## BIOGRAPHICAL SKETCH

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NAME: Wei Li

eRA COMMONS USER NAME (credential, e.g., agency login): Weili2

POSITION TITLE: UTHSC Distinguished Professor and Director of UTCoP Drug Discovery Center
Founder and CSO, SEAK Therapeutics, LLC

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 |
|---|---|---|---|
| University of Science and Technology of China | B.S. | 07/1992 | Chemistry |
| Columbia University in the City of New York | Ph.D. | 07/1999 | Chemistry |

**A. Personal Statement:**

A chemist by training, I have developed significant expertise in chemical biology and small molecule anti-cancer drug discovery over the past 25 years. My lab is equipped with software for computer-aided drug design, equipment for medicinal chemistry studies, complete cell culture labs, and equipment for biological investigations of drug actions. I have developed several approved animal protocols for pharmacokinetics (PK),*in vivo* efficacy, and toxicity studies.

We discovered a new generation of tubulin inhibitors targeting the colchicine-binding site, represented by the current investigational new drug **Sabizabulin** (earlier names as VERU-111 or ABI-231, originally invented in my lab). The VERU-111 scaffold has been comprehensively patented (WO2011/109059 and WO2012/027481) and licensed to Veru Inc. for commercial development. Sabizabulin has completed multiple advanced clinical trials. These clinical trials showed that Sabizabulin is well-tolerated and has promising clinical efficacy and good safety profiles. I also founded a startup company in 2018, SEAK Therapeutics LLC, to develop a potentially more effective therapy for epilepsy.

I have been working with Dr. Yue for several years, and we have jointly published several peer-reviewed papers as exemplified below. Specific to this project, we modified the structure of the best reported ASAP1 antagonist, UCS15A, with the goal to generate a more metabolically stable, less toxic analog for *in vivo* efficacy studies. This effort led to the synthesis of HL142 which is well tolerated in mice and shows good *in vivo* efficacy as described in the preliminary studies. Working with Dr. Yue and the other team members, we will scale up the synthesis of HL142 to support the proposed mechanistic work and perform highly focused structural modifications to the HL142 scaffold to generate more drug-like analogs for proof-of-concept evaluations. As an experienced medicinal chemist, I am committed to working with Dr. Yue and the rest of the team members to complete this project efficiently and successfully.

The following examples demonstrate the productive collaboration between mine and Dr. Yue's lab:


1. Lin Z, Marepally SR, Ma D, Myers LK, Postlethwaite AE, Tuckey RC, Cheng CY, Kim TK, **Yue J**, Slominski AT, Miller DD, **Li W**. "Chemical Synthesis and Biological Activities of 20S,24S/R-Dihydroxyvitamin D3 Epimers and Their 1alpha-Hydroxyl Derivatives". J Med Chem. **2015**;58:7881-7887. PubMed PMID: 26367019; PMCID: PMC4613797.
2. Wang B, Li X, Zhao G, Yan H, Dong P, Watari H, Sims M, **Li W**, Pfeffer LM, Guo Y, **Yue J**. "miR-203 inhibits ovarian tumor metastasis by targeting BIRC5 and attenuating the TGFbeta pathway". J Exp Clin Cancer Res. **2018**;37:235. PubMed PMID: 30241553; PMCID: PMC6150978.
3. Zhang P, Zhao G, Ji L, Yin J, Lu L, **Li W**, Zhou G, Chaum E, **Yue J**. "Knockdown of survivin results in inhibition of epithelial to mesenchymal transition in retinal pigment epithelial cells by attenuating the

TGFbeta pathway". Biochem Biophys Res Commun. **2018**;498:573-578. PubMed PMID: 29522718; PMCID: PMC5920696.

4. Guo H, **Zhang W**, Wang J, Zhao G, Wang Y, Zhu BM, Dong P, Watari H, Wang B, **Li W**, Tigyi G, and **Yue J**. Cryptotanshinone inhibits ovarian tumor growth and metastasis by degrading cMyc and attenuating the FAK pathway. Front Cell Dev Biol. **2022**. doi: 10.3389/fcell.2022.959518.

**Currently Ongoing Projects:**

PI: R01CA276152 (NIH/NCI) Seagroves (MPI) 4/2023-3/2028
Targeting brain and bone metastases in metastatic breast cancer for improved patient survival.

PI: R01CA148706 (NIH/NCI) Miller (MPI) 1/2011-6/2026
Targeting the colchicine site in tubulin for cancer therapy.

PI: R01CA240447 (NIH/NCI) Zhou (MPI) 7/2020-6/2025
Dual inhibition of MDM2 and XIAP as a therapeutic strategy in cancer.

PI: HT9425-23-1-0216 (DoD) 7/2023-6/2027
Development of an orally available and low-toxic chemotherapy for improved ovarian cancer therapy.

MPI: RF1AG072703 (NIH/NIA) Liao (contact PI); Bhaskar (MPI) 4/2022-3/2025
Validation of a novel tau clearance mechanism.

MPI: R61/R33NS124923 (NIH/NINDS) Jiang (contact PI) 12/2021-11/2024
Targeting TRPC3 channels for epileptic seizures.

PI: R41NS135658 (NIH/NINDS) 9/2023-8/2024
Developing a selective TRPC3 ion channel inhibitor for epilepsy treatment

Co-I: R01CA276135-01A1 (NIH/NCI) Zhou (PI) 12/2023-11/2028
Discovery of a novel MDM2-tubulin signaling pathway as a therapeutic target in AML.

Co-I: R01NS128336 (NIH/NINDS) Ram Mahato (PI) 7/2022-5/2027
Lipid nanomedicine targeting multiple signaling pathways of medulloblastoma.

Co-I: R41AG082524 (NIH/NIA) Darryl Quarles (PI) 9/2023-8/2024
Optimizing small molecule mechanomimetics to treat age-related osteoporosis.

**B. Positions and Honors**

**Positions and Employment**

| | |
|---|---|
| 2024-present | Co-leader, Chemical Biology Program, UTHSC Center for Cancer Research |
| 2023-present | Executive Committee member, University of Tennessee Research Foundation |
| 2022-present | Executive Committee member (2022-present); Secretary/Treasurer (elected for the 2024-2026 term), Division for Drug Discovery and Development, ASPET |
| 2020-present | UTHSC Distinguished Professor |
| 2018-present | Founder and CSO, SEAK Therapeutics LLC |
| 2017-present | Director, UTHSC College of Pharmacy Drug Discovery Center, UTHSC |
| 2016-present | Vice President and Executive Committee Member, MALTO Medicinal Chemistry. |
| 2015-present | Member of American Society for Pharmacology and Experimental Therapeutics (ASPET) |
| 2015-2017 | Secretary and Exec Committee Member, American Chemical Society Memphis Section |
| 2014-2020 | Professor and Faculty Director of Shared Instrument Facility, UTHSC, Memphis, TN |
| 2009-2014 | Associate Professor with tenure, UTHSC, Memphis, TN |
| 2004-present | Member of the American Association for Cancer Research (AACR) |
| 2004-2009 | Tenure track Assistant Professor, UTHSC, Memphis, TN |
| 2001-2004 | Non-tenure track Assistant Professor, UTHSC, Memphis, TN |
| 1999-2001 | Instructor, University of Tennessee Health Science Center, Memphis, TN |
| 1998-present | Member of American Chemical Society (ACS) |
| 1994-1999 | Graduate Research Assistant, Department of Chemistry, Columbia University, New York. |
| 1992-1994 | Research Assistant, Dalian Inst. of Chem. Phys., the Chinese Academy of Sciences, China. |
| 1987-1992 | Undergraduate Research, University of Science and Technology of China, China |

**Honors**

| | |
|---|---|
| 2022 | Memphis Business Journal Health Care Hero Award |
| 2015 | Outstanding Alumni Lecturer, Dalian Inst. of Chem. Phys., the Chinese Academy of Sciences |
| 2012, 2014 | Research Award, University of Tennessee Research Foundation |
| 2010, 2014 | University of Tennessee Research Foundation Innovation Awards |
| 1986 | First Prize in National Young Chemist Competition for Chemistry Olympia, China |

**Journal and Grant Reviewer**

Journal reviewer: Journal of American Chemical Society; Bioorganic Chemistry; Bioorganic Medicinal Chemistry Letters; Bioorganic Medicinal Chemistry; The Open Magnetic Resonance Journal; Molecular Diversity; European Journal of Medicinal Chemistry; Journal of Medicinal Chemistry; International Journal of Nanomedicine; PLoS One; Anti-cancer Agents in Medicinal Chemistry; Royal Society of Chemistry Journals; Medicinal Research Reviews; Molecule Cancer Therapeutics; Cancer Research; Oncotarget; Scientific Reports; Molecular Cancer Research; Chemical Sciences; PNAS; Nature.

Grant reviewer: NIH (2011/07: ZRG1 BCMB-U 30; 2012/03: ZRG1 BCMB-R 30; 2012/07: BCMB I; 2012/11: NCI SBIR/STTR; 2014/03: NCI SBIR/STTR; 2014/07: NCI SBIR/STTR; 2015/03: NCI SBIR/STTR; 2015/06: NCI SBIR/STTR; 2015/12: NCI SBIR/STTR; 2016/01: NCI ZRG1 OTC-Y (02) M; 2016/03: NCI SBIR/STTR; 2016/09: NCI ZRG-OTC K(04); 2016/11: NCI SBIR/STTR; 2016/12: NCI SBIR/STTR; 2017/03: NCI SBIR/STTR; 2017/10: ZRG1 BCMB-D; 2017/10: ZRG1 BCMB-N; 2018/03, NCI SBIR/STTR; 2018/07, ZRG1 IDM-C(50)R; 2018/11, NCI SBIR/STTR; 2019/10-12, NIH, ZRG1-MOSS-R70, NIH Director's DP2 Award-2020; 2020/03, NCI, OTC-T SBIR/STTR; 2020/10-12, NIH Director's DP2 Award-2021; 2021/10, EBIT; 2021/10-12, NIH Director's DP2 Award-2022; 2022/06, NCI CDDT SBIR/STTR; 2022/11, NCI CDDT SBIR/STTR; 2023/09, NCI SPORE (P50)); 2024/07, NCI CDPT SBIR/STTR.

American Chemical Society; Human Frontier Science Program; National Science Foundation; Florida Department of Health; Estonian Science Foundation; US Army. Oklahoma Center for the Advancement of Science & Technology (OCAST); Czech Science Foundation; Health Research Council of New Zealand; The Cancer Society of New Zealand; Prostate Cancer UK; French National Cancer Institute (INCa).

**Editorial Appointment:**

Guest editor, *Pharmaceutical Research*, Theme Issue on drugs targeting tubulin inhibitors, Vol 29, 2012.
Guest editor, *Molecules*, Theme issue on Tubulin Inhibitors, 2017. Special Issue on Tubulin Inhibitors, 2020; Special Issue to honor Dr. Duane Miller, 2020.
Guest editor, *Acta Pharmaceutica Sinica B*, Theme Issue on drug targeting and resistance, 2018.
Guest editor, *Frontiers in Pharmacology*, 2023. A special issue on drug resistance.
Editorial Board and Section Editor (Anti-Cancer Agent section): *Current Medicinal Chemistry*, 2014-2024.
Editorial Board member, *Acta Pharmaceutica Sinica B*, 2016-2020; *Molecules*, 2018-present; *Genes & Diseases*, 2018-present; *Cancer Letters*, 2020-present.

**C. Contribution to Science (208 peer-reviewed papers, 14 issued US patents and 6 book chapters)**

1. **Determine effects of confined environments on photochemical reactions.** When I was a graduate student at the chemistry department of Columbia University working under the direction of Professor Nick Turro, I contributed to elucidate the effects of confined environments on photochemical reactions.

   a. **Wei Li**, Xuegong Lei, George Lem, Ann McDermott, Nicholas J. Turro, Nils Bottke and Waldemar Adam, "Oxygen and structural effect on silicalite $^{29}$Si spin-lattice relaxation studied by high resolution $^{29}$Si solid state NMR", **Chem. Mater.**, 12, 731-737 (**2000**).

   b. Nicholas J. Turro, Xue-Gong Lei, **Wei Li**, Zhiqiang Liu, and M. Francesca Ottaviani, "Adsorption of Cyclic Ketones on the External and Internal Surfaces of a Faujasite Zeolite (CaX). A Solid-State $^{2}$H NMR, $^{13}$C NMR, FT-IR, and EPR Investigation", **J. Am. Chem. Soc.**, 122, 12571-12581 (**2000**).

   c. Takashi Hirano, **Wei Li**, Lloyd Abrams, Paul J. Krusic, M. Francesca Ottaviani and N. J. Turro, "Reversible Oxygenation of a Diphenylmethyl Radical Rendered Supramolecularly Persistent" **J. Am. Chem. Soc**.,121, 7170-7171 (**1999**).

   d. Nicholas J. Turro, Ann McDermott, Xuegong Lei, **Wei Li**, Lloyd Abrams, M. Francesca Ottaviani, Hege Stogard Beard, Kendall N. Houk, Brett R. Beno and Patrick S. Lee, "Photochemistry of ketones adsorbed on size/shape selective zeolites. A superamolecular approach to persistent carbon centered radicals", **Chem. Commun**., 697-698 (**1998**).

**2. Discovery of non-calcemic vitamin D analogs for autoimmune diseases**. Another area I have been working on is to develop tissue selective, non-hypercalcemic vitamin D analogs as potential anti-inflammatory or cancer prevention agents. My initial contributions were the elucidation of structures for a large number of novel vitamin D metabolites by P450scc enzymes. Subsequently, we designed strategies to stereo-specifically synthesize biologically active metabolites identified. We have also been working to synthesize new analogs to further improve their drug-like properties without causing hypercalcemia at doses well above potential therapeutic doses.

a. Zongtao Lin, Srinivasa Reddy Marepally, Dejian Ma, Linda K. Myers, Arnie E. Postlethwaite, Robert C. Tuckey, Tae-Kang Kim, Junming Yue, Andrzej T. Slominski, Duane D. Miller, **Wei Li**, "Chemical synthesis and biological activities of 20S,24S/R-dihydroxyvitamin D3 epimers and their 1α-hydroxyl derivatives", **J. Med. Chem.**, 58(19):7881-7887, (**2015)**. PMID: 26367019 PMCID: PMC4613797

b. Zongtao Lin, Srinivasa R. Marepally, Dejian Ma, Tae-Kang Kim, Allen SW. Oak, Linda K. Myers, Robert C. Tuckey, Andrzej T. Slominski, Duane D. Miller, **Wei Li**, "Synthesis and Biological Evaluation of the Active Vitamin D3 Metabo-lite 20S,23S-Dihydroxyvitamin D3 and Its 23R Epimer", **J. Med. Chem.**, 59 (10): 5102–5108, (**2016)**. PMID: 27070779, PMCID: PMC5330258.

c. Zongtao Lin, Hao Chen, Anna Y. Belorusova, John C. Bollinger, Edith K.Y. Tang, Zorica Janjetovic, Tae-Kang Kim, Zhongzhi Wu, Duane D. Miller, Andrzej T. Slominski, Arnold E. Postlethwaite, Robert C. Tuckey, Natacha Rochel, and **Wei Li**, "1α,20S-Dihydroxyvitamin D3 Interacts with Vitamin D Receptor: Crystal Structure and Route of Chemical Synthesis", **Sci. Rep.**, 7:10193, (**2017).** PMID: 28860545 PMCID: PMC5579064.

d. Lin Z, Marepally SR, Goh ESY, Cheng CYS, Janjetovic Z, Kim TK, Miller DD, Postlethwaite AE, Slominski AT, Tuckey RC, Peluso-Iltis C, Rochel N, **Li W**, "Investigation of 20S-hydroxyvitamin D3 analogs and their 1α-OH derivatives as potent vitamin D receptor agonists with anti-inflammatory activities", **Sci. Rep**., 8:1478, (**2018**). PMID: 29367669 PMCID: PMC5784132.

**3. Discovery and development of a new generation of tubulin inhibitors for cancer therapy.** Starting from my independent academic career in 2004, I have worked towards the goal of developing a useful therapeutic agent. One major area that I have been working on is to develop a new generation of orally bioavailable tubulin inhibitors. In the past 10+ years, we have discovered novel series of orally bioavailable tubulin inhibitors targeting the colchicine binding site and their targeted delivery to tumor cells. We have obtained high-resolution crystal structures of tubulin protein with more than 20 of our potent compounds and deposited the structures to the PDB databank (examples of PDBs deposited: 5H7O, 6BR1, 6BRF, 6BRY, 6BS2, 6C47, 6C4B, 6C7U, and 6D88). I have been serving as the primary investigator in these studies.

a. Kinsie Arnst, Yuxi Wang, Dong-Jin Hwang, Yi Xue, Terry Costello, David Hamilton, Qiang Chen, Jinliang Yang, Frank Park, James T. Dalton, Duane D. Miller, and **Wei Li**, "A potent, metabolically stable tubulin inhibitor targets the colchicine binding site and overcomes paclitaxel drug resistance",**Cancer Res**, 78(1):265-277, **(2018)**. PMID: 29180476.

b. Hao Chen, Shanshan Deng, Yuxi Wang, Najah Albadari, Gyanendra Kumar, Dejian Ma, Weimin Li, Stephen W. White, Duane D. Miller, and **Wei Li**, "Structure Activity Relationships Study of Novel 6 Aryl-2-Benzoyl-Pyridines as Tubulin Polymerization Inhibitors with Potent Antiproliferative Properties", **J Med Chem,** 63(2):827-846**, (2020),** PMID: 31860298.

c. Deng S, Banerjee S, Chen H, Pochampally S, Wang Y, Yun MK, White SW, Parmar K, Meibohm B, Hartman KL, Wu Z, Miller DD, **Li W**, "SB226, an inhibitor of tubulin polymerization, inhibits paclitaxel-resistant melanoma growth and spontaneous metastasis", **Cancer Letters,** 555:216046 (**2023**), PMID: 36596380 PMCID: PMC10321023.

d. **Issued US Patents related to this area of contributions:** Compounds for treatment of cancer, US 8,592,465, issued on 11/26/2013; US 8,822,513, issued on 9/2/2014; US 9,029,408, issued on 5/12/2015; US 9,334,242, issued on 5/10/2016; US 9,447,049, issued on 9/20/2016; US 9,981,915, issued on 5/29/2018; US 10,022,356, issued on 7/17/2018; US 10,155,728, issued on 12/18/2018; US 10,301,285, issued on 5/28/2019; US 10,525,037, issued on 1/7/2020; US 10,865,196, issued on 12/15/2020; US 11,084,811, issued on 8/10/2021; US 11,465,987, issued on 10/11/2022.

**4. Discovery of small molecule selective TRP ion channel inhibitors**. My lab recently discovered a unique

scaffoldfor selective TRPC3 ion channel inhibition. TRPC3 has been reported to involve in a number of disease indications, including neurological diseases such as epilepsy, neurodegenerative diseases such as Alzheimer's Diseases, and cardiovascular diseases such as hypertensions.

a. Zhang S, Romero LO, Deng S, Wang J, Li Y, Yang L, Hamilton DJ, Miller DD, Liao FF, Cordero-Morales JF, Wu Z, **Li W**. Discovery of a Highly Selective and Potent TRPC3 Inhibitor with High Metabolic Stability and Low Toxicity. **ACS Med Chem Lett. 2021**;12(4):572-8. PubMed PMID: 33859797; PMCID: PMC8040052.
b. Nagib MM, Zhang S, Yasmen N, Li L, Hou R, Yu Y, Boda VK, Wu Z, **Li W**, Jiang J. Inhibition of TRPC3 channels by a novel pyrazole compound confers antiseizure effects. **Epilepsia**. **2022**;63(4):1003-15. PubMed PMID: 35179226; PMCID: PMC9007831.
c. Yu Y, **Li W**, Jiang J. TRPC channels as emerging targets for seizure disorders. **Trends Pharmacol Sci**. **2022**;43(9):787-98. PubMed PMID: 35840362; PMCID: PMC9378536.
d. Vijay K. Boda, Nelufar Yasmen, Jianxiong Jiang* and **Wei Li**, "Pathophysiological significance and modulation of the transient receptor potential canonical 3 ion channel", **Medicinal Research Reviews**, accepted on 4/23/2024.

**5. Collaboration with researchers in other biomedical fields using expertise in chemistry**. I have also contributed to other projects using my expertise in analytical chemistry and medicinal chemistry. These efforts have resulted in joint papers in various biomedical research fields outside my own research focus.

a. Wang B, Liu Y, Huang L, Chen J, Li JJ, Wang R, Kim E, Chen Y, Justicia C, Sakata K, Chen H, Planas A, Ostrom RS, **Li W,** Yang G, McDonald MP, Chen R, Heck DH, Liao FF. A CNS-permeable Hsp90 inhibitor rescues synaptic dysfunction and memory loss in APP-overexpressing Alzheimer's mouse model via an HSF1-mediated mechanism. **Mol Psychiatry**, 22:990-1001, **(2017)**. PMID: 27457810, PMCID: PMC5323357
b. Zhousheng Xiao, Jerome Baudry, Li Cao, Jinsong Huang, Hao Chen, Charles R. Yates, **Wei Li**, Christopher M. Waters, Jeremy C. Smith, L. Darryl Quarles, "Polycystin-1 interacts with TAZ to stimulate osteoblastogenesis and inhibit adipogenesis", **J Clin Investig**, 128(1): 157-174, (**2018**). PMID: 29202470, PMCID: PMC5749530.
c. Bhattarai RS, Kumar V, Romanova S, Bariwal J, Chen H, Deng S, Bhatt VR, Bronich T, **Li W**, Mahato RI. "Nanoformulation design and therapeutic potential of a novel tubulin inhibitor in pancreatic cancer". **J Control Release**. **2021**, 329:585-597. PubMed PMID: 33010334. PMCID: PMC7904572.
d. Zhousheng Xiao, Li Cao, Micholas Smith, Hanxuan Li, **Wei Li**, Jeremy Smith, and L. Darryl Quarles, "Genetic interactions between Polycystin-1 and TAZ in osteoblasts define a novel mechanosensing mechanism regulating bone formation in mice", **Bone Research**, **2023**, 11,57.

**Complete List of Published Work in MyBibliography:**
http://www.ncbi.nlm.nih.gov/sites/myncbi/wei.li.11/bibliography/45414079/public/?sort=date&direction=ascending