

Rational design for First-in-class inhibitors of APC-Asef interaction against colorectal cancer migration

Dr. Jian Zhang
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Time : 11:15am - 12:15pm

Venue : LT 17 Wong To Yick Tong Lecture Theatre, 4/F, Yeung Kin Man Academic Building

Abstract

The binding of adenomatous polyposis coli (APC) to its receptor Asef relieves the negative intramolecular regulation of Asef and leads to aberrant cell migration in human colorectal cancer. Because of its crucial role in metastatic dissemination, the interaction between APC and Asef (APC-Asef interaction) is an attractive target for anti-colorectal-cancer therapy. We rationally designed a series of peptidomimetics that act as potent inhibitors of the APC interface. By using the peptidomimetic inhibitor as a chemical probe, we found that CDC42 was the downstream GTPase involved in APC-stimulated Asef activation in colorectal cancer cells. Then, we adopted the rational-design strategy involving the introduction of intramolecular hydrogen bonds and optimization of the lipophilic substituents to improve the binding affinities of peptides, leading to the discovery of MAI-400. Recently, we put forward the inhibitors of the APC-Asef interaction into a better MAI-516, with an IC_{50} of $0.041 \pm 0.004 \mu M$ through a "double anchor" screening strategy. Our work demonstrates the feasibility of exploiting APC-Asef interaction to regulate the migration of colorectal cancer cells, and provides what to our knowledge is the first class of protein-protein interaction inhibitors available for the development of cancer therapeutics targeting APC-Asef signaling.

About the Speaker

Dr. Jian Zhang received his BS in Pharmacology from Peking University in 2002 and his PhD in Medicinal Chemistry from Chinese Academy of Sciences in 2007. Dr. Zhang joined the faculty at Shanghai Jiaotong University School of Medicine as Professor in 2009 and was rewarded the Changjiang Scholars Program in 2017. Dr. Zhang serves as the Director of the Medicinal Chemistry & Bioinformatics Center at Shanghai Jiaotong University and is the Dean of the School of Pharmacy at Ningxia Medical University.



Dr. Zhang has published 120+ peer-reviewed papers (e.g. Nat Chem Biol, Chem) as the corresponding author, an inventor of 16 issued patents, and hundreds of international invited talks. He was the 2017 top-ten science and technology young scientist in China, was elected as Member of the Academic Degrees Committee of the State Council in 2020, was awarded as the Fellow of Royal Society of Chemistry and Excellent Research Advisor of American Chemical Society in 2022. He is the Associate Editor for RSC Medicinal Chemistry and serves on the editorial board for several international journals.

In addition to his academic role, Dr Zhang is a founder of Nutshell Therapeutics, which were established to develop innovative anticancer medicines with technologies.

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All are welcome!