# Platelet Biomarkers for Precision Medicine in Hematology and Oncology

An Expert Interview with Wadie F Bahou

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*DOI: https://doi.org/10.17925/OHR.2018.14.2.72*

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*Wadie F Bahou, MD, is professor of medicine at Stony Brook University School of Medicine, NY, US. Dr Bahou is former Chief of Hematology, Hematology/Oncology Fellowship Director, and Vice Dean for Research in the School of Medicine. He currently serves as Director of the Stony Brook Stem Cell Facility. Dr Bahou's research provided the initial proof-of-concept foundation for large-scale profiling of platelet RNAs. He maintains an active research program funded by the National Institutes of Health (NIH) focusing on application of platelet genetics for novel cellular target identification and biomarker development relevant to cancer, thrombo-inflammatory disorders, and gestational diseases. Parallel interests include redox biologic control of cellular proliferation and hematopoietic lineage development.*

**Keywords**

Precision medicine, biomarkers, platelets, platelet-derived biomarkers

**Disclosures:** Wadie F Bahou has nothing to disclose in relation to this article.

**Acknowledgments:** Medical writing assistance was provided by Katrina Mountfort of Touch Medical Media, and supported by Touch Medical Media.

**Review Process:** This is an expert interview and, as such, has not undergone the journal's standard peer review process.

**Authorship:** The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval to the version to be published.



**Received:** October 27, 2018

**Published Online:** November 26, 2018

**Citation:** *Oncology & Hematology Review*. 2018;14(2):72–3

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**Support:** No funding was received in the publication of this article. Research supported by grant NIH HL 119096 to Wadie F Bahou: "Platelet systems biology in health and disease".

The development of precision medicine relies on the identification of biomarkers for monitoring and detecting disease. Current studies of biomarker identification have focused on serum and plasma, but in doing so, they have missed a rich source of biomarkers: platelets.[1] In addition to their functions in coagulation and maintaining hemostasis following mechanical injury of the blood vessels, platelets contain vast amounts of bioactive molecules in their granules, including growth factors, chemokines, cytokines, and proteases, which they can secrete on activation.[2] In addition, they express various receptors that may contribute to cancer progression and metastasis.[3] Platelet-related biomarkers have therefore become a focus of recent research. In an expert interview, Wadie Bahou discusses the latest advances in platelet biomarker research.

## Q. What is the role of platelets in tumor biology and metastasis?

Platelets sit at the interface between the vasculature and the coagulation cascade, and have been largely studied because of their critical role in normal hemostasis. Quantitative platelet disorders are common in oncology, typically evident as thrombocytopenia in the setting of chemotherapy,[4] or as thrombocytotic reactions in disseminated malignancies. The role(s) of platelets in tumor biology and metastases are underappreciated. Platelets directly interact with tumor cells, and are able to promote tumor survival and metastases by sustaining proliferative signals and attenuating apoptotic pathways, in part, through remodeling of the extracellular matrix.[5,6] Platelets also maintain activation-dependent secretory release of proangiogenic factors such as platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-beta, and vascular endothelia growth factor, all of which collectively provide critical signals for growth and tumor angiogenesis.[3,7,8]

## Q. Which platelet-related biomarkers have proven useful in the detection and monitoring of hematologic and oncologic diseases?

Routine platelet-activation markers linked to $\alpha$-granule release (i.e., cell-surface P-selectin) retain limited disease specificity, prompting recent application of platelet genetic mRNAs and microRNAs (miRNAs) as disease-specific biomarkers. Platelets are invested with megakaryocyte-derived ribosomes and a wide range of mRNAs and miRNAs, while maintaining translational capacity linked to the mTOR (mammalian target of rapamycin) signaling pathway. These initial observations provided documentation that small subsets of these genetic markers

may be used for diagnostics of myeloproliferative disease.[9–11] This concept has now been expanded to various solid tumors where platelet genetic profiles are altered in the setting of active malignancy. While the mechanism for this effect remains an area of intense investigation, one explanation is direct exchange of genetic material from cancer cell-derived exosomes into circulating platelets. Platelets have a circulating half-life of 5–7 days, and the entire platelet population is turned over in 2 weeks. This turnover rate provides conceptual support for application of platelet biomarkers in monitoring disease progression and treatment response.[12]

## Q. How can these be quantified?

Biomarker quantification from blood samples is typically obtained from serum or plasma. Circulating platelet granules contain bioactive proteins synthesized from precursor megakaryocytes, or by selective absorption through an endocytotic mechanism resulting in concentrated biomarker storage greater than that in plasma. Thus, exclusive quantification from plasma or serum may be insufficient for characterizing biological processes or biomarkers assessment. The availability of pure platelet preparations by routine venipuncture provides the source for both protein and RNA biomarker detection using standard laboratory methods such as antigen-capture/detection techniques or high-throughput fluorescent multiplexed technologies for either miRNA or mRNA biomarkers.[13,14]

## Q. What research has demonstrated the clinical significance of these biomarkers?

Platelet biomarker research has now established the utility of protein or RNA quantification in wide-ranging malignancies including prostate, ovarian, colorectal, or primary brain cancer;[15–19] development includes both diagnostic and prognostic clinical indications. What is consistent among many of these studies is strong evidence supporting differential platelet biomarker expression, although the identification of selective, reproducible, and easily evaluable subsets by disease category remains ongoing.

## Q. What further studies are planned in this area?

The application of this work to clinically-relevant diagnostic/prognostic therapeutics requires validation in larger cohorts, along with development of assays readily amenable to clinical laboratories. For these assays to reach the clinical arena, simplified methodologies for platelet isolation and processing must be developed that satisfy Clinical Laboratory Improvement Amendments (CLIA)-certified testing. Many of the biomarkers are identified initially by sophisticated genetic-based or mass spectrophotometric methodologies that are not readily completed in most clinical laboratories. Post-cohort validation will require greater scrutiny for sensitivity/specificity analyses, along with ease-of-assay development. Nonetheless, the evolution of platelets from "microscopic dust" seen on peripheral blood smears to functionally relevant cellular engines of disease will continue to fuel this direction of research. ❑


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