HEALTH RESEARCH ABSTRACT SUBMISSIONS #13

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Title of Research *	Specificity, Structure, Dynamics and Inhibition of Tiam1 PDZ Domain/Syndecan1 Complex
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Introduction & Purpose *

The T-cell lymphoma invasion and metastasis gene 1 (Tiam1) is a guanine exchange factor for the Rho-family GTPase Rac1 that is crucial for cell-cell adhesion and cell migration. Deregulation of Tiam1/Rac1 signaling leads to various malignancies, including cardiovascular disease and cancer. Tiam1 contains several protein-protein interaction domains, including a PDZ domain. We have previously shown that cell adhesion receptor syndecan1 activates Rac1 signaling through interaction with the Tiam1 PDZ domain, but little is known about interaction specificity in syndecan family to PDZ domain and the structure features of these interactions. In this study, we sought to investigate the specificity, structure and dynamics of the Tiam1 PDZ domain/syndecan1 complex and identify primary inhibitors targeting this complex.

Experimental Design *	We used fluorescence anisotropy-based equilibrium binding experiments to determine the binding specificity to PDZ domain within syndecan family. To understand the structural feature of this specificity, we determined the structure of PDZ domain with syndecan1 peptide using x-ray crystallography. In silico docking screening as well as AlphaScreen-based high throughput screening (HTS) were employed to identify specific small-molecule inhibitors targeting Tiam1 PDZ/syndecan1 interaction.
Results *	In this work we show that the Tiam1 PDZ domain specifically interacts with syndecan1 and has significantly less affinity for syndecan2 and syndecan4. Using X-ray crystallography, we elucidate the structure basis of the Tiam1 PDZ/syndecan1 binding specificity. Targeting this structure, we identify several inhibitors by in silico screening and further validate them by NMR.
Conclusions *	Taken together, our data indicate Tiam1 PDZ domain specifically interacts with syndecan1. The structure studies provide us insights to this specificity. Several primary compounds were identified by structure-based docking. Further optimization on these compounds will be performed using quantitative structure-activity relationship analysis. The optimized inhibitors will ultimately help investigate Tiam1/syndecan1 signaling in cells and further develop lead compounds that are effective against cancer.

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