THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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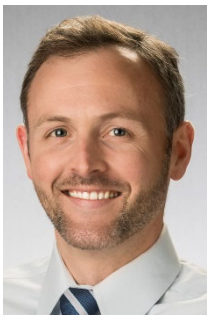

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Comprehensive Platelet Proteomics to Improve Neonatal Transfusion Practices

One out of every 10 infants are born preterm in the United States, predisposing more than 360,000 U.S. infants every year to health complications. With the increased risk of death or lifelong morbidity, preterm birth exerts a staggering toll. Many preterm infants, including up to 90% of babies born weighing less than 1 kg, experience low blood platelet counts (small non-nucleated blood cells that facilitate blood clotting). Such low counts may result from myriad conditions during initial hospitalization, causing bleeding by reducing the ability of the blood to clot normally. Bleeding can occur inside the body, beneath the skin, or at the surface of the skin, but when it occurs in the brain (intraventricular hemorrhage) it is particularly devastating and often leads to severe lifelong neurocognitive challenges. To prevent bleeding when platelet counts drop to levels deemed unsafe by medical caregivers, many preterm infants receive platelet transfusions. The problem is that platelets donated by adults function differently from normal fetal and neonatal platelets. Worse, evidence for increased bleeding and mortality in premature infants who have received prophylactic adult platelet transfusions has existed for more than 15 years. Sadly, despite growing clinical demand, transfusion practices have not changed; in part because no alternative platelet transfusion products exist and in part, because the difficulty in altering standard of care in the absence of a mechanistic explanation for why such transfusions may cause problems. Fortunately, to expand the platelet supply, researchers are seeking to generate transfusable platelets from human stem cells, using tissue culture protocols that are designed to mirror fetal blood cell development. Transfusions of such laboratory-grown, in vitro derived platelets (iPlts) are now being tested in clinical trials in adult patients. Since iPlts are produced using cell culture systems that recapitulate fetal conditions, it is expected that iPlts more nearly resemble neonatal platelets and will be more appropriate for transfusion in preterm infants. However, while justification for development of derived platelets is supported by clinical rationale, little is known about essential differences in their platelet biology. Given that protein-based signaling mechanisms dictate the biology, I propose to characterize platelet function by analyzing protein content and molecular signaling activity (protein phosphorylation) to ascertain differences between iPlts, versus endogenous neonatal and adult platelets. If I am successful in comprehensively defining the difference in proteins and signaling mechanisms that underlie functional diversity in source platelets, it will inspire clinical trials to adapt iPlts for use in infant transfusions. If trial results are favorable, a change in standard of care would directly benefit thousands of vulnerable U.S. infants every year.