Vascular NanoRx

Technology Overview
The Wyss Institute of Biologically Inspired Engineering at Harvard University has developed a targeted vascular nanotherapeutic (Vascular NanoRx) platform that targets drugs to stenotic (narrowed) sites in blood vessels to treat life-threatening and debilitating clotting disorders, such as stroke, pulmonary embolism, acute coronary syndrome (myocardial infarction, unstable angina), thrombosed hemodialysis access sites, and potentially atherosclerosis. This technology is based on engineered, platelet-sized, drug-carrying microaggregates (3-6 µm in diameter) composed of clusters of nanoparticles (~180 nm in diameter). When exposed to pathological levels of shear stress (>70 dynes/cm²) present in vessels narrowed by blood clots, the microaggregates are triggered to disaggregate, and the drug-carrying nanoparticles deploy and selectively concentrate at the site of the clot (figure). The nanoparticles utilized are composed of biocompatible, biodegradable polymers that have been used in FDA-approved devices such as sutures and implants and are in clinical trials for the delivery of drugs in cancer patients. The current formulation utilizes drugs that are FDA-approved tethered to the microaggregates using FDA-accepted chemistries. The formulation and spray dry manufacturing processes used to generate the microaggregates are scalable and amenable to commercial production. The combination of our vascular nanotherapeutic formulation with existing or novel drugs represents a significant opportunity to treat a wide range of patients with life-threatening vascular diseases more effectively, safer, faster, and with less drug.

Initial therapeutic indication: The treatment of clotted blood vessels
While the Vascular NanoRx drug delivery platform has the potential to deliver a broad array of therapeutics and/or diagnostics, our initial development program combines shear-targeted microaggregates coated with tissue plasminogen activator (tPA), a drug approved by the FDA to treat blood clots associated with acute ischemic strokes, acute myocardial infarctions, and massive pulmonary emboli. Scientific studies conducted in the laboratories of our founders and published in Science indicate that shear-targeted microaggregates coated with tPA dramatically lower the dose of tPA required to dissolve blood clots (potentially lowering the risk of adverse side effects) by selectively targeting the drug directly to clot sites. Vascular NanoRx/tPA dissolved endogenous thrombi and re-opened the obstructed arteries in a mouse arterial injury model. The same Vascular NanoRx-tPA dose caused rapid clot dissolution, restored normal blood flow dynamics, and increased the survival rate to >80% in an otherwise fatal mouse pulmonary embolism model. Importantly, this was achieved using 1/100th the effective dose of soluble tPA. In these studies, injected microaggregates that do not target the clot were cleared from the circulation within a few


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minutes after injection, thereby minimizing the adverse side effects associated with systemic tPA exposure and increasing the overall safety profile of the drug. The Vascular NanoRx should, therefore, address the major clinical limitation associated with tPA administration — bleeding due to systemic exposure — and enable the safe use of tPA at much lower therapeutic doses by a broader range of healthcare providers. It also could potentially extend use of this life-saving therapy to allow emergency responders to treat patients outside of the hospital setting.

**Commercial Opportunity**
The Vascular NanoRx platform represents a tremendous commercial opportunity in that the same shear activated drug delivery platform can be used to target virtually any therapeutic or diagnostic agent to a constricted or occluded blood vessel. Thus, this nanotechnology could be used to treat stroke, acute myocardial infarction, unstable angina, pulmonary embolism, or thrombosed hemodialysis access sites when coated with a clot-dissolving agent; to treat coronary/cerebral spasm with contractility inhibitors; to suppress vulnerable plaque progression with anti-inflammatories or angiogenesis inhibitors; and to prevent neointimal hyperplasia of vascular stents with anti-proliferative agents.

Our initial nanof ormulated tPA proof-of-concept studies are compelling because tPA (alteplase; Activase®) is already FDA-approved for acute ischemic stroke, acute myocardial infarction, and acute massive pulmonary embolism. Heart disease is the leading cause of death for both men and women: Approximately 800,000 events of acute myocardial infarction occur in the U.S. each year with an estimated market of $316 billion. This population represents an accessible market of over $1.2 billion annually, but currently less than 3% of these patients receive tPA because of adverse side effects due to systemic bleeding. Stroke treatment is another important market opportunity and a major unmet need. However, less than 5% of the more than 700,000 acute stroke patients in the U.S. are treated with tPA due to concerns about bleeding and the short timeframe between the onset of a stroke and treatment during which tPA is effective in clot dissolution. Unstable angina represents a growing therapeutic area of $2.8 billion annually with limited treatment options for patients. A uniquely targeted and safer nanof ormulated tPA could provide a much-needed solution to the growing unmet medical need for this disorder as well.

With many cardiovascular drugs coming off patent, there is a clear opportunity to apply our Vascular NanoRx platform to improve upon existing drugs or to strengthen novel drugs in clinical pipelines through targeted delivery and increased safety. In addition, the clot busting capability of the Vascular NanoRx system will be attractive alone or in combination with approved medical devices to “interventionalists” (neurologists, cardiologists, radiologists, vascular surgeons) for numerous other applications in which rapid clot removal with lower, and hence safer, doses of thrombolytic agents are desired (e.g., thromboembolic disorders affecting the arteries of the gastrointestinal tract; combination of tPA with clot-removal stentriever devices).

**Intellectual Property**
To date, two patent applications with claims directed to compositions of matter, methods of use, and methods of manufacture have been filed with the USPTO and EPO. Our international filings will be prosecuted in multiple, commercially attractive, countries. The team has additional disclosures in process related to compositions, methods of manufacture, and methods of use.

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