PURDUE
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Organic Chemistry Seminar

Tuesday, January 23, 2024
4:30 – 5:30 PM, WTHR 104

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I. Title and Abstract:

"Discovery of The First-In-Class SHP1 Covalent Inhibitor for Cancer Immunotherapy."

Cancer immunotherapy refers to the approach leveraging patients' immune system against tumor, which has gained tremendous progress hallmarked by immune checkpoint blockade and adoptive cell therapies. However, contemporary strategies suffer from limited responses, adverse side effects, and low tissue penetration due to utilization of macromolecules, calling for more efficacious and safer alternative strategies. SHP1 is a protein tyrosine phosphatase (PTP) primarily expressed in hematopoietic cells and has been shown to negatively regulate immune responses in T cells and natural killer (NK) cells, and SHP1 deletion in these cells has shown to promote their anti-tumor functions. Recent studies also demonstrated that inducible SHP1 knockout inhibited tumor growth *in vivo* through immune activation. Although presented as an attractive target, no high-quality small molecule inhibitors have been reported for SHP1 due to its undruggable nature. Through high-throughput screening and extensive medicinal chemistry, we have acquired the first-in-class SHP1 covalent inhibitor M029, which shows >25-fold selectivity against SHP2, its closest analogues and >60-fold selectivity against other PTPs and cysteine-based proteins. Further proteomics studies reveal that M029 is superiorly selective for SHP1 *in cellulo*. Additionally, M029 is stable in 100-fold excessive glutathione with a half-life of >35 hours and non-toxic up to 100 μM to healthy cells, such high stability was also reflected by its oral bioavailability with a F% of 10%. M029 treatment significantly activated T cell receptor signaling in T cells and NK cells killing effects *in vitro*. Furthermore, oral dosage of M029 significantly delayed tumor progression in mice bearing MC38 tumors through enhanced T cell and NK cell infiltration and activation and prolonging of T cell exhaustion.

Collectively, we have developed the first SHP1 covalent inhibitor with high selectivity and strong anti-tumor efficacy. This study is the first characterization of pharmacological SHP1 inhibition as cancer immunotherapy and solidified its potential as an immunotherapeutic target. The development of M029 will also enlighten drug discovery strategies against SHP1 or other undruggable PTPs.