Project Summary

Overview

Blood clots are a mixture of red blood cells, platelets, and a polymeric fibrin matrix that prevent the loss of blood during wound healing. During blood clot formation, fibrin polymerizes into a 3-D gel wherein the fibers have inherent tension. After polymerization, clots are subject to applied tension, which originates from numerous sources including platelet contraction, blood hemodynamics, and the motility of cells trapped within the fibrin gel. The fibrin network must withstand vascular forces during wound healing but then be dissolved afterwards, to avoid blood vessel occlusion, in a process called fibrinolysis.

A key knowledge gap lies in understanding the extent to which, and the mechanisms by which, inherent and applied tension regulate the fibrinolytic process. Demonstrating the existence and importance of tension in clots during lysis has been a foundational part of the research programs of all three PIs over the past 4-5 years, and they anticipate this research continuing over the next decade. The PIs have previously demonstrated that inherent tension helps to accelerate lysis, while applied tension hinders lysis. This proposal extends these initial findings to perform the first multiscale study correlating amounts of fiber and clot tension with fibrinolytic rates. Each aim of the proposal centers on testing one hypothesized mechanism of how tension affects lysis: 1) causing structural rearrangements in the gel prior to lysis, shrinking the volume and expelling lytic enzymes; 2) altering the binding kinetics of enzymes to fibrin; and 3) causing structural rearrangements within the fibers and network structure during lysis, thereby clearing the fibrin more rapidly from the clot volume. Each hypothesis will be tested using a multidisciplinary research approach involving tensile testing, time-resolved microscopy, and mathematical modeling.

In addition to the important research questions, topics of tension and lysis provide important instructional models for students from diverse academic backgrounds and educational levels. At the elementary school level, the PIs will expand/improve a summer camp that discusses tension, lysis, and other STEM topics using LEGO®. At the collegiate level, the PIs have published numerous papers with undergraduate first authors focused on tension and lysis and actively engage in REU mentoring programs. Interdisciplinary lysis studies also have resulted in training Masters and PhD students. This grant proposes to continue these successful training programs and adds an exchange student component, where students will visit the labs of the other PIs on the grant to obtain cross-disciplinary training.

Intellectual Merit

A comprehensive understanding of lysis requires a determination of how vascular forces influence the digestion of blood clots across the molecular, fiber, and network scales. The PIs' collaborative, multidisciplinary approach combines multiscale experiments and mathematical models to interrogate these processes and enables the isolation of different mechanisms by which tension regulates fibrinolysis. The Bannish group has developed the most biochemically- and structurally-detailed mathematical model of lysis to date, which connects micro- and macroscale lysis. The Hudson Lab has pioneered the microscale studies of fibrinolysis, emphasizing the importance of fiber tension. The Tutwiler Lab has expertise in macroscale experiments related to clot structure, mechanics, and fibrinolysis. To date, models of fibrinolysis completely ignore tension and often focus on a limited spatial scale. This work will result in a transformative combinatorial multiscale mathematical and experimental model that can predict lytic outcomes as a function of mechanical forces. A significant advance forward from the current state of the art, this work will lay a foundation for others to study lysis biomechanics.

Broader Impacts

Diseases of the cardiovascular and circulatory systems are leading causes of death and disability worldwide, and all result, in part, from a failure of the fibrinolytic system. This work will provide the first framework for understanding the importance of fibrin tension in regulating the fibrinolytic process, which ultimately could contribute to improved therapeutics for cardiovascular diseases. It will also broaden participation in STEM of undergraduate students, recruited from underrepresented groups, who have less exposure to research opportunities. Elementary school children will be exposed to STEM principles through weeklong summer programs (piloted in summer 2022) that teach engineering and design principles, focused on tension, through Lego®. Graduate and undergraduate students funded by this grant will help develop materials for the summer programs that can be broadly distributed by the PIs.