of Prostate Cancer. J Med Chem. 2019 Jan 24;62(2):941-964. doi: 10.1021/acs.jmedchem.8b01631. Epub 2019 Jan 10.

v) Bai L, Zhou H, Xu R, Zhao Y, Chinnaswamy K, McEachern D, Chen J, Yang CY, Liu Z, Wang M, Liu L, Jiang H, Wen B, Kumar P, Meagher JL, Sun D, Stuckey JA, **Wang S***. A Potent and Selective Small-Molecule Degrader of STAT3 Achieves Complete Tumor Regression In Vivo. Cancer Cell. 2019 Nov 11;36(5):498-511.e17. doi: 10.1016/j.ccell.2019.10.002. PMID: 31715132

C. Research Support (partial list)

1R01 CA208267 (Shaomeng Wang, PI) 04/01/18 - 03/31/23
Targeting the menin-MLL1 complex for new therapeutics
This research project aims at the design, synthesis and development of small-molecule inhibitors of the menin-MLL complex for the treatment of acute leukemia.

1R01CA219345 (Shaomeng Wang, PI) 08/01/17 - 07/31/22
Small-molecule MDM2 degraders
This research project aims at the design, synthesis and development of small-molecule degraders of MDM2 protein for the treatment of acute leukemia

1R01CA215758 (Shaomeng Wang, PI) 04/01/17 - 03/31/22
Small-molecule degraders of BET proteins
This research project aims at the design, synthesis and development of small-molecule degraders of BET bromodomain proteins for the treatment of human breast cancer.

1R01CA244509 (Shaomeng Wang, PI) 12/6/2019-11/30/2024
Small-molecule STAT3 degraders
This project has the goal to discover and develop small-molecule degraders of STAT3 for the treatment of human cancer.

P50 CA186786 (Overall PI: Chinnaiyan), Project 3 Leader: Shaomeng Wang) 09/03/19 - 08/31/24
SPORE in Prostate Cancer
Project 3: EXPLORING ABLATION OF THE ANDROGEN RECEPTOR AS A THERAPEUTIC APPROACH FOR CASTRATION-RESISTANT PROSTATE CANCER