COLLEGE OF PHARMACY
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

Public Oral Examination
For the Degree of Doctor of Philosophy

Wenbin Tu

"Development of Potent and Selective Small-Molecule PROTAC Degraders of SMARCA2 Protein"

Wednesday, November 29, 2023 at 10:00am
NCRC B10 Research Auditorium

Zoom option:
Meeting ID: 958 5036 4222
Passcode: medchem
Invite Link: https://umich.zoom.us/j/95850364222

Committee Members:

Dr. Shaomeng Wang (Chair)
Dr. Nouri Neamati
Dr. Zaneta Nikolovska-Coleska
Dr. Amanda Garner

Abstract:

Epigenetic dysregulation is a prominent feature involved in almost all human cancers. Therefore, targeting key epigenetic regulators that promote tumor progression has been recognized as potential therapeutic strategies for cancer treatment. In particular, the mammalian SWItch/Sucrose Non-Fermentable (mSWI/SNF) complexes play a crucial role in regulating gene expression and have been found to be mutated in approximately 20% of all human cancers. One ATPase subunit of mSWI/SNF complex, SMARCA4, is frequently mutated in various types of cancers including ovarian cancer, melanoma and non-small-cell lung cancer with an average mutation rate of 11%. Multiple studies have established the synthetic lethal relationship between SMARCA4 and its mutually exclusive ATPase subunit SMARCA2, thus making SMARCA2 an attractive therapeutic target for cancers with SMARCA4 deficiency. Early efforts have been focused on developing small molecule inhibitors of SMARCA2 bromodomain and ATPase domain, but neither strategy was proved to be successful. The bromodomain inhibitors exhibit no antiproliferative effects against SMARCA4-deficient cancer cells, while the ATPase inhibitors demonstrate dose limiting toxicities in vivo due to the co-inhibition of SMARCA4. These findings suggest that selective targeting of SMARCA2 is a must to avoid SMARCA4-related toxicities and achieve anti-cancer efficacy in patients with SMARCA4-deficient cancers, which redirected us to pursue the proteolysis targeting chimera (PROTAC) strategy to develop efficacious and selective SMARCA2 targeting agents.

In this thesis, we report the design, synthesis, and biological evaluation of potent and selective SMARCA2 PROTAC degraders. Our efforts have yielded several potent and selective SMARCA2 degraders, with the most promising one named SMD-3040. SMD-3040 achieves DC50 = 12 nM and Dmax > 90 % for SMARCA2 protein in our HiBit degradation assay and importantly, only degrades around 50% of SMARCA4 protein. These data demonstrate the best selectivity profile among all SMARCA degraders reported so far to the best of our knowledge. SMD-3040 selectively inhibits cell growth in SMARCA4-deficient cancer cell lines while sparing SMARCA4-wild type cancer in cell growth

inhibition studies. SMD-3040 effectively inhibited tumor growth in two SMARCA4-deficient xenograft tumor models in mice with well-tolerated dose schedules. However, the suboptimal potency and poor in vivo DMPK properties of SMD-3040 make it unsuitable for further development.

To optimize the degradation potency and DMPK properties, we next designed and synthesized a new class of spiro SMARCA bromodomain ligands through structure-based drug design. Following medicinal chemistry efforts have led to the discovery of a set of extremely potent and highly selective SMARCA2 PROTAC degraders, exemplified by SMD-3236. SMD-3236 achieves DC50 = 0.5 nM and Dmax = 96% for SMARCA2 protein and only a Dmax = 41% for SMARCA4 protein in HiBit degradation assay, which translates into a S2/S4 DC50 ratio of over 1000 folds and a ΔDmax of 55%. SMD-3236 demonstrates potent antiproliferative effects only in SMARCA4-deficient cancer cells, and is 9-16 times more potent than SMD-3040. SMD-3236 achieves durable and effective PD effect, excellent PK profile in vivo with little CYP inhibition or hERG liability. SMD-3236 exhibits strong anti-tumor activity in two SMARCA4-deficient xenograft tumor models and is well tolerated. Collectively, our data demonstrate that SMD-3236 is a promising candidate for advanced preclinical studies. Future optimization of SMD-3236 might lead to development candidates for the treatment of human cancers with SMARCA4 deficiency.

Select Publications:

1. Yang, L.;# **Tu, W.;#** Huang, L.; Miao, B.; Kaneshige, A.; Jiang, W.; Leng, L.; Wang, M.; Wen, B.; Sun, D.; Wang, S. Discovery of SMD-3040 as a Potent and Selective SMARCA2 PROTAC Degrader with Strong in vivo Antitumor Activity. *J. Med. Chem*. **2023**, *66*, 10761-10781.
2. Yang, L.;# **Tu, W.;#** Huang, L.; Leng, L.; Jiang, W.; Wang, M.; Wen. B.; Sun, D.; Kirchhoff, P.; Stuckey, J.; Wang, S. Strategies toward Discovery of SMD-3236 as a highly Potent and Selective Proteolysis Targeting Chimera Degrader of SMARCA2 Protein for the Treatment of Cancer. *Manuscript in preparation*

Future Plans:

Wenbin is seeking potential opportunities in the biotech venture capitalist field.