[P-T-646] DEVELOPING ANTIDOTE CONTROLLED ANTIPLATELET THERAPIES BY TARGETING THE VWF - GP IB-IX-V INTERACTION

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Introduction: A number of antiplatelet drugs have emerged in the last decade that have improved clinical outcomes for thrombosis patients but their use can cause acute complications such as significant bleeding that increase patient morbidity and mortality. We designed a drug-antidote pair by employing the unique characteristics of nucleic acids in order to inhibit platelet aggregation without undermining patient safety.
Methods: SELEX: We have isolated a number of aptamer molecules that bind to vWF with very high affinity using Systematic Evolution of Ligands by Exponential Enrichment (SELEX).
Binding Assays: Kd values were determined using double-filter nitrocellulose filter binding assays.
PFA-100: We utilized a Platelet Function Analyzer (PFA-100, Dade Behring, Deerfield, IL) and collagen/ADP cartridges to activate the platelets and measure the amount of time taken to form a clot in anticoagulated whole blood.
Platelet Aggregometry: Chrono-log Whole Blood Lumi Ionized Aggregometer (Chrono-log, Haverton, PA) was used to provide a measurement of platelet aggregation in platelet-rich plasma.
Results: We have isolated 3 aptamer molecules that bind to vWF with very high affinity (Kd<15 nM). Two of these aptamer molecules inhibit platelet activity completely as measured by PFA-100 and ristocetin induced platelet aggregation. Furthermore, we designed antidote oligonucleotides that can reverse these aptamers quickly (complete reversal in <2 mins.), effectively (~100% reversal) and for a prolonged time period (>4 hrs.)
Conclusions: The overall goal of this project is to develop a safe, reversible and clinically effective antiplatelet agent that inhibits thrombus formation. To that end, we first employed combinatorial chemistry to develop an antiplatelet agent that blocks the interaction between von Willebrand Factor and its platelet surface receptor, glycoprotein Ib-IX-V. We then used rational design to develop specific antidotes that rapidly and effectively reverse the inhibitors antiplatelet activity.
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