Yiwu Yao

Current Position: Senior Research Fellow, Department of Pathology, Michigan Medicine, University of Michigan

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EDUCATION

Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, Guangdong, China **Jun. 2016**

Ph.D., Medicinal Chemistry

China Pharmaceutical University, Nanjing, Jiangsu, China **Jun. 2012**

M.S., Medicinal Chemistry

China Pharmaceutical University, Nanjing, Jiangsu, China **Jun. 2009**

B.S., Pharmacy

EXPERIENCE

Grembecka/Cierpicki Lab **Senior Research Fellow, Aug. 2019 - Present**
Research Fellow, Aug. 2016 - Jul. 2019

- Development of first-in-class small molecule inhibitor targeting PRC1 core component Bmi1-Ring1b E3 ligase. **I lead this project.**

  Bmi1-Ring1b mediate the mono-ubiquitination of H2AK119 *via* protein-protein interaction with the nucleosome. This is a very challenging target

owing to the fact that it has no substrate, no pocket, no linear peptide at the binding surface with the nucleosome.

This project is still in progress. We have achieved:

1. Identification of several hits by performing ^{1}H-^{15}N HSQC protein NMR experiments to screening a commercial library of ~1000 fragments, the most potent hit is **RB-1** with ~7 mM binding affinity (Kd).
2. Using grow strategy through medicinal chemical modification, we identified lead compound **RB-3** with ~3 μM Kd. Compare with **RB-1**, the potency increased 2000-fold. **RB-3** inhibits H2A ubiquitination in several cancer cell lines and induces differentiation of leukemia cells.
3. Development of two convergent and divergent synthesis routes that facilitated the SAR study. So far, over 200 **RB-3** analogues were synthesized, each with 10 to 20+ steps.
4. With more soluble and more potent inhibitors, 4 co-crystal structures were solved. Compare with *apo* protein, the Bmi1-Ring1b structures show significant conformational change to form a binding pocket in presence of inhibitors.
5. With the insight of the detailed binding mode, I rational designed and synthesized several inhibitors show nanomolar Kd, which is ~200-fold improvement compare with **RB-3**, and several compounds with sub-micromolar cellular activity.
6. Development of NMR titration, ITC, AlphaLISA assay, ubiquitination assay, and NanoBit assay for the potency evaluation, and pull-down assay for target engagement validation.
7. Extensive cell-based studies are ongoing.

Sheng Jiang Lab **PhD, Sep. 2013 – Jun. 2016**

Assistant Investigator, Aug. 2012 – Aug. 2013

M.S., Oct. 2010 – Jun. 2012

- Development of novel cyclic depsipeptides and small molecules HDAC inhibitors. **I played a key role in both projects**.
    1. Based on FDA approved drug nature product romidepsin (FK228), we designed a series of cyclic depsipeptides HDAC inhibitors which show improved selectivity and reduced toxicity. **The lead compound entered preclinical studies.**
    2. I improved the total synthesis route so that divergent analogues (40+) and gram-scale synthesis is feasible.
    3. Design and synthesis of small molecular HDAC inhibitors using click chemistry, followed by scaffold-hopping lead to compounds demonstrating class I and IIb subtype selectivity.
- Total synthesis of biologically active nature products (-)-norsecurinine, (-)-niruroidine and (-)-flueggine A.
- Designed, synthesized and antitumor activity evaluation two series of dual inhibitors, EGFR/NAMPT and MTH1/NAMPT.
- Practical synthesis of prostaglandin E1.

Hequan Yao Lab **M.S., Jul. 2010 – Sep.2010**

- Total synthesis of hyrtiocarboline.

Hongbin Sun Lab **B.S. Intern, Feb. 2009 – May 2009**

- Synthesis the $5HT_{2A}$ inhibitor naftidrofuryl and its stereoisomers.

EXPERTISE

Medicinal Chemistry, Hit/Lead Optimization, Fragment-Based Drug Discovery, Structure-Based Drug Design, Total Synthesis of Bioactive Nature Products, Epigenetics, Protein-Protein Interaction

PUBLICATIONS

1. Shirish Shukla[*], Weijiang Ying[*], Felicia Gray[*], **Yiwu Yao**[*], Qingjie Zhao, Hongzhi Miao, HyoJe Cho, Paula González-Alonso, Miranda Simes, Alyssa Winkler, George Lund, Trupta Purohit, Shihan He, Caroline Nikolaidis, Juliano Ndoj, Jingya Wang, Łukasz Jaremko, Mariusz Jaremko, Russell Ryan, Monica L. Guzman, Jolanta Grembecka, Tomasz Cierpicki. First-in-class small molecule inhibitors of Polycomb Repressive Complex 1 (PRC1) RING domain. ***Nat. Chem. Bio.*** **In Revision**. ([*]**equal contribution**)
2. **Yiwu Yao**, Weijiang Ying, …, Jolanta Grembecka, Tomasz Cierpicki. First-in-Class Polycomb repressive complex 1 (PRC1) Inhibitors: Fragment-Based Lead Discovery and Structure–Activity Relationship Study. ***J. Med. Chem.*** **In Preparation. Expected 2021.**
3. **Yao, Y.**, Tu, Z., Liao, C., Wang, Z., Li, S., Yao, H., Li, Z. & Jiang, S. Discovery of Novel Class I Histone Deacetylase Inhibitors with Promising in Vitro and in Vivo Antitumor Activities. ***J. Med. Chem.*** *58*, 7672-7680, (2015).
4. Ma, N.[*], **Yao, Y.**[*], Zhao, B.-X., Wang, Y., Ye, W.-C. & Jiang, S. Total synthesis of securinega alkaloids (-)-norsecurinine, (-)-niruroidine and (-)-flueggine A. ***Chem. Commun.*** *50*, 9284-9287, (2014). ([*]**equal contribution**)
5. **Yao, Y.**, Li, Z., Qiu, Y., Bai, J., Su, J., Zhang, D. & Jiang, S. Unprecedented reactions: from epichlorohydrin to epoxyglycidyl substituted divinyl ether and its conversion into epoxyglycidyl propargyl ether. ***Sci. Rep.*** *5*, 14231pp., (2015).
6. **Yao, Y.**, Liao, C., Li, Z., Wang, Z., Sun, Q., Liu, C., Yang, Y., Tu, Z. & Jiang, S. Design, synthesis, and biological evaluation of 1, 3-disubstituted-pyrazole derivatives as new class I and IIb histone deacetylase inhibitors. ***Eur. J. Med. Chem.*** *86*, 639-652, (2014).

7. Zhang, K. *, **Yao, Y.** *, Qiu, Y., Chen, D., Jiang, S., Tu, Z., Wang, Z., Liao, C., Hamilton, D. J. & Li, Z. Discovery of class I histone deacetylase inhibitors based on romidpesin with promising selectivity for cancer cells. ***Future Med. Chem.*** *12*, 311-323. (2020) (*__equal contribution__)
8. Zhang, W. *, Zhang, K. *, **Yao, Y.** *, Liu, Y. *, Ni, Y., Liao, C., Tu, Z., Qiu, Y., Wang, D., Chen, D., Qiang, L., Li, Z. & Jiang, S. Dual nicotinamide phosphoribosyltransferase and epidermal growth factor receptor inhibitors for the treatment of cancer. ***Eur. J. Med. Chem*****.** 113022. (2020) (*__equal contribution__)
9. Jin, Y., **Yao, Y.**, Chen, L., Zhu, X., Jin, B., Shen, Y., Li, J., Du, X., Lu, Y., Jiang, S. & Pan, J. Depletion of γ-catenin by histone deacetylase inhibition confers elimination of CML stem cells in combination with imatinib. ***Theranostics*** *6*, 1947-1962, (2016).
10. Sun, Q., **Yao, Y.**, Liu, C., Li, H., Yao, H., Xue, X., Liu, J., Tu, Z. & Jiang, S. Design, synthesis, and biological evaluation of novel histone deacetylase 1 inhibitors through click chemistry. ***Bioorg. Med. Chem. Lett.*** *23*, 3295-3299, (2013).
11. Zhu, X., Chen, L., Jiang, S., Chen, C., **Yao, Y.**, Chen, D., Xue, H. & Pan, J. PQJS380: a novel lead compound to induce apoptosis in acute lymphoblastic leukemia cells. ***Cancer Biol. Ther.*** *15*, 119-127, (2014).
12. Su, J., Qiu, Y., Ma, K., **Yao, Y.**, Wang, Z., Li, X., Zhang, D., Tu, Z. & Jiang, S. Design, synthesis, and biological evaluation of largazole derivatives: alteration of the zinc-binding domain. ***Tetrahedron*** *70*, 7763-7769, (2014).
13. Li, X., Tu, Z., Li, H., Liu, C., Li, Z., Sun, Q., **Yao, Y.**, Liu, J. & Jiang, S. Biological evaluation of new largazole analogues: Alteration of macrocyclic scaffold with Click chemistry. ***ACS Med. Chem. Lett.*** *4*, 132-136, (2013).

14. Su, K., Qiu, Y., **Yao, Y.**, Zhang, D. & Jiang, S. 8-hydroxyquinoline-N-oxide-promoted copper-catalyzed C-S cross-coupling of thiols with aryl iodides. ***Synlett*** *23*, 2853-2857, (2012).
15. Hao, J., Chen, B., **Yao, Y.**, Hossain, M., Nagatomo, T., Yao, H., Kong, L. & Sun, H. Practical access to four stereoisomers of naftidrofuryl and their binding affinity towards 5-hydroxytryptamine 2A receptor. ***Bioorg. Med. Chem. Lett.*** *22*, 3441-3444, (2012).

PATENTS

1 Cierpicki, T., Grembecka, J., Ying, W., **Yao, Y.**, Gray, F. & Zhao, Q. Preparation of pyrrole derivatives as PRC1 inhibitors and methods of treatment therewith. WO2019236957A1 (2019).

2 Jiang, S., Tu, Z., Hao, H., Yao, H., Qiu, Y., **Yao, Y.** & Chen, D. Preparation of heterocyclic urea compounds as anticancer agents. WO2018133716A1 (2018).

3 Jiang, S., Tu, Z., Zheng, D., Qin, D., Bai, J., Qin, X., **Yao, Y.**, Liu, Y., Qiu, Y. & Chen, J. Preparation of 3-(pyridin-3-yl)acrylamide derivatives as nicotinamide phosphoribosyltransferase inhibitors useful for the treatment of cancer. WO2016095581A1 (2016).

4 Jiang, S., Yao, Z., **Yao, Y.**, Qiu, Y., Lu, C., Su, K. & Yao, X. Cyclic peptide compound, and preparation method, pharmaceutical composition and use thereof. WO2015027959A1 (2015).

5 Jiang, S., Li, S., Yao, Z., **Yao, Y.**, Zhang, F., Chao, Y., Ye, H. & Chen, M. Preparation of cyclopeptides as histone deacetylase inhibitors. WO2013071715A1 (2013).

6 10 Chinese Patents. CN107674059A (2018), CN106928192A (2017), CN106866571A (2017), CN104557863A (2015), CN103524598A (2014),

CN103601742A (2014), CN103086971A (2013), CN102311398A (2012), CN102391359A (2012), CN102276689A (2011).

AWARDS & HONORS

- National Scholarship, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 2015
- The Third Prize GIBH Scholarship, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 2015
- Merit Student, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 2014&2015

PRESENTATIONS

- Chinese Academy of Sciences Guangzhou Branch Symposium, 2015 (Oral)
- 2011&2015 Chinese Medicinal Chemistry Symposium & 3rd&5th CPA-RSC Symposium on Medicinal Chemistry (Poster)
- 7th CCS National Organic Chemistry Conference 2011(Poster)
- 3rd&4th Lingnan Organic Chemistry Forum 2013&2014 (Poster)