KDDF
Korea Drug Development Fund

Asset #38
Dana-Farber Cancer Institute

Highly Selective Focal Adhesion Kinase (FAK) Inhibitors

Therapeutic Area	Oncology	**Indications**	Breast and Gastric Cancer
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

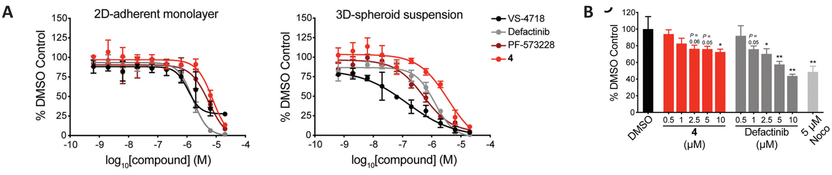
- Several FAK inhibitors based on cyclic or bicyclic core scaffolds have been advanced to clinical trials. These molecules are ATP-competitive inhibitors and display either dual kinase inhibition or significant activity against other kinases. Off-target effects from non-selective inhibitors can lead to undesirable cellular toxicity or hinder the development of combination formulations by interacting negatively with other drugs. In addition, there is a need in chemical biology research for more selective inhibitors to serve as chemical probes in studies exploring the role of FAK in cancer progression.
- Researchers at Dana Farber Cancer Institute have discovered a tricyclic core that serves as an effective scaffold for the development of selective and potent kinase inhibitors.

Technology Advantages

- A detailed and systematic structure-activity relationship campaign identified substituents with extremely high selectivity for FAK
- Further modifications to the side chains yielded several candidates with high potency against FAK (IC50 < 50 nM).
- Observed anti-proliferative effects and reduced migration of malignant cells in 3D breast and gastric cancer models.

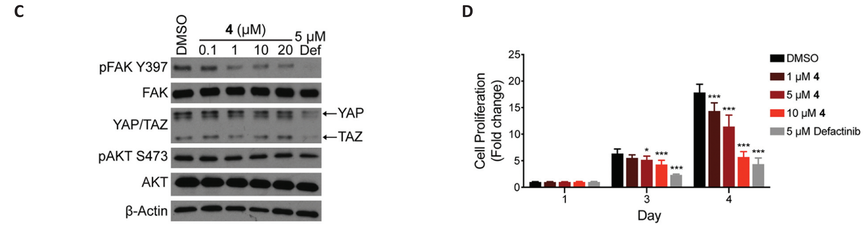
Key Data

FAK inhibition decreases proliferation in 3D-spheroid suspensions and migration of breast cancer cells.



(A) Across the compound series, we observed that MDA-MB231 cells were more sensitive to FAK inhibition in 3Dspheroids. Of our series, 4, 11, 12, 17, and 34 displayed the most pronounced antiproliferative effects in 3D-spheroids, with little to no effects in 2D-monolayer cultures. (B) Treatment with 4 led to a statistically significant albeit modest effect on migration of MDA-MB-231 cells. These effects were more pronounced upon treatment with defactinib and nocodazole, an agent that disrupts microtubule polymerization.

FAK inhibition decreases aberrant signaling and proliferation of gastric cancer organoids



(C) Treatment of gastric organoids with 4 led to loss of active, phosphorylated FAK (pFAK Y397), which was more pronounced with defactinib after 24 h. (D) Treatment with 4 led to dose-dependent activity on gastric organoid proliferation, which was more pronounced with defactinib treatment

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2020-031791 (2020.05.07)

Patent Family
PCT, US, EP, CN, CA, AU

Publication(s)

- Groendyke, B. J. et al. (2020). Discovery of a pyrimidothiazolodiazepinone as a potent and selective focal adhesion kinase (FAK) inhibitor. ACS Medicinal Chemistry Letters, 12(1), 30–38.