Department of Chemistry
香港城市大學
City University of Hong Kong

Special Departmental Seminar

By

Dr. Hao WU

Scientist 4
Peptide Therapeutics
Departments of Early Discovery Biochemistry
Genentech, Inc., South San Francisco, CA, USA

Morphing Peptide into Druglike Molecule

Date: **3 July 2024 (Wednesday)**

Time: **11:00 am - 12:15 pm**

Venue: **B5-308 (Blue Zone, 5th Floor)**
Yeung Kin Man Academic Building
City University of Hong Kong

For abstract, please refer to the attached sheet.

Contact: Miss Daisy YIM (3442-7095, wlyim7@cityu.edu.hk)

~ All Are Welcome ~

Abstract

Peptide drugs are a unique kind of pharmaceutical compounds due to their different biochemical and therapeutic characteristics. In this talk, various peptide discovery platforms will be introduced, followed by a case study about how we discovered the potency-enhanced peptidomimetic VHL ligands with improved oral bioavailability. In this study, we present a comprehensive structure-activity relationship (SAR) approach, combined with cellular target engagement assays. The von Hippel Lindau (VHL) protein plays a pivotal role in regulating the hypoxic stress response and has been extensively studied and utilized in the targeted protein degradation field. VHL functions as a substrate receptor of the Cullin RING E3 ligase CRL2. Given its potential as a therapeutic target for modulating the hypoxic stress response, such as in anemia, and its utility in generating bivalent degraders, we aimed to enhance the existing VHL ligands. Through systematic modifications on the left-hand side of the molecule, we identified the 1,2,3-triazole group as an optimal substitute for the amide bond that yields 10-fold higher binding activity. Moreover, incorporating conformational constrained alterations on the right-hand side led to the development of highly potent VHL ligands with picomolar binding affinity and significantly improved oral bioavailability. We anticipate that our optimized VHL ligand will serve as a valuable tool compound for investigating the VHL pathway and advancing the field of targeted protein degradation.

Biography

Dr. Hao Wu is currently Scientist 4 at Genentech, Departments of Early Discovery Biochemistry, Peptide Therapeutics Division. He has been involved in many projects of Hit to lead (H2L), and Lead to Candidate optimization, including improve potency, DMPK, and other the drug-like properties of peptides, using rational design, structure-guided design, and combinatorial chemistry approach. Before joining Genentech, Dr. Wu had postdoctoral training at The Scripps Research Institute – Florida using peptidomimetics targeting intracellular targets, and obtained his Ph.D. in Department of Chemistry, National University of Singapore, training in organic chemistry, developed small molecule microarray platform for PPI inhibitor discovery.