E4B Innovation Executive Summary

Date: December 8th, 2019
Innovation title: Hemalibrium
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One Line Pitch: We propose a novel method for rapid evaluation of patients with suspected acquired von Willebrand syndrome (aVWS), a disease consisting of von Willebrand factor (VWF) deficiency and subsequent uncontrollable bleeding.

Project Summary: Von Willebrand factor (VWF) is a critical protein in the blood and central component in blood hemostasis. Specifically, VWF binds platelets to the blood vessel wall, initiating clot formation at a site of vascular injury. Von Willebrand syndrome (VWS) is a condition in which VWF is deficient or dysfunctional and can lead to pathological bleeding. While VWS can be genetically inherited, acquired von Willebrand syndrome (aVWS), is associated with other medical conditions and can be "masked" by other disease symptoms, pharmaceutical therapies, or complications, making it significantly more difficult to diagnose and manage. A significant but unquantified subset of aVWS population is associated with "high blood shear" scenarios, i.e. blood is exposed to flow at non-physiologic conditions (> 10 Pa). In such conditions, VWF can change structure, become unfolded or elongated, and susceptible to cleavage. When cleaved, VWF is not effective in binding platelets and initiating clot formation, leading to bleeding. These "high shear" scenarios are often seen in patients on mechanical circulatory support (i.e. ventricular assist devices, extracorporeal membrane oxygenators, etc.) but also in cases of arterial defects (i.e. aortic stenosis, ventricular septal defect, etc.). Unfortunately, these same patients are at a high risk of clotting at the site of implantation or disease, and are therefore put on anti-thrombotic therapy, further enhancing bleeding. There are over 10,000 people suffering from this horrible disease.

Our goal is to develop a bench top medical diagnostic device that can rapidly identify which patients have aVWS for improved targeted therapy. Specifically, targeted virotherapy can increase functioning vWF that causes life-threatening hemorrhaging. We also can utilize an alternate treatment of injectable vWF to better manage bleeding. Focusing on this subset of users will hopefully reduce complications for a group that already requires careful management.

Management: Our strengths are based on previous experiences developing medical therapeutics for targeted patient use. We are situated within institutions that can support the development of diagnostic approaches and extensive validation methods. Together, we have diverse backgrounds for tackling such a problem.

End-user Problem: Patients who require mechanical circulatory support (MCS) are at risk for developing acquired von Willebrand syndrome (aVWS), leading to bleeding that is often mis-diagnosed and difficult to identify. These patients need solutions to address hemorrhaging when using MCS devices.
When considering mechanical circulatory support (MCS) devices with blood-shearing complications, ventricular assist devices (VADs) and extracorporeal membrane oxygenators (ECMO) are typically

discussed because they are the most invasive devices with highest blood-shear introduction. Despite this, they are much needed in patients with end-stage heart failure and are often used to keep them alive until transplants are available. Currently, only 1/3 of people on heart transplant receive an organ and even if these patients are at the top of the list, median time to receive a heart is between 78-85 days; therefore, most patients will require some form of circulatory support during that time. Unfortunately, increasing evidence has shown that MCS can lead to serious hemodynamic complications, with nearly all MCS leading to acquired VWS, specifically exhibited by a loss in high molecular weight multimers necessary for platelet binding and clot formation. Unfortunately, these patients are also put on anti-coagulant/anti-platelet therapies.

Target Market:
According to last INTERMACS report in 2017, > 22,000 people were implanted with a VAD or TAH between 2006 and 2016 and > 8,000 ECMO cases were performed during the same time frame (from ECLS Registry). With > 5 million people in the US with heart failure, and an estimated 8 million people by 2030, the number of MCS device implantations is only increasing. Even with design improvements on MCS, the supra-physiologic shear is enough to cause hemodynamic complications. Of the 3.2 million people who are affected by the vWF genetic mutation within the United States, 50,000 of these individuals require some form of mechanical circulatory support (MCS) system. We plan on targeting this customer base for our proposed products.
https://www.cdc.gov/ncbddd/vwd/facts.html

Customer Validation: Identifying and communicating with these patients would require going through an Internal Review Board (IRB) at various academic hospitals that sponsor research. We would have to obtain proper FDA approval before conducting a clinical trial because our device would classify as Class 2 under the FDA regulations that exist today. This trial would allow us to validate our proposed solutions. We would also need less capital due to our ability to file a 510k with the FDA due to our product having existing approval in application and device similarity. The device we are hoping to use as an approved pathway platform will be the Abbott i-STAT blood analyser.

Technology Validation: After talking to our interviewers, we see that it would require working with hospitals and companies that already provide mechanical circulatory support (MCS) systems to validate whether our approaches could add value to the market that exists today. The current standard for diagnosing vWF is using blood vials of 50mL and running that blood sample through large multi-faceted laboratory equipment. Our validation would use this current method for determining the vWF presence (<50 IU) with our clinically viable device. This would include centrifuging whole collected blood to isolate the hematocrit from the plasma and buffy coat. The hematocrit would then be placed within a cartridge for analysis. Our innovation would come in the form of using an electrochemical operation to determine the availability of vWF in the sample. We would also need to use quantitative retrospective analysis to determine the accuracy and preciseness of our device. This would require hundreds of thousands of tests to prove the efficacy of our device.

Sales/Marketing Strategy: Experimental studies would establish the efficacy of our solutions as an initial beginning to our company. Testing in-vitro with experimental prototyping would be the first step in our strategy. Moving forward to small and large in-vivo animal trials would further prove our

solutions to be safe and effective. We will have to seek approval for use in clinicals via the FDA and use that acquired data to show the accuracy and precision of our device, while promoting our product to potential customers. Our company would look to collaborate with current medical institutions for implementation of our product as a diagnostic tool while care is being administered. This model would align with our wish to have our product used within a large amount of established medical institutions providing care.

Business Model: The upfront cost of our product would be many millions of dollars. The initial cost would require government funding through NIH and NSF grants for entrepreneurial innovations. Private investments would also be desirable, but retaining ownership would need to be discussed with our various co-founders before large amounts of venture capital can be accepted. Once established, our product would cost under three dollars to produce if the technology is proven. We obtain this through estimating the: amount of users present within the United States market, consumable nature of our product, need for performing diagnostic tests as a standard method of care, ability to find lower production costs with a strong international supply chain. Even though the initial cost would be substantial based upon our targeted population, lifetime savings by insurance companies and providers would warrant using our product with cost-lost analysis favoring our product over the alternative, which is what is currently being supported by the market. We would potentially save 100 million dollars by eliminating the need of emergency department and intensive care unit visits when unexpected and adverse developments occur. We anticipate that if our product is implemented and has a success rate of 99%, we believe that we can lower the admittance of patients into the healthcare system for emergency visits by over 75%. Our company would also have extremely high product margins- upwards of 70%.

Competitors/alternative solutions: At this point, we would not face any direct competitors for the consumer population we are targeting due to the price point we are focusing on. The cost of performing such a test can be up to 100 dollars, and we can drastically reduce this cost. We also aim to have a more portable device that can be used within clinic rooms rather than the established blood analysis suite currently used by healthcare institutions. We believe that our network and funding abilities would overcome any competition we face. From our market research, the current standard for determining vWF levels is based upon large blood analyzers (<1000 sqft) which require at minimum 5mL of patient blood per test. We view our technology as requiring 200 uL in order to obtain the same result in less time.

Competitive Advantage: The advantage that we possess is our timeline and strategic entrance into a market that has yet to be addressed. Being first with an effective product can give us a large market share will allow us to challenge any competitors who wish to enter the space.

Ethical Risk Assessment: Due to the nature of our solutions, a more rapid decline in health would be the most detrimental outcome if our solutions did not work. The upside of our solutions would permanently address the vWF deficiency. Our methods would model other therapies currently used that harness the body's natural ability to correct itself. We would model our risks after these treatments with full disclosure of all outcomes to users.

Risk Assessment: The biggest risk to our startup would be lawsuits that implicate our company as negligent. Having a prepared legal apparatus to deal with these lawsuits would help us mitigate this risk if such accusations are made.

Risk factor	**Risk mitigation strategy**
Financial solvency throughout the development stage.	Establish liquid channels of capital before expending resources.
Operational objectives inhibiting growth.	Promote transparency about company standards and objectives before bringing on new talent.
Product pricing is not supported by market.	Immediately discuss corporate position regarding pricing and make adjustments in each aspect of the business.

Use of Funds: We have compiled a brief overview of the required funds to develop a functional prototype with necessary marketing for future expansion and validation.

Source of funds	**Specific activity**	**Funds required**	**Deliverable**	**Delivery by**
Initial funds	Laboratory space/equipment	200,000	Functional prototype	3/15/20
	Marketing Officer	70,000	Advertising interest in product (responses)	12/09/19
	Finance Officer	50,000	Comprehensive reports on expenditures of capital	12/09/19
	Research Staff	150,000	Workforce able to find solutions to problems	3/15/20
	Consultant (FDA)	20,000	Outline regulatory path for medical	12/09/19

			diagnostic device	
	Surplus Emergency Funds	30,000	Needed for unforeseen obstacles	12/09/19
	Economic Viability Study	15,000	Report highlighting the viability of our product in its intended market	12/09/19
Total initial funds		535,000		
Subsequent funds needed	**Specific activity**	**Funds required**	**Funding source**	
Total subsequent funds				

Other relevant information:

8th annual INTERMACS report on VAD and TAH implantation:
https://www.jhltonline.org/article/S1053-2498(17)31896-X/pdf
Good review on MCS bleeding/clotting balance:
http://asheducationbook.hematologylibrary.org/content/2015/1/61.long#ref-1
ELS Registry for ECMO use:
https://www.elso.org/Portals/0/Files/Reports/2017/International%20Summary%20January%202017.pdf