stimulates AC activity, causing a rise in intracellular cAMP levels and activation of PKA (see figure). In turn, PKA phosphorylates a set of downstream substrates, which inhibit specific aspects of platelet activation, such as G protein-coupled receptor signaling, small GTPases, increase in intracellular calcium levels, cytoskeletal reorganization, and integrin activation. In addition to the small number of established PKA substrates, Beck et al recently described a bewildering list of potential PKA substrates, revealing an unappreciated complexity of this inhibitory pathway. Although much is already known about the ADP and PGI2 signaling pathways, usually depicted as a simple linear series of biochemical events, it remains elusive as to how they are integrated into a network that steers platelets toward an activated or resting state. Besides revealing how phosphorylation facilitates platelet activation in response to ADP, in this issue Beck et al provide novel insights about how these signals are counteracted by iloprost, which reverses activation and returns platelets to their resting state. Intriguingly, ADP-induced platelet shape change and aggregation were almost completely reversed, but only a third of the quantified phosphopeptides were affected by iloprost treatment, and the remaining two-thirds were unchanged in comparison with their corresponding ADP temporal profiles, suggesting that full reversal of ADP-evoked phosphorylation is not necessary to return platelets to a basal state. Half of the altered phosphorylation sites were upregulated, and as was expected, many of these represent established and potential PKA substrates. Notably, the other half of iloprost-regulated phosphorylation events were downregulated, again revealing a major and previously unrecognized role of phosphatases in PGI2-mediated platelet inhibition. Although, the function of the newly described phosphorylation events remains unknown, this study will no doubt open new avenues of research and serve as a database for the platelet community. One limitation to bear in mind is that although phosphoproteomics detect a large number of phosphorylation events, this is not an exhaustive list, and a considerable portion of all phosphorylation sites are still not accessible by this approach in its current state.

The mechanisms regulating platelet accumulation at sites of vascular injury remain major questions in the field, with important clinical implications for future antiplatelet therapies. From mouse thrombosis models and intravital imaging studies, it is clear that a thrombus can be divided into a fully activated and stably adhered inner “core” region and a partially activated and less stable outer “shell” region, which is critically dependent on P2Y12 signaling. Platelet accumulation and thrombus size may be at least partially determined by the opposing activities of ADP and PGI2 signals at the outer region of a thrombus, although this remains to be proven. Whether this is in fact the case, the study by Beck et al considerably advances our understanding of how platelet activation is balanced by inhibitory signals on a systems level.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on McGann et al, page 155

Making a case for more sickle cell initiatives in Africa

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In this issue of Blood, McGann et al provide a comprehensive review of sickle cell anemia (SCA) in sub-Saharan Africa, focusing on clinical care and research opportunities. It is estimated that the nearly 100,000 Americans with SCA account for over 1.1 billion dollars of health care expenditures annually, but these figures fail to capture the pain and suffering of individuals afflicted by SCA, or the enormous global burden of this condition. There are over 300,000 children born each year with SCA worldwide, and a recent quantitative investigation predicted that nearly 80% of these births will occur in sub-Saharan Africa. In high-income countries such as the United States and United Kingdom, over 95% of children with SCA born today are expected to live to adulthood, and progress with early diagnosis and treatment in middle-income countries such as Jamaica and Brazil has resulted in marked improvements in survival. In some African countries, 50% to 90% of these children will not survive to their fifth birthday. What can be done to bridge this chasm between continents?

Today, most people living in areas of the world with the highest gene frequencies do not know that they in fact have SCA. Improving diagnostics is essential. Standardized, high-throughput methods such as isoelectric focusing and high-performance liquid chromatography are being used currently in Africa; however, the authors offer their perspective about these methods, as well as the utility of point-of-care testing for SCA, supported by very limited albeit intriguing data. Although screening for SCA in sub-Saharan Africa is crucial, it alone is not sufficient to achieve the goal of improving survival. The authors outline ways to implement preventive care measures in lower-resourced countries and they cite published...
data from sub-Saharan Africa for some of these interventions, including penicillin prophylaxis, immunizations, and antimalarials. They provide credible evidence from studies in the United States and western Europe to support their assertion that further clinical efficacy trials in Africa may be unnecessary to proceed with implementation of these measures. Are there additional screening studies or interventions that are feasible? Could hydroxyurea reduce vaso-occlusive pain episodes and acute chest syndrome in Africa while also reducing early mortality as it has in the United States?5 There are limited data on safe blood banking in Africa, yet transfusions have been an effective intervention for numerous SCA acute and chronic complications.6 Stem cell transplantation and other curative therapies are appealing as definitive treatments, however, donor availability and high costs appear to put these interventions out of reach for now.

Although the clinical and public health aspects of SCA are foremost, enhanced research partnerships could also profoundly impact SCA in Africa. Many fundamental observations of SCA have stemmed from research in Africa, including the relative protection of sickle cell trait against malaria, and the identification of β-globin haplotypes from the multiple geographic loci from which the sickle mutation originated. Given the high burden of disease in African countries, opportunities for collaborative research in Africa could enhance our understanding of genotype-phenotype relationships, identify additional genetic modifiers, and reduce sickle cell–related mortality with early detection and improvements in care.

This review is timely in that it highlights several of the American Society of Hematology (ASH) Sickle Cell Research Priorities, and supports the ASH Sickle Cell Disease Call to Action as well as initiatives by the National Heart, Lung, and Blood Institute to address global issues in SCA. Understanding the opportunities as outlined in this manuscript is a critical step in making a profound impact on conquering SCA worldwide.

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TRANSPANT BIOMARKERS READY FOR THE CLINIC?

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Biomarkers promise to refine the prediction of allogeneic stem cell transplantation (SCT) outcomes. In this issue of Blood, a phase 3 clinical trial reported by Abu Zaid et al brings us closer to routine biological profiling of major complications that occur after allogeneic SCT.1

In the last few years, pioneering studies, notably by Paczesny and colleagues, have discovered a range of molecules that can be assayed in plasma, which has proven to be strongly related to some key transplant complications that define transplant survival.2
Making a case for more sickle cell initiatives in Africa

Alexis A. Thompson