GrafDefense: Nano-polyplexes for Improving Saphenous Vein Graft Patency

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Technology

Saphenous vein grafts are the most commonly used conduit in coronary and peripheral artery bypass surgery with approximately 1 million peripheral bypass grafts and 600k coronary artery bypass grafting surgeries annually (total of 1.6 million surgeries)[1]. Though bypass grafting may improve survival, there was a 45% per patient vein graft failure rate at 12-18 months in the PREVENT IV trial[2]. Grafdefense has recently developed a technology, termed nano-polyplexes (**NPs**, see **Fig. 1A**), for the pre-treatment of saphenous vein grafts *ex vivo* to improve graft patency. This technology has been examined in preclinical models of vein grafting including a rabbit model and excised human saphenous vein. In an *in vivo* rabbit jugular vein interposition model, vein grafts treated with a therapeutic peptide (**MK2i**) incorporated into our proprietary NP formulation resulted in significantly reduced intimal hyperplasia and lower graft failure rates when compared to the therapeutic peptide alone (**Fig 1B**). In an *ex vivo* human saphenous vein (**HSV**) organ culture model, HSV explants treated with the therapeutic MK2i peptide in the GrafDefense NP formulation resulted in complete abrogation of intimal hyperplasia whereas the MK2i therapeutic alone had a marginal effect (**Fig. 1C)**

Market

Cardiovascular disease (CVD) is the most prevalent and costly disease in the U.S. with a total cost around $300 billion annually and an expected growth to over $1.48 trillionby 2030[3]. With this very large clinical burden, there are relatively very few drug candidates in development (3 drugs / 10,000 deaths)[4]. Artery disease results in 1.2 million hospital stays and is the most expensive of the CVD treatments with an estimated $44 billion in expenses. More than half of these patients received percutaneous coronary intervention or coronary artery bypass grafting. As noted above, 45% of SV grafts fail in the first 18 months leading to costly recurrent surgeries, heart attack, and death. The total estimated financial burden of graft failure is greater than $10 billion. Based on our promising pre-clinical data, we anticipate reducing the cost of recurrent events significantly imparting large savings on medical insurance. If successful, even conservative estimates of this technology suggest cost savings at $5-10 billion per year. For revenue, even a small market share of the available 1.6 million procedures per year would yield annual revenues exceeding $500 million.

Commercialization Strategy

Patent portfolio: A collaborating company, Moerae Matrix, Inc. partially owned by CM Brophy, has submitted patent application 2012/02/63680 for the proprietary MK2i peptide. The **NPs** have provisional patent protection under the patent application US 61/811,078.

Regulatory Approval: For full approval, the FDA requires *ex vivo* treatments of human tissues to be considered under the investigational new drug mechanism. Grafdefense will apply for FDA ExpIND to begin a Phase 0 clinical trial utilizing micro-dose approaches. After the initial investment, clinical batches will be created under cGMP to be used during the Phase 0 study. After the second round of funding, Phase I clinical studies will begin with 18-month evaluations of patient graft patency. Phase II and III clinical trials will be conducted by the licensing company due to the increased cost of Phase II and III clinical trials.

Investment strategy: Initial research has been funded through government agencies including NSF and NIH and the non-profit AHA. GrafDefense will seek an initial investment of $500k for first year funding from initial investors to continue pre-clinical investigation in return for 20% equity stake. Second stage funding will be more ambitious seeking $2-5 million required to fund the Phase I clinical investigation ($22k per patient[1], 100-200 patients) for an additional 20% equity stake.

Exit Strategy: The primary exit strategy in this venture would be acquisition by a larger pharmaceutical company (Merck, Johnson and Johnson, Medtronic, etc.) once we have demonstrated safety (Phase 0) and initial clinical effectiveness (Phase 1). Acquisitions of this nature provide a large return on investment.

Figures

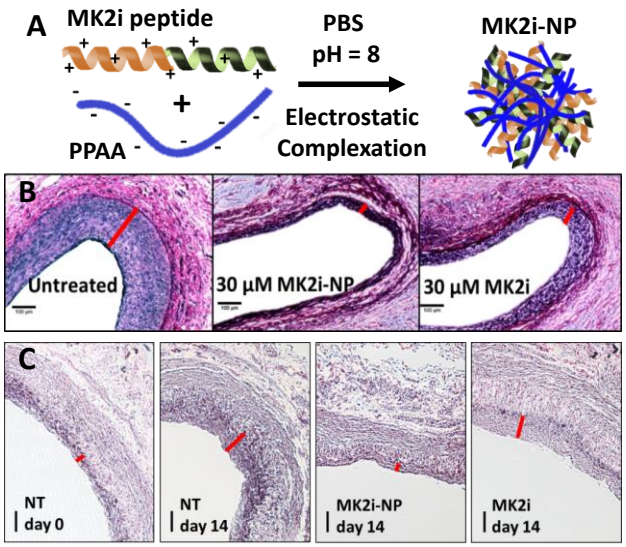

Figure 1: A) Polyplex nanoparticle synthesis scheme. **B)** Representative images of rabbit vein grafts 28 days post op **C)** Representative microscopy images of treated human saphenous vein. Red bars demarcate intimal thickness

References: [1] Circulation 2012;125;e2-e220. **[2]** *Jama.* 2005; 294(19): 2446-2454. [3] AHA: 2013 Heart Disease and Stroke Statistics [4] Roy ASA, Manhattan Institute Project FDA Report. 2012;Apr

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