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Editorial

Precision Chemistry in Precision Diagnostics

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With the rapid advancement of molecular profiling and imaging technologies, coupled with the emergence of powerful bioinformatics and artificial intelligence (AI) tools, precision diagnostics have become highly feasible and also increasingly in demand for modern healthcare, aiming to detect disease at early stages with reduced uncertainty, classify subtypes accurately, monitor progression in real-time, and guide precision medicine.[1−3] Accomplishment of this goal demands diagnostic platforms with high analytical accuracy, sensitivity, and reproducibility,[4−9] and clinically relevant biomarkers that can reliably inform disease detection and stratification.[10−13]

Fabrication of effective diagnostic platforms relies heavily on advances in precisely controlled chemical and material synthesis.[7,14−17] Marker discovery depends on comprehensive and precise multimodal measurements,[18−20] and the resultant high-dimensional data sets need to be interpreted by AI and machine learning methods to extract useful information.[21−23] All of these are key research areas of *Precision Chemistry*. Therefore, this Special Issue entitled "Precision Diagnostics" features the research works that exploit controllable chemical/material/biomolecule synthesis and precise device fabrication, in many cases often integrated with ML algorithms, to empower precision diagnostics.

Epigenetic factors regulate gene transcription and expression without changing the underlying DNA sequence, strongly impacting cancer development, and thus are considered as highly valuable markers in cancer diagnostics.[24,25] A review by Lin et al. provides a comprehensive overview of three types of epigenetic markers: DNA methylation, histone modification, and chromatin accessibility, and elucidates the bulk, single-cell, and spatial epigenomics sequencing technologies that lead to their discovery.[26] It also discusses the present as well as foreseeable applications of epigenomic markers and sequencing technologies in cancer detection, management and treatment. Moreover, the studies covered by this review demonstrate that, integrating epigenomic sequencing with other -omics platforms can help reveal the regulatory mechanisms underlying cancer metastasis, different degrees of malignancy, and the critical factors driving tumorigenesis and development, greatly improving precision cancer diagnostics.

MicroRNAs (miRNAs) are also part of the epigenetic regulatory circuits, and many miRNA-based disease markers have been reported.[27] While miRNAs can be found inside cells, they can be exported to the extracellular space.[28] Encapsulation in extracellular vesicles (EVs) can not only prevent them from degradation by endogenous RNases, but also assist in their delivery to the recipient cells to regulate gene expression and impact cellular functions.[29,30] Both circulating EVs and EV-miRNAs carry great potential as specific and easily accessible diagnostic biomarkers.[31] However, since all cells can produce EVs, it is necessary to pinpoint those derived from the cells highly relevant to the disease of interest for improved diagnostic precision.[29,32] In this collection, Yang et al. review the latest studies that reveal the obesity complication-related functions of a specific group of miRNAs enclosed in the EVs originated from the white adipose tissue (WAT).[33] As found by these studies, the WAT-derived EV-miRNAs can be transported into cells of major metabolic organs, including liver, pancreas, and brain, where they impact the metabolic functions and lead to increased risk of obesity-related complications. This review supports that, in order to realize the full potential of EVs and EV-miRNAs as diagnostic biomarkers and guiding personalized therapeutics, comprehensive understanding on the biogenesis and destination of EVs and the sorting and uptake pathways of EV-miRNAs are highly critical.

While the EV-encapsulated cargos are promising markers, EVs themselves, for example, the tumor-derived EVs, hold great promise as noninvasive biomarkers for disease detection and monitoring. In the review prepared by Tseng et al., they introduce EV Digital Scoring Assays, a new class of liquid biopsy platforms that integrate click chemistry mediated EV enrichment with reverse transcription digital PCR (RT-dPCR) for absolute mRNA quantification.[34] This two-step "enrich-then-count" strategy enables precise molecular profiling of tumor EVs from minimal plasma volumes, achieving high analytical sensitivity and reproducibility. Demonstrated across multiple cancer types, including pancreatic, hepatic, sarcomatous, and prostate tumors, the assays provide quantitative digital scores that outperform traditional serum biomarkers in early detection and treatment monitoring. By combining controllable bio-orthogonal chemistry, digital molecular readouts, and machine learning−based data integration, this approach exemplifies how precision chemistry empowers next-generation precision diagnostics, offering a modular and

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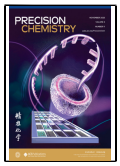

scalable framework for real-time, noninvasive cancer management.

Although markers present in biofluids permit easy access by noninvasive routes, their abundances are typically very low, in particular, during early stages of disease development, and their detection signals are easily masked by the highly abundant matrix components. Holladay et al. report a 3D printed microfluidic device to enable examination of the biomarkers for preterm birth (PTB) risk.[35] The team integrates immunoaffinity extraction (IAE) and solid-phase extraction (SPE) on this miniaturized platform to simultaneously isolate and concentrate the PTB biomarkers—corticotropin releasing factor (CRF), ferritin, and lactoferrin—from sera. While trapped on the SPE monolith, these proteins can also be labeled *in situ* by fluorescent dyes to further improve detection sensitivity. In addition, fabrication by 3D printing facilitates convenient configuration alteration to adapt for different integration routes. Their work demonstrates the promising potential of this sample processing platform for early prediction of PTB, which in turn can lead to timely intervention to reduce PTB mortality, and its versatility in point-of-care testing (POCT): by changing the antibodies, it can be used for extraction and concentration of protein markers for other diseases.

Besides preconcentration, another way of enhancing the detectability of trace biomarkers is to boost the intensity of signals produced by every marker recognition event. Meanwhile, in precision diagnostics, simultaneous detection of multiple biomarkers is essential for high specificity, which poses significant analytical and computational challenges. The enormous volume of acquired data complicates the extraction of valuable information and the derivation of accurate conclusions. This collection thus includes reviews and research reports that attack these challenges from four different angles: improving the performance of signaling tags; exploiting unique optical phenomena offering large signal-to-noise ratios; taking advantage of nucleic acid–based amplification; and employing machine learning approaches.

Fluorescent Polymer dots (Pdots) offer substantial advantages as signaling tags, including high brightness, good photostability, and small physical footprint; but their applications in multiplex analysis is limited by their broad absorption and excitation spectra.[36,37] The work reported by Yao et al. overcomes these limitations by grafting multiple chromophores like BODIPY dyes onto a polymer backbone.[38] Precise control of the grafting ratio result in narrow spectra profiles; and grafting on polymer chains also reduces the interaction between chromophores to help extend excited state lifetime, making the Pdots suitable for Stimulated Emission Depletion (STED) microscopy. The three-color Pdots can be used for imaging multiple pathological markers in cells and tissues with single-particle resolution, representing valuable tools for obtaining critical spatial information from biological samples in pathological investigations, and for gaining high sensitivity and specificity in diagnostic bioassays.

Dots, diverse types of nanomaterials have been developed and employed in high-throughput biomarker analysis. Li et al. review the recently developed nanomaterials that enable simultaneous optical detection of multiple markers.[39] Multiplexity can be achieved using nanomaterials with distinguishable optical properties for marker labeling, or employing them to capture different markers at discrete locations on the specially designed platforms. If neither optical property nor location can distinguish the signals from different markers, data deconvolution by leveraging machine learning tools can be employed. The content of this review well demonstrates the significant contribution of controllable material design in improving the sensitivity, throughput, and portability of marker detection for precision diagnostics.

On the other hand, precisely fabricated platforms with unique optical phenomena can be exploited to achieve high detection sensitivity. Metro et al. report an array of the nanopore-based zero-mode waveguides (ZMWs) that can be used for single-particle characterization of EVs with wide-field fluorescence microscopy.[40] ZMWs are nanosized apertures constructed in a metallic, optical cladding layer that confine incident radiation to an evanescent field within a zeptoliter optical volume, eliminate far field light propagating modes, and minimize background fluorescence from the bulk. With precisely controlled dimensions, ZMWs can trap particles with sizes < 300 nm in the one-particle-one-aperture manner while excluding the larger ones, permitting high-throughput analysis of the dye-labeled EVs with minimum sample preparation.

In addition to advanced materials and platforms, chemical or biochemical reactions can be exploited for signal amplification in biomarker analysis. The review prepared by Li et al. discusses the principles and diagnostic applications of nonenzymatic DNA amplification reactions (NDARs), giving particular attention to the stimuli-responsive and cascade amplification NDAR systems.[41] NDARs rely on thermodynamic principles to achieve signal amplification. Elimination of enzymes from the reaction system makes them more robust and less costly compared to enzymatic approaches, offering great potential in POCT. By strategically choosing the reaction units and precisely modulating the reaction routes, NDARs can even respond to specific environmental or physiological stimuli and power multiple reaction cycles, realizing dynamic target monitoring and exponential signal amplification. Again, these examples showcase the close relationship between precision chemistry and precision diagnostics.

The presence and quantity of biomarkers are the most frequently assessed information during clinical diagnosis. However, as pointed out by Sahli et al. in their research article, it is difficult to just rely on a few markers for precise disease diagnosis and prognosis, not to mention guiding treatments.[42] Leveraging a series of machine learning and statistical approaches to process the complex data sets comprised of different clinical and molecular features collected from ovarian cancer patients and benign controls, the team reports several features more useful than the rest in distinguishing these two groups, as well as the effective combinations of algorithms to enhance ovarian cancer prediction.

In summary, this Special issue of *Precision Chemistry* highlights several of the critical aspects for achieving precision diagnostics. The precise design of chemicals and materials enabling efficient sample processing and sensitive molecular measurement with high temporal and spatial resolution, combined with effective markers discovered via advanced -omics technologies and proper dissection of multimodal data with machine learning and statistics tools, can significantly improve disease monitoring and prognosis, and assist in planning personalized treatments.

Wenwan Zhong orcid.org/0000-0002-3317-3464
Yang Liu orcid.org/0000-0003-1830-948X

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Rong Fan orcid.org/0000-0001-7805-8059

AUTHOR INFORMATION

Complete contact information is available at:
https://pubs.acs.org/10.1021/prechem.5c00208

Notes

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