

**A potent and selective inhibitor of KIAA1363/AADACL1 that impairs prostate cancer pathogenesis.**

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**Public Summary:**

Cancer cells show alterations in metabolism that support malignancy and disease progression. Prominent among these metabolic changes is elevations in neutral ether lipids (NELs). We have previously shown that the hydrolytic enzyme KIAA1363 (or AADACL1) is highly elevated in aggressive cancer cells, where it plays a key role in generating the monoalkylglycerol ether (MAGE) class of NELs. Here, we use activity-based protein profiling-guided medicinal chemistry to discover a highly potent and selective inhibitor of KIAA1363, the carbamate JW480. We show that JW480, and an shRNA probe that targets KIAA1363, reduce MAGEs and impair the migration, invasion, survival, and in vivo tumor growth of human prostate cancer cell lines. These findings indicate that the KIAA1363-MAGE pathway is important for prostate cancer pathogenesis and designate JW480 as a versatile pharmacological probe for disrupting this pro-tumorigenic metabolic pathway.

**Scientific Abstract:**

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