Antidote for New Oral Anticoagulants: Mechanism of Action and Binding Specificity of PER977

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The new oral anticoagulants (NOACs) offer significant advantages over the heparins and warfarin therapies with regards to route of administration, drug interactions and predictability of bioactivity. Currently NOACs lack a specific reversal agent and concern over the need for rapid reversal for emergency procedures, serious bleeding or potential over dosage is heightened. As such we rationally designed, synthesized, and characterized a synthetic small molecule anticoagulant antidote (PER977).

In silico modeling data predicted the locations of non-covalent hydrogen bonding between PER977 and NOACs and heparins. In vitro dynamic light scattering (DLS) data reversal data correlate the in silico predicted non-covalent binding specificity of PER977 directly to NOACs and heparins (e.g. enoxaparin). Dynamic light scattering (DLS) of mixtures of PER977 and enoxaparin evidence the formation of molecular complexes formed at 1:1 and increasing in size at 10:1 ratios, indicating a strong physical, non-covalent association between PER977 and enoxaparin that accounts for the enoxaparin reversal activity of PER977.

Pre-clinical in vivo anticoagulant (rat-tail transection bleeding) assays demonstrate full reversal of all NOACs, with edoxaban requiring the lowest dose for full reversal of edoxaban by PER977. Importantly, PER977 exhibits no binding to any human plasma coagulation factors or albumin. Thromboelastography (TEG) measurements also demonstrate that PER977 returns edoxaban anti-coagulated rats to their naïve coagulation state. TEG reaction time (TEG-R) measurements demonstrate a statistically significant decrease (p<0.05) back to normal TEG-R levels in edoxaban anticoagulated rats administered PER977 within 30 minutes of administration, as compared to rats receiving edoxaban followed by a saline sham.

In vivo and in vitro toxicology and safety studies have been completed and a first-in-human clinical trial to demonstrate safety and efficacy in healthy human volunteers with PER977 and edoxaban will follow. PER977 has also shown no pro-coagulant properties as measured in human blood. In conclusion, PER977 directly and specifically binds NOACs and heparins reversing their anticoagulant properties.