current issues in molecular biology

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Editorial

Editorial for the Special Issue "Molecular Insights into Cancer Biomarkers: Identification and Practical Applications"

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1. Introduction

Cancer biomarkers are valuable not simply because they reveal molecular differences, but because they may improve clinical decisions by identifying who needs further investigation, which treatment may be appropriate, and how disease should be monitored. This Special Issue, titled "Molecular Insights into Cancer Biomarkers: Identification and Practical Applications", brings together ten contributions addressing these goals through circulating analytes, prognostic signatures, signaling pathways, genomic variants, and emerging therapeutic targets. Together, they illustrate both the promise of precision oncology and the distance between a promising molecular candidate and a validated clinical tool.

2. Liquid Biopsy: Accessible Signals, Distinct Biological Meanings

A central theme of this Special Issue is the use of accessible samples to obtain information about tumors in the form of cancer biomarkers. Ruden reviews this multi-biofluidic approach for detecting cell-free tumor DNA and RNA, including blood, urine, saliva, cerebrospinal fluid, and pleural fluid [1]. The discussion covers mutation analysis, methylation profiling, fragmentomics, and emerging technologies. The study clearly shows that the choice of biofluid and analytical strategy should follow tumor anatomy and the intended clinical question rather than assume that blood is always the optimal sampling compartment.

Chikamatsu et al. demonstrate a related issue in head and neck squamous cell carcinoma: the molecular and clinical characteristics of circulating tumor cells vary according to the epithelial-related markers used for their identification [2]. Comparing EPCAM-, EGFR-, and MET-defined populations, the investigators identify distinct expression profiles, including differences in epithelial–mesenchymal transition and immune-regulatory features. These findings show that liquid biopsy is not a single test. Even within one analyte class, marker selection can determine which tumor subpopulations are observed and which associations become apparent.

The study of plasma hsa-miRNA-145 in Peruvian women by Acosta O. et al. underlies another class of circulating biomarkers [3]. The authors combined digital PCR measurements with in silico analyses of pathways relevant to breast cancer connecting circulating measurements with hypotheses involving cancer-associated signaling and metabolism.

Dragu et al. review exosomal programmed death-ligand 1 (ExoPD-L1) as a potential biomarker of immune evasion and treatment resistance. The review highlights its functional role in suppressing antitumor immunity, showing its value as a circulating marker and also its potential as a therapeutic target [4]. Strategies discussed include interference with exosome formation or release, neutralization of exosomal PD-L1, and modulation of PD-L1 expression.

Check for updates

Received: 9 November 2026
Accepted: 11 November 2026
Published: 14 November 2026

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The mechanistic basis was given by Chen et al., who showed that melanoma-derived exosomes carry surface PD-L1 and suppress CD8 T-cell function, while circulating exosomal PD-L1 dynamics were associated with anti-PD-1 response [5]. These findings support investigation of ExoPD-L1 as a functional circulating biomarker. Selective targeting, assay standardization, and the distinction between baseline and longitudinal measurements remain important translational questions.

Together, these studies highlight the potential of complementary liquid biopsy to reveal distinct aspects of tumor biology. By aligning biofluid selection, marker identification, and molecular analysis with specific clinical questions, they help in developing more informative and individualized strategies for cancer detection and monitoring.

3. Prognostic Signatures, Genomic Variants, and Candidate Therapeutic Targets

Several articles identified the genomic alterations or prognostic gene signatures for cancers illustrating complementary approaches to connecting molecular alterations with cancer prognosis and therapeutic response.

Thus, in gastric cancer, Suzuki et al. associated the ERBB2 R678Q mutation with a lower response rate to oxaliplatin-based regimens using data from a national genomic database [6]. This finding highlights the importance of variant-specific interpretation, as alterations within the same gene may have distinct biological and therapeutic implications. The study paves the way for prospective investigations and mechanistic analyses aimed to clarify whether ERBB2 R678Q can contribute to more individualized treatment selection.

Papamattheou et al. investigated Hippo pathway markers in metaplastic breast carcinoma, a rare and heterogeneous malignancy [7]. Their findings identify the YAP/TAZ pathway as a biologically relevant feature associated with worst prognosis, providing a foundation for larger investigations and exploring its therapeutic potential.

In hepatocellular carcinoma, Shi et al. developed a three-gene signature comprising STC2, CKS1B, and PSAT1 by integrating bulk and single-cell transcriptomics with cross-platform validation [8]. The study connects functional enrichment analysis indicating gene involvement in proliferative programs, with computational drug sensitivity analysis, and suggests that the proposed three-gene signature may have a role in prognostic stratification of the hepatocellular carcinoma patients.

Ka et al. provide a complementary mechanistic perspective by reviewing DCTPP1, a nucleotide pool-regulating enzyme emerging as a candidate target gene in liver cancer [9]. The review connects nucleotide homeostasis with replication stress, metabolic adaptation, and resistance-related biology, highlighting an interface between cancer metabolism and therapeutic response.

Kaštelan et al. examine the integration of molecular profiling and liquid biopsy in ocular melanoma [10]. A central consideration is the distinction between uveal and conjunctival melanoma, whose molecular landscapes and therapeutic implications are different. Thus, in uveal melanoma, GNAQ/GNA11 pathway alterations and changes involving BAP1, SF3B1, and EIF1AX contribute differently to tumor biology and metastatic risk. By bringing together tissue-based characterization and circulating biomarkers, the review highlights promising opportunities to develop individualized surveillance and residual disease assessment.

Collectively, these contributions advance the transition from molecular characterization toward clinically informative biomarkers and candidate therapeutic targets. They establish promising directions for further validation, linking the understanding of the molecular mechanisms with potential treatment strategies.

Extending biomarker research beyond established cancer, Zachariou et al. review clinical, hormonal, genetic, and epigenetic indicators linking male infertility with cancer

susceptibility [11]. The study identifies shared abnormalities in the development of infertility and cancer that offer a biological framework for investigating these associations. The review opens valuable avenues for interdisciplinary collaboration in the domains of andrology and oncology, providing a foundation for prospective studies that could refine counseling, early detection, and appropriate therapy.

4. From Analytical Signal to Clinical Evidence

Technical and biological challenges remain central to the translation of these findings. Interlaboratory variations are the ones that weaken the clinical use of liquid biopsy. One reason for this is that circulating analytes differ in origin, abundance, stability, and clinical meaning. A negative result may reflect low tumor shedding or insufficient assay sensitivity rather than absence of malignancy. Conversely, a detected alteration may originate outside the tumor. Leal et al. illustrated this problem in gastric cancer by analyzing matched plasma and white-blood-cell DNA to distinguish tumor-associated alterations from clonal hematopoiesis [12]. Correctly identifying the source of a signal is therefore important to its analysis.

Pre-analytical and analytical variation are also affecting reproducibility. Collection conditions, processing time, storage, extraction, assay thresholds, sequencing depth, and bioinformatic pipelines can alter results. Narayan et al. discuss these issues in the context of liquid biopsy development and emphasize the importance of standardization that enables comparison across studies and determines whether an assay is sufficiently reliable to be used in clinical care [13].

The ESMO Precision Medicine Working Group's 2022 recommendations support validated ctDNA tests for identifying actionable mutations in advanced cancer, while noticing that evidence was then insufficient for routine use in cancer screening and molecular residual disease assessment [14].

5. Future Perspectives and Conclusions

Several promising directions emerge from this collection. Clearly defining each biomarker's intended use—screening, diagnosis, prognosis, prediction of treatment response, or monitoring—can guide its development toward specific clinical needs. Independent validation across relevant populations and clinical settings can strengthen confidence in its performance, while prospective studies can demonstrate how biomarker-informed decisions improve management, patient experience, and health outcomes [14–16].

By bringing together diagnostic, prognostic, predictive, and therapeutic perspectives, this Special Issue highlights the potential of molecular biomarkers to advance cancer care. Its contributions provide a foundation for connecting biological discovery with clinical application. Continued collaboration, rigorous validation, and patient-centered evaluation can help translate these advances into more informed decisions and better outcomes.

We sincerely thank all contributing authors for their valuable work, the reviewers for their constructive assessments, and the editorial team of *Current Issues in Molecular Biology* for supporting this Special Issue.

Data Availability Statement: No new data were created or analyzed in this editorial. Data sharing is not applicable to this article.

Conflicts of Interest: The author declares no conflict of interest.

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