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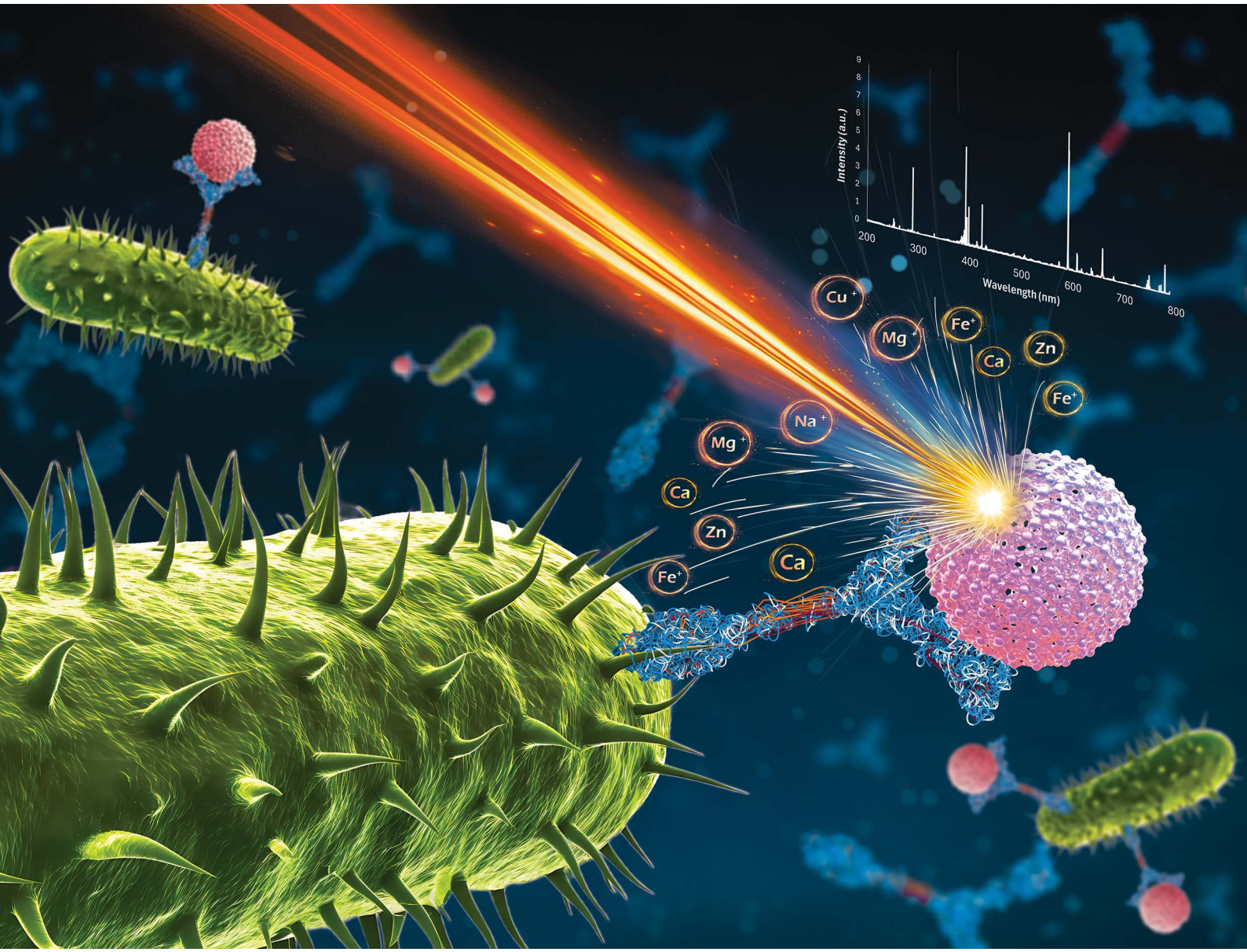

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Tag-laser induced breakdown spectroscopy (Tag-LIBS): progress and prospects

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Tag-Laser Induced Breakdown Spectroscopy (Tag-LIBS) is an emerging technique designed to enhance the analytical performance of conventional LIBS using specific tagging strategies. This review of Tag-LIBS presents studies on its applications since its introduction in 2009. We describe the methodology of Tag-LIBS, with focus on the types of tags used, the mechanisms behind tagging, and the approaches used to achieve molecular or elemental specificity. In addition, we review common assay types and techniques for separation and enrichment that enhance both sensitivity and selectivity. Applications of Tag-LIBS in biomedicine, specifically in biomarker detection and bacterial pathogen identification, are highlighted, followed by an analysis of its capabilities compared to other bioassay techniques, considering metrics beyond the conventional Limit of Detection (LOD).

1 Introduction

Tagging (or labeling) strategies are well-established tools in analytical science that are widely applied in spectroscopy and spectrometry.[1–6] These methodologies are employed to selectively enhance the signal, reduce background interference, and surpass the limitations of direct measurements, particularly within complex sample matrices. They rely on the principle that unique tags, such as fluorophores[7] (commonly used in fluorescence spectroscopy), isotopic tags[8] (prevalent in mass spectrometry), quantum dots[9] and nanoparticles,[10] are conjugated to recognition molecules that selectively bind the target analyte, enabling the generation of characteristic signals for detecting the analyte within a complex background matrix. Over the past few decades, these tagging approaches have been used to

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Ali Safi

Ali Safi's path into spectroscopy began with hands-on experiments during his Master's at Shahid Beheshti University, Iran, where he later earned his PhD in Photonics. Since 2012, he has advanced Laser-Induced Breakdown Spectroscopy (LIBS), from double-pulse detection to plasma characterization, and gained international research experience in Italy and Germany. He has authored several publications, served as a reviewer, and received multiple fellowships. Now a Research Scientist at UMass Lowell, he develops spectroscopy and machine-learning methods for biomedical applications, with the long-term goal of creating practical diagnostic tools.

Noureddine Melikechi

Noureddine Melikechi has contributed to spectroscopy, analytical chemistry, and atomic physics, advancing both fundamental science and applied technologies. His precision measurements of hydrogen and its isotopes have provided key tests of quantum models. In biomedical research, he develops spectroscopic methods to identify early markers of cancer, Alzheimer's disease, and conditions affecting veterans, improving diagnostic potential. He integrates machine learning with spectroscopy to analyze complex data and has led advances in Laser-Induced Breakdown Spectroscopy (LIBS), including high-sensitivity approaches such as Tag-LIBS. His work bridges atomic physics, biomedicine, and data science, expanding spectroscopy's scientific and practical impact.

enhance the selectivity, sensitivity, and multiplexing capabilities.[11]

Specificity refers to the ability to minimize interference from other sample constituents, ensuring that only analytes associated with a particular tag are detected. Sensitivity reflects the capacity of labels to amplify the detectable signal per analyte, as an individual tagging occurrence can integrate numerous reporter molecules or atoms, significantly enhancing the detectability of analytes. Multiplexing arises from the ability to design distinct tags for different analytes, enabling the simultaneous detection of multiple species within a single measurement, thereby enhancing the analytical efficiency.

Tagging techniques in spectroscopy and spectrometry are highly versatile, supporting a wide range of applications from biomolecular imaging to environmental and industrial analyses.[3–5,12–16] In practice, however, their predominant use is in biomedical and clinical contexts, particularly for biomarker detection, immunoassays, and molecular diagnostics, where tagging approaches enable high specificity, multiplexing, and compatibility with complex biological samples. Several review articles offer comprehensive overviews of these methods. For example, one review presents the fundamental reactions in MS-based chemical tagging and lists the primary chemical tags and their applications in bioanalytical chemistry and omic-driven systems biology.[1] A different review focuses on advances in aptamer-based biosensors and lists electrochemical, optical, and mass-sensitive techniques and their applications.[3] A third review, focused on environmental applications, presents labeling techniques for micro- and nanoplastics and their use.[17]

Conventional atomic analysis techniques, including atomic absorption spectroscopy (AAS),[18] inductively coupled plasma optical emission spectroscopy (ICP-OES),[19] X-ray fluorescence (XRF),[20] and inductively coupled plasma mass spectrometry (ICP-MS),[20] provide the ability to quantify the elemental composition of samples. In their standard configurations, they are often regarded as "label-free" methods, relying solely on the characteristic atomic emission, absorption, or mass-to-charge ratio of the elements themselves. However, a significant limitation arises when attempting to utilize these elemental readouts to detect a specific molecule or identify a particular biological or structural feature. In such cases, where the elemental signal must serve as a proxy for molecular information, the incorporation of a labeling strategy becomes essential to link the detected element back to the molecule or structure of interest.[13,21]

The use of elemental tags has significantly broadened the capabilities of atomic analysis techniques for bioanalytical applications requiring molecular specificity. For instance, ICP-MS has utilized elemental labeling in immunoassays, achieving notable sensitivity and multiplexing capabilities that surpass traditional fluorescence-based methods.[1,22] Similarly, XRF microscopy has adopted metal-based probes conjugated with affinity tags to enable high-resolution imaging of specific biomolecules and organelles, enhancing its utility beyond bulk elemental analysis.[23]

Building on this growing trend, recent efforts have sought to translate labeling strategies into Laser-Induced Breakdown Spectroscopy (LIBS). Conventional LIBS, like other atomic spectroscopy techniques, lacks molecular specificity.[24] It cannot readily distinguish whether a detected element originates from a target analyte or from other constituents in a complex sample matrix. While some researchers have explored the molecular applications of LIBS, its fundamental strength lies in elemental analysis, and its capabilities remain limited compared to dedicated molecular spectroscopy methods.[25] Tag-LIBS addresses this limitation by incorporating external elemental tags that are conjugated to recognition molecules designed to bind specific target analytes.[26,27] This enhances both the specificity and sensitivity of LIBS and enables its application in complex biological and environmental matrices where conventional LIBS falls short.

This review begins with a brief overview of LIBS before focusing comprehensively on Tag-LIBS. We explored the emergence of Tag-LIBS, including its initial proposal and first applications, followed by an examination of analyte tagging methodologies, covering the nature of tags and specificity mechanisms by which recognition molecules bind target analytes and conjugate with the associated tags, and overall assay types. The review then examines Tag-LIBS applications in biomedicine and compares its performance with other bioassay techniques used in biomedical research. Finally, we discuss opportunities and challenges for further development, with particular emphasis on its potential to extend into broader analytical domains.

2 LIBS

LIBS is a versatile atomic emission spectroscopy technique. It has been used for the detection, identification, and quantification of elemental composition in a wide range of sample types.[28] In LIBS, a high-energy pulsed laser ablates a small amount of material, typically ranging from nanograms to micrograms, generating a plasma whose optical emission is analyzed to determine its elemental composition (Fig. 1). LIBS has gained significant attention over the past two decades as a rapid atomic emission technique capable of multielement analysis with minimal sample preparation. The technique can be performed *in situ*, in real time, and with remote features that have enabled its use in diverse fields, from industrial quality control to planetary exploration.[29,30]

LIBS has seen remarkable progress over recent decades, with advancements in methodology, instrumentation, and applications, including innovations such as calibration-free LIBS (CF-LIBS), which has overcome persistent challenges in quantitative analysis, yielding precise, matrix-independent elemental measurements.[31]

One of the fastest-growing application areas of LIBS is in the biomedical field, owing to its ability to perform rapid, multielement detection with minimal sample preparation, even in complex biological matrices.[24] Biomedical applications exploit LIBS-derived elemental and chemical composition data from human and animal tissues for purposes such as pathology and disease diagnosis.[32] The technique has been successfully

applied to hard tissues (*e.g.*, bones and teeth) as well as to soft tissues and liquid biosamples.[33,34]

Instrumentally, advancements in developing LIBS systems smaller and more durable have led to portable and handheld units, broadening their use in field applications like environmental monitoring and industrial process control.[35] The extensive literature on LIBS, including recent review articles, offers insights into the technique's principles, plasma characterization, instrumentation, and diverse applications.[24,28–30,36,37]

Despite its versatility, LIBS faces persistent challenges, most notably its relatively low sensitivity and higher detection limits, compared to established techniques such as ICP-MS.[29] To overcome these limitations, a range of enhancement strategies have been developed, including double-pulse LIBS (DP-LIBS)[38,39] and nanoparticle-enhanced LIBS (NELIBS),[40] both of which substantially improve the signal intensity and analytical performance. Tag-LIBS represents a more recent innovation aimed at addressing not only LIBS's limited sensitivity but also its inherent lack of molecular specificity. In the following sections, we provide a comprehensive review of the Tag-LIBS approach, including its conceptual framework, current applications, and emerging potential.

3 Tag-LIBS

Tag-LIBS provides a potential approach for detecting analytes that cannot be directly observed through conventional LIBS. As LIBS is an elemental analysis method, the tag must contain an element of spectroscopic interest, and the readout must be based on the plasma emission lines characteristic of that element. Given LIBS's ability to detect a broad range of elements, it offers exceptional flexibility in the choice of tags. Once tagging is completed, through the association of a tag–recognition molecule conjugate with the target analyte, LIBS spectra can be acquired from the bound tags, and the resulting emission lines can be correlated with the presence of that specific target analyte.

In the context of Tag-LIBS, precise terminology is essential for clarity, given the multi-step nature of immunochemical and molecular recognition assays. In this review, we adopt the following definitions to maintain consistency and avoid ambiguity. A tag refers to the LIBS-detectable component, a material or compound containing a unique elemental signature, such as nanoparticles, rare-earth complexes, or metal-doped materials that produce the analytical signal during LIBS measurement. It serves as the ultimate label from the perspective of elemental detection. When composed of materials bearing unique elemental compositions detectable by LIBS, these tags are referred to as elemental tags, a term widely used in atomic spectroscopy and elemental labeling strategies.

A recognition molecule, such as an antibody, an aptamer, or a nucleic acid probe, is a biomolecule engineered to bind selectively and with high affinity to a specific analyte. Its role is to direct the tag to the appropriate molecular target. While essential for detection specificity, the recognition molecule is distinct from the tag, which alone generates the LIBS signal. Conjugation refers to the chemical or physical linkage of a tag to a recognition molecule, as seen in nanoparticle–antibody constructs. In contrast, the subsequent non-covalent interaction between the recognition molecule and the analyte is described as binding, not conjugation.

The term tagging (or labeling) describes the overall process of associating a LIBS-detectable tag with the target analyte. This typically involves conjugation of the tag to a recognition molecule, followed by the application of the resulting conjugate in an assay where it binds the analyte. Tagging thus encompasses both conjugate preparation and its functional deployment in bioanalytical workflows. In the context of Tag-LIBS, a sandwich complex refers to an assay architecture in which the target analyte is bound by two distinct recognition molecules, a capture recognition molecule and a detection recognition molecule that is conjugated to a tag.

A tagged analyte complex refers to the final bound entity resulting from the tagging process, where the tag is functionally associated with the target analyte, enabling LIBS detection. A target analyte is the molecule, cell, or structure of interest whose presence or quantity is being measured. The targeting, often used in a broader design context, refers to the selective focus of a recognition molecule toward its intended analyte.

Tag-LIBS was proposed for the first time when researchers investigated its application in ovarian cancer diagnosis. In the first study,[26] Markushin *et al.* introduced the concept of Tag-LIBS by combining microparticle tags with LIBS to detect the cancer biomarker CA-125. Silicon (Si) microparticle tags were conjugated with anti-CA-125 antibodies and incubated with CA-125-coated agarose beads, leading to aggregation through antigen–antibody binding. After washing and filtration, the retained aggregates were analyzed *via* LIBS, and the Si emission intensity was used to quantify binding. Two assay types were explored. In the direct assay format, antibodies conjugated to silicon (Si) microparticle tags bound to the CA-125-coated beads, producing a strong LIBS signal. In another approach, antibodies conjugated to Si microparticle tags were pre-incubated with free CA-125 in solution, blocking some of them from binding to the beads, resulting in a weaker LIBS signal. This approach allowed the estimation of the amount of free CA-125 present in the solution.

In addition to CA-125, Tag-LIBS was used to detect avidin, a test protein, using iron oxide microparticles coated with

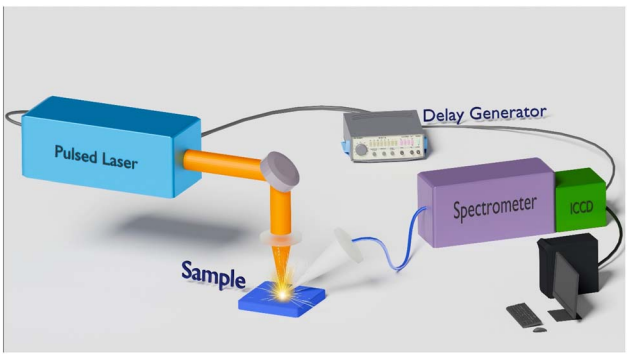

Fig. 1 A schematic of a typical LIBS setup.

biotin. This setup achieved detection at a concentration as low as approximately 30 ppb. Additionally, they assembled composite microparticles by combining Si–avidin and Fe–biotin particles, confirming the presence of both elements in a single LIBS scan and illustrating the potential for multiplexed detection. This foundational study established the principles of Tag-LIBS, showing that elemental tagging of microbeads *via* conjugation to recognition molecules allows for sensitive, scalable, and label-based biomarker detection using LIBS.

Although Tag-LIBS was first introduced in 2009, it initially received limited attention. This may be due to the fact that, unlike conventional LIBS, Tag-LIBS requires a labeling step. However, this slight increase in procedural complexity is, in some situations, justified by the improved analytical performance of Tag-LIBS. This enables greater specificity, sensitivity, and opens possibilities for multiplexing. Thus, the preparative step in Tag-LIBS effectively enhances the technique's diagnostic value, making it particularly suitable for demanding applications such as clinical biomarker analysis and pathogen detection.

Since the initial introduction of Tag-LIBS, several related approaches have emerged. These include digital barcodes of suspension arrays using LIBS and elemental tag-laser-induced breakdown spectroscopy (ETLIBS).[41,42] Despite the variation in terminology, these methods share the same foundational strategy: the use of elemental tags or labels enables indirect detection of analytes *via* LIBS. Whether one uses encoded beads, elemental nanoparticles, or lanthanide-labeled biomolecules, these techniques fundamentally fall under the Tag-LIBS umbrella, as they rely on indirect, tag-based readout to link LIBS detection to target analyte quantification. Essentially, we suggest that it encompasses a broad range of indirect, label-enabled LIBS assays.

In recent years, interest in this technique has grown significantly, with various research groups applying it across a range of applications. In the following sections, we provide a comprehensive review of studies that have employed Tag-LIBS, highlighting its methodological developments and emerging uses.

4 Tag-LIBS principles

Tag-LIBS operates through a multi-step analytical workflow that includes conjugation, capturing, separation, and detection. These interconnected stages collectively define the specificity, sensitivity, and practicality of the technique. Although the steps of conjugation and capturing are often collectively referred to as "labeling" in the literature, this review distinguishes between them to highlight their distinct mechanistic roles: conjugation refers to the chemical or physical linking of LIBS-detectable tags to recognition molecules, while capturing refers to the specific binding of these conjugates to target analytes within a given assay format. The separation phase encompasses washing steps and physical isolation methods that remove unbound reagents, minimize the background signal, and enrich the population of tagged analyte complexes. The final detection step involves LIBS-based ablation and analysis of the elemental tags, with attention to sample presentation and signal acquisition. This section outlines the experimental framework and critical parameters associated with each of these steps. In addition, we discuss hybrid techniques that combine Tag-LIBS with additional strategies, such as NELIBS, Raman spectroscopy, and Lateral Flow Assays (LFA), to improve the sensitivity, specificity, and multiplexing performance in a range of analytical contexts.

4.1 Conjugation

A critical foundation of Tag-LIBS lies in the preparation of conjugates that enable selective and detectable analyte recognition. This involves two key elements: the selection of suitable tag materials that offer strong and distinguishable LIBS signals and the chemical or physical linking of these tags to specific recognition molecules such as antibodies or aptamers. In this section, we first review the properties and design considerations of commonly used elemental tags, followed by the various conjugation strategies employed to attach these tags to recognition elements with stability and functional integrity.

4.1.1 Tag materials. The effectiveness of Tag-LIBS depends on the properties of the tag material. Various nano- and microparticles have been utilized as elemental tags. The selection of tag materials is, in several cases, guided by the need for elements that yield strong, well-resolved emission lines during LIBS measurement. In addition, these elements should also have low natural abundance in the sample matrix to minimize spectral interference and improve detection specificity.

Metal oxide nanoparticles and microparticles have been used as tags (see Table 1). These include copper nanoparticles (CuNPs),[42] silver nanoparticles,[43] silicon dioxide (SiO_2), titanium dioxide (TiO_2),[44] and iron(III) oxide (Fe_2O_3)[44] microparticles. These particles were selected as tags for their notable chemical and physical stability, paired with surfaces that have relatively strong functionalization properties.[45] The surface chemistry of many metal oxides facilitates their conjugation to recognition molecules such as antibodies, proteins, or DNA, enabling specific binding to target analytes.[46]

Beyond elemental nanoparticles, semiconductor nanocrystals known as Quantum Dots (QDs) have also been utilized as tags in the context of Tag-LIBS literature.[47] QDs offer unique optical properties, but for Tag-LIBS, their elemental composition is the key feature.[9] The utilization of QDs broadens the palette of available tag materials beyond simple metallic or metal oxide particles. QDs often possess surface chemistries (*e.g.*, capping ligands) that can be readily functionalized for conjugation to recognition molecules, offering potentially advantageous routes for preparing tag–biomolecule conjugates compared to bare inorganic nanoparticles. However, surface functionalization remains a common prerequisite for most nanoparticle types employed in bioconjugation.[9,48] The detection principle remains the same: essentially identifying the characteristic elemental emission from the tag material (*e.g.*, Cd from CdS QDs).[47]

Upconversion nanoparticles (UCNPs) have emerged as powerful tags in Tag-LIBS and other labeled detection platforms, owing to their unique optical properties and exceptional

Table 1 Summary of Tag-LIBS applications

Application	Analyte	Tag	LOD	Ref.
Ovarian cancer biomarker	CA-125	Si and Fe oxide micro-particles	30 ng mL^{-1}	26
	CA-125	Si and Fe oxide micro-particles	1 U mL^{-1}	27
	Leptin	Si and Fe oxide micro-particles	17 800 ng mL^{-1}	44
	HE4	Si and Fe oxide micro-particles	55×10^{-6} ng mL^{-1}[a]	69
	CA-125	Ti and Fe oxide micro-particles	0.01 U mL^{-1}	70
Tumor disease biomarker	MT	Cd-containing QDs (CdTe and CdS)	0.7 ng mL^{-1}	47
Biomarkers	HSA	Yttrium-doped UCNPs	0.29 ng mL^{-1}	83
	HSA	Ag nanoparticles	10 ng mL^{-1}	43
Breast cancer	HER2	Yttrium-containing UCNPs	7000 ng mL^{-1}	49
Prostate cancer	PSA	Combination of magnetic microbeads and UCNPs	0.04 ng mL^{-1}	50
COVID-19	IL-6	Lanthanide-complexed polymers	230 ng mL^{-1}	68
Biological detection (antibodies and DNA)	Mouse and rabbit IgG, ssDNA	Ag, Cu_2O, MgO, and ZnO nanoparticles	—	41 and 82
Bacterial pathogens	*Staphylococcus aureus*	Ag_xAu_y bimetallic nanoparticles	1.6 CFU mL^{-1}	59
	E. coli	Lanthanide-complexed polymers	1050 ng mL^{-1}	53
	Salmonella typhimurium	Cu nanoparticles	61 CFU mL^{-1}	42
Environmental application	Copper ions	Ag nanoparticles	0.0029 ng mL^{-1}[b]	65

[a] For HE4, the reported 0.0022 pM LOD was converted to ≈0.055 pg mL^{-1} using an approximate molecular weight of 25 kDa. [b] For copper(II) ions, the reported 0.045 nM LOD was converted to ≈2.86 pg mL^{-1} using the molar mass of Cu (63.55 g mol^{-1}).

photostability.[49–52] For instance, in LFAs, UCNPs are increasingly favored over QDs, which, despite good fluorescence and photostability, suffer from high background interference under UV excitation.[51] UCNPs, excited by near-infrared light, offer superior signal-to-noise ratio, brightness, and detection sensitivity compared to both QDs and traditional fluorescent dyes.[51] These nanoparticles, typically doped with lanthanide ions such as Er^{3+}, Tm^{3+}, or Yb^{3+}, are capable of absorbing multiple low-energy photons, typically in the near-infrared (NIR) region, and emitting higher-energy photons in the visible or ultraviolet region through a nonlinear optical process. Their surfaces can be readily functionalized for conjugation to recognition molecules, enabling specific binding to target analytes.

The properties of lanthanides, including their low natural abundance in biological matrices, sharp and well-resolved emission lines, and minimal spectral overlap with common biological elements, make them particularly attractive as elemental tags to be used in Tag-LIBS. These ions have been incorporated in various forms, such as lanthanide-complexed polymers (LCPs), enabling sensitive and specific detection in complex biological environments.[53,54] Their chemical stability, particularly when chelated or embedded in nanoparticle carriers, supports robust conjugation to recognition molecules. This ensures the structural and functional integrity of the tag throughout sample preparation, storage, and LIBS measurement, ultimately contributing to improved analytical reproducibility.

It is worth noting that several proof-of-concept studies have employed nanoparticles composed of biogenic elements such as iron, zinc, copper, or magnesium as labeling agents in Tag-LIBS. While these approaches effectively demonstrate methodological feasibility and the potential for multiplexing, their applicability to real biological samples is limited. The endogenous presence of these elements in matrices such as blood, urine, or tissues introduces considerable background signal, significantly reducing analytical specificity. As such, these labeling strategies are largely restricted to model systems. For future development of Tag-LIBS platforms intended for biological or clinical applications, it is critical to prioritize tags based on elements with low biological abundance, such as lanthanides or other rare-earth metals, to ensure robust signal discrimination and assay reliability.

4.1.2 Conjugation of tags to recognition molecules. A key feature of Tag-LIBS is its reliance on specific molecular recognition mechanisms, whereby elemental tags are conjugated to recognition molecules that bind selectively to target analytes, ensuring that the detected emission signal accurately reflects the presence or concentration of the molecule/s of interest. This specificity is essential for transforming elemental readouts into biologically or chemically meaningful information. Analytical techniques frequently utilize tagging strategies to achieve molecular specificity. The predominant approach relies on biological recognition elements such as antibodies or aptamers that bind selectively to the target analyte, while chemical conjugation methods are used to attach LIBS-detectable elemental tags to these recognition molecules. These strategies are derived from established labeled analytical methods, such as immunoassays, ICP-MS with elemental tags, and fluorescence-based methods.[7,12,16,55,56] These approaches rely on robust conjugation of elemental tags to recognition molecules. In Tag-LIBS, such recognition strategies have been successfully employed to achieve molecular specificity through elemental spectroscopic detection.

Biological recognition strategies exploit the inherent molecular affinity of engineered binding units to achieve target selectivity.[56] In the context of Tag-LIBS, two of the most widely adopted approaches are tagging with antibodies and tagging with aptamers, both of which offer high specificity, adaptability to diverse analytes, and compatibility with complex sample matrices.

4.1.2.1 Conjugation of tags to aptamers. Aptamers are single-stranded oligonucleotides that adopt well-defined three-dimensional structures, enabling high-affinity and high-specificity binding to a wide range of targets, including proteins, small molecules, and even whole cells.[3] Their chemical stability, ease of synthesis, and modifiable functional groups make them highly suitable for conjugation with elemental tags in Tag-LIBS platforms. For instance, Yang *et al.*[42] demonstrated aptamer-based Tag-LIBS for the rapid and quantitative detection of *Salmonella typhimurium*, using Cu nanoparticle tags.

4.1.2.2 Conjugation of tags to antibodies. Antibodies, particularly monoclonal antibodies, are widely employed in analytical platforms due to their high specificity for target epitopes.[57,58] Antibody-based tagging utilizes this specificity to conjugate antibodies with tags, facilitating precise detection in techniques such as immunoassays, where antibodies bind antigens, or fluorescence-based methods with signal-emitting tags. In Tag-LIBS, this approach is applied by conjugating antibodies to elemental tags such as microparticles, upconversion nanoparticles, or lanthanide-complexed polymers, which act as elemental carriers for spectroscopic analysis.[26,44,49,53,59]

To attach elemental tags to recognition molecules such as antibodies or aptamers, a variety of well-established bioconjugation chemistries are available.[60–63] These include covalent approaches such as carbodiimide (EDC/NHS) coupling between carboxyl and amine groups,[64] thiol–maleimide chemistry targeting cysteine residues,[64] and bioorthogonal "click" reactions between azide and alkyne moieties.[63] Non-covalent strategies, such as biotin–streptavidin interactions, are also used in modular assay design.[64] Each method offers different advantages in terms of stability, site-specificity, and compatibility with the recognition element's binding function. As the detailed chemistry of these conjugation methods is well documented in the bioconjugation literature, it is beyond the scope of this review; readers are referred to comprehensive resources for in-depth protocols and comparative analyses.

While most Tag-LIBS implementations employ recognition molecules to localize elemental tags to specific analytes, there are rare examples that bypass biological recognition entirely. For instance, Cao *et al.* developed a Tag-LIBS method for copper(II) ion detection in water using click chemistry to catalyze the *in situ* formation of BSA–triazole–BSA that incorporated silver nanoparticle tags *via* Cu(I)-mediated azide–alkyne cycloaddition.[65] In this design, the analyte (Cu^{2+}, reduced to Cu^{+} by sodium ascorbate) serves as the catalyst for the click reaction, resulting in the conjugation of elemental tags without the need for recognition molecules such as antibodies or aptamers. Such purely chemical tagging strategies can be effective for certain inorganic analytes, but their applicability in complex biological matrices is often constrained by selectivity and potential interferences.

4.2 Capturing

The capturing step in Tag-LIBS refers to the selective binding of the tag–recognition molecule conjugates to their specific target analytes within a sample matrix. This molecular interaction, typically based on antibody–antigen affinity, nucleic acid hybridization, or aptamer–ligand recognition, forms the core of assay specificity. These recognition processes rely on non-covalent interactions, which are individually weaker than covalent bonds but, when combined in large numbers, provide high-affinity and high-specificity binding strong enough to withstand subsequent washing and separation steps.[66,67] Capturing transforms the prepared conjugates into functionally localized complexes, enabling the subsequent detection of the target analyte *via* its associated elemental tag. The efficiency of this step is influenced by both the biochemical affinity of the recognition molecules and the assay format, such as direct, sandwich, or competitive designs, and whether the assay is performed in suspension or on a solid-phase support. Subsequent processes such as washing, physical isolation, and enrichment are discussed in the following section on separation.

In Tag-LIBS, assay formats are selected to match the nature of the target analyte, the chosen tagging strategy, and the intended analytical objective. In immunochemistry, these formats are well-established and are commonly classified as direct, indirect, sandwich, or competitive assays, each representing a distinct approach to how the target analyte is recognized.

In direct labeling approaches, elemental tags, such as metal-loaded polymers or nanoparticles, are covalently conjugated to recognition molecules prior to sample introduction. These recognition molecules directly bind the target analyte during the binding step, simplifying the workflow. An example of a direct Tag-LIBS assay is found in a study where copper nanoparticles were directly conjugated to aptamers and used to bind *Salmonella typhimurium* prior to capture on a nanostructured substrate.[42] In contrast, an indirect Tag-LIBS assay employs an untagged primary recognition molecule that first binds the target analyte, followed by a tagged secondary recognition molecule (*e.g.*, a secondary antibody conjugated to an elemental tag) that binds specifically to the primary recognition molecule. An example of an indirect Tag-LIBS assay is demonstrated in a study where yttrium-containing UCNPs, conjugated to streptavidin, were linked to HER2-expressing cells *via* a biotinylated secondary antibody for differentiation between HER2-positive and HER2-negative cells.[49]

A widely used variation is the sandwich assay format, in which the target analyte is captured between a surface-bound recognition molecule and a second tag–recognition molecule conjugate. This dual-binding architecture enhances specificity and enables signal amplification, as multiple tag–recognition molecule conjugates can bind to a single primary recognition molecule, thereby increasing the detectable signal per analyte molecule. An example of a sandwich-format Tag-LIBS assay is illustrated in a study targeting human serum albumin (HSA).[43] In this study, the analyte was captured between a surface-bound recognition antibody and a biotinylated detection antibody, which was subsequently conjugated to streptavidin-coated silver nanoparticles. LIBS detection of the Ag signal at the capture site enabled quantitative analysis of HSA.[43] A

competitive assay format has also been applied in Tag-LIBS for detecting CA-125. Silicon microparticle tags conjugated to anti-CA-125 IgG were pre-incubated with free CA-125, reducing available antibody sites. When introduced to CA-125-coated agarose beads, fewer particles could bind, resulting in a lower LIBS silicon signal. This inverse correlation between the analyte concentration and signal reflects a classic competitive immunoassay adapted for LIBS detection.[26]

4.3 Separation

Separation and enrichment are critical steps in Tag-LIBS workflows, especially when analyzing complex biological or environmental samples. These steps serve to isolate tag–analyte complexes from the background material and increase their local concentration, thereby improving the signal-to-noise ratio and detection sensitivity during LIBS analysis. Several strategies have been developed for this purpose, including magnetic separation, lateral-flow formats, and membrane-based enrichment.[27,50,53,59] Each approach offers distinct advantages depending on the assay type and application.

Magnetic separation uses functionalized magnetic beads (MBs) conjugated to recognition molecules, which bind selectively to the target analyte. Once bound, the tag–analyte complexes can be rapidly isolated using an external magnetic field.[26,50] After each binding step, the unbound material is removed, while the MB tagged analyte complexes remain immobilized. This approach simplifies washing steps and enhances preconcentration, increasing the density of elemental tags for LIBS analysis.

Nitrocellulose membranes are frequently utilized in Tag-LIBS, often within lateral-flow immunoassay (LFIA) configurations, due to their porous structure.[53,59,68] In LFIA, the sample flows along a nitrocellulose strip where conjugates bind the target analyte at test lines coated with immobilized recognition molecules (see Fig. 2). Unbound tags are washed away by the running buffer, eliminating separate washing steps, while bound tags accumulate at the test line for preconcentration. After drying, the enriched test line is ablated by LIBS.

Centrifugal filtration offers an alternative approach for analyte enrichment in Tag-LIBS.[44,69,70] This method employs centrifugal force to separate sample components based on size or molecular weight, retaining the tag–analyte complexes on a filter membrane while smaller molecules and contaminants pass through. It is particularly effective for samples with complex matrices, ensuring a cleaner, concentrated analyte for LIBS analysis.

The washing step in Tag-LIBS assays is adapted to the specific assay type used. The choice of washing buffer is critical, as its chemical composition directly affects the balance between removing nonspecifically bound materials and preserving specific tag–analyte complexes. Optimized buffers and wash protocols help reduce background interference. Tag-LIBS assays typically use buffered saline (PBS) or Tris buffer at a stable pH (usually around 7.2–7.6), often supplemented with nonionic surfactants like Tween-20 and protein blockers such as BSA to prevent nonspecific binding. These components minimize the adsorption of unrelated substances to the substrate or capture beads.

4.4 Detection

The final step in the Tag-LIBS workflow is the detection phase, where the prepared sample is analyzed by LIBS to identify the elemental signal from the tags. This stage involves preparing the sample and using LIBS to identify the elemental signatures of the tags. Tag-LIBS samples typically start as liquids, but analyzing liquids with LIBS poses distinct challenges compared to solids. Splashing, aerosol formation, and reduced plasma stability complicate the process.[71,72] To overcome these issues, researchers deposit liquid samples onto substrates,[73] analyze droplets,[74,75] use microfluidic systems,[76,77] or study frozen samples.[78] The most common approach in Tag-LIBS is to dry the tagged analyte complexes on an appropriate substrate. This transition to the solid phase improves plasma consistency and signal reliability.

In some Tag-LIBS assays, the same substrate used for analyte enrichment is subsequently used for LIBS measurement.[26,44] In fact, tagged complexes are captured and immobilized during the enrichment step and then dried in place. In others, the sample is transferred to a clean substrate after enrichment for final analysis. In both cases, drying is a necessary step, as residual moisture can interfere with laser ablation and plasma formation. For instance, Cao *et al.* utilized the second approach by spotting the reaction supernatant onto an aluminum plate, allowing it to dry, and then performing LIBS detection directly on the dried sample (see Fig. 2).[65] The choice of substrate is guided not only by practical considerations such as ease of drying and surface uniformity but also by spectral compatibility. An ideal substrate should lack any elements used as tags to prevent spectral overlap. To ensure this, researchers often perform blank LIBS runs on the substrate and matrix components.

In addition to sample preparation and substrate selection, optimization of LIBS instrumental parameters is critical. Factors such as laser energy, delay time, gate width, focusing and collecting optics, and surrounding media all have a significant impact on signal intensity, background noise, and reproducibility.[79]

4.5 Hybrid Tag-LIBS techniques

Recent advances in Tag-LIBS have explored hybrid approaches that integrate it with complementary platforms, such as immunoassays, NELIBS and Raman spectroscopy, suspension arrays, and signal amplification systems.

A recent study demonstrated that integrating NELIBS with Tag-LIBS can enhance sensitivity. NELIBS, an LIBS-based technique, has been developed to improve the analytical performance of conventional LIBS.[40] We note that the underlying mechanisms and applications between NELIBS and Tag-LIBS differ. NELIBS achieves enhanced sensitivity by depositing metallic nanoparticles, typically gold or silver, onto the sample surface, which increases the local electromagnetic field during laser ablation, resulting in stronger plasma generation, greater

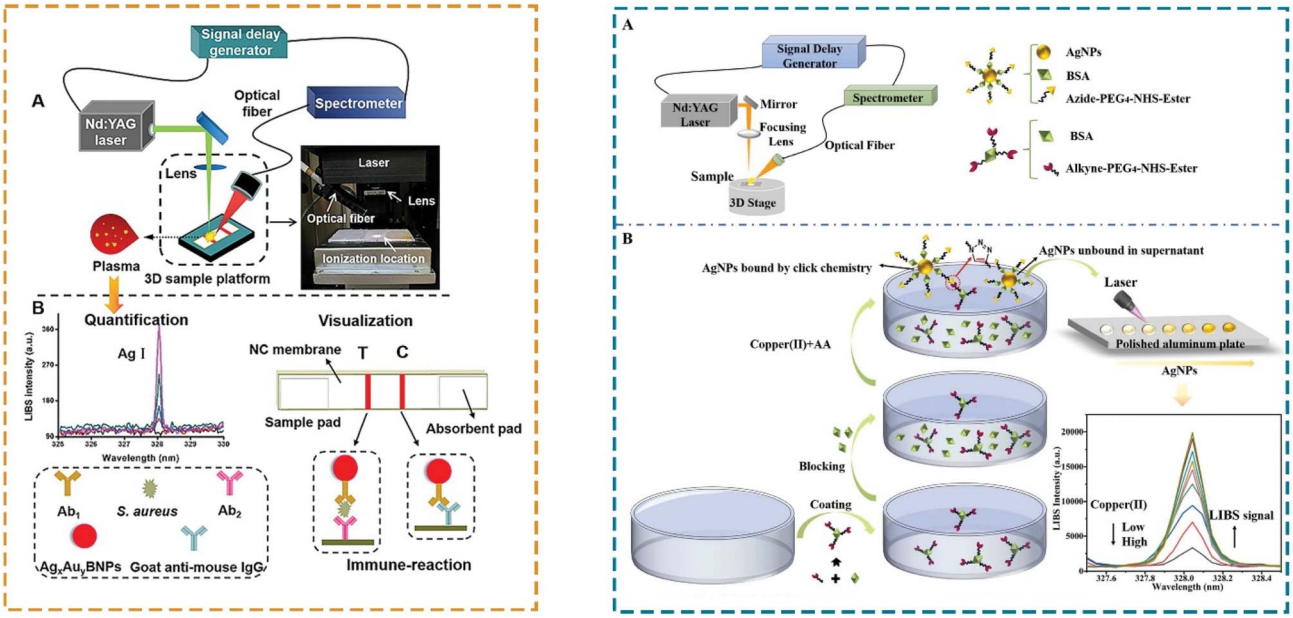

Fig. 2 Left: Schematic of the LIBS-LFS sensor for *S. aureus* analysis: (A) LIBS system; (B) principle: immune-reaction on the NC membrane, visual detection by color change on the T line, and LIBS quantification of Ag(I). Reproduced from ref. 59 with permission from Elsevier, copyright [2025]. Right: Schematic of the CuAAC & LIBS sensor for copper(II) ions: (A) LIBS system for analysis on an aluminum plate; (B) principle of the CuAAC & LIBS sensor for assaying copper(II) ions. Reproduced from ref. 65 with permission from Elsevier, copyright [2025].

emission intensity, and improved signal to noise ratios. This method presents multiple advantages in that it improves the sensitivity of LIBS. This has been demonstrated in various applications such as environmental monitoring, biomedical analysis, and archaeological studies.[56,80,81] Conversely, as described above, Tag-LIBS relies on the conjugation of elemental tags to recognition molecules that bind selectively to the target analyte. The measured emission primarily originates from this elemental tag, enabling highly specific detection of the target analyte. Although these tags may also enhance the emission intensity, their principal function is to provide selective analyte identification rather than general signal amplification. Safi *et al.* used NELIBS combined with Tag-LIBS to detect lanthanide-labeled antibodies, employing europium (Eu) and ytterbium (Yb) metal-loaded polymers as elemental tags.[54] The study optimized silver nanoparticle (Ag NP) concentrations to enhance the LIBS signal emission and revealed distinct behaviors for neutral and ionized species. Eu showed a tenfold increase in both neutral and ionized emission lines at 0.1 mg per mL Ag NPs, while Yb exhibited a twelvefold enhancement in ionized lines at 0.05 mg mL^{-1}. Although quantitative analysis was not performed in this study, the observed signal enhancements highlight the potential of this approach to improve detection sensitivity in Tag-LIBS applications.

One study demonstrated the combination of Tag-LIBS with suspension array technology for digital barcoding. He *et al.* introduced a digital barcoding strategy for suspension arrays using Tag-LIBS.[41] Polystyrene beads doped with specific combinations of metal or metal oxide nanoparticles (Ag, Cu_2O, MgO, and ZnO) served as elemental tags, creating unique, interference-free LIBS barcodes for each bead. This approach enabled highly multiplexed detection of biological targets (antibodies and DNA) in a single assay, with sharp, stable LIBS emission peaks supporting robust bead identification. Building on this concept, Chen *et al.* later developed a dual-encoded suspension array by integrating LIBS barcodes with Raman spectral encoding.[82] In this system, polymer microbeads encapsulated distinct Raman reporters, while their surfaces were coated with elemental nanoparticles (Ag, Cu_2O, MgO, and ZnO), enabling simultaneous identification by both Raman and LIBS. Each bead type was further functionalized with a specific antibody, allowing multiplexed immunoassays for mouse, rabbit, and rat IgG. The combination of dual-readout barcoding and QD-labeled secondary antibodies enabled sensitive and specific detection while effectively avoiding fluorescence crosstalk.

Some studies have combined Tag-LIBS with LFA and double pulse techniques, improving Tag-LIBS performance.[59,83] The minimally destructive nature of Tag-LIBS deserves careful attention. In hybrid setups combining multiple methods, Tag-LIBS is ideally suitable as a secondary technique.

5 Applications

Since its introduction, Tag-LIBS has been applied across diverse analytical contexts, with the greatest emphasis on biomedical research. The following sections focus on two major domains: (i) biomarker detection and (ii) bacterial pathogen identification. Although these biomedical uses dominate the field, Tag-LIBS has also been successfully adapted to non-biomedical applications. For example, Cao *et al.*[65] demonstrated a highly sensitive method for detecting copper(II) ions in water,

illustrating the adaptability of Tag-LIBS to non-biological analytes. This approach leveraged a chemical tagging mechanism and LIBS readout to achieve a detection limit of 0.045 nM across a broad range, 0.05–10,000 nM, with performance exceeding many conventional fluorescence and electrochemical assays.

5.1 Biomarker detection

One of the main applications of Tag-LIBS is biomarker detection, where it has shown strong potential for highly selective and sensitive analysis in biomedical research. The Melikechi group has been a pioneering contributor to the development of Tag-LIBS for the early detection of ovarian cancer, advancing strategies for the sensitive and specific identification of blood biomarkers. Markushin and Melikechi demonstrated the use of Tag-LIBS for detecting the ovarian cancer biomarker CA-125 using dual-element microparticle tags in PBS buffer supplemented with 5% BSA to mimic blood conditions.[27] Streptavidin-coated silicon microparticles and protein G-modified iron oxide microparticles, each conjugated to specific antibodies, enabled selective binding and elemental detection. The workflow achieved a detection limit of approximately 1 U mL^{-1} for CA-125, which was comparable to that of commercial Enzyme-Linked Immunosorbent Assay (ELISA) available at the time.[84]

In a different research by the Melikechi group, Tag-LIBS was utilized for CA-125 in blood plasma. They introduced a femtosecond Tag-LIBS (fs-Tag-LIBS) assay for the detection of CA-125, in undiluted human blood plasma.[70] The assay employed a dual-element microparticle tags using titanium dioxide and iron oxide microparticles, each conjugated to specific monoclonal antibodies (Fig. 3). Titanium served as the quantification element, while iron acted as an internal standard for signal normalization. The method achieved a detection limit of 0.01 U mL^{-1}, significantly outperforming standard ELISA assays available at the time.[85] The use of femtosecond laser pulses enhanced reproducibility. Statistical evaluation showed coefficient of variation as low as 2–3% using combined spectral analysis.

Melikechi and Markushin further reported a Tag-LIBS assay for detecting leptin, an ovarian cancer biomarker, using dual-element microparticle tags, silicon dioxide (SiO_2) and iron oxide (Fe_3O_4), each conjugated to specific recognition antibodies.[44] Biotinylated antibodies were conjugated to microparticles, and after incubation with leptin, magnetic separation and filtration were used to isolate tagged analyte complexes. Femtosecond LIBS analysis of Si and Fe emission lines enabled a dual-tag configuration that yielded 1.3- to 10-fold signal enhancements compared to single-tag assays. The study demonstrated the feasibility of a one-step conjugation and assay dual-element Tag-LIBS approach, highlighting its potential for multiplexed biomarker detection (Fig. 3).

The detection of human epididymis protein 4 (HE4), another clinically relevant ovarian cancer biomarker, was investigated by a different research group through application of Tag-LIBS. Karunanithy *et al.* developed a sandwich-type Tag-LIBS assay integrated with LIBS for the ultra-trace detection of HE4.[69] The assay employed protein A-coated Fe_3O_4 magnetic microparticles conjugated to anti-HE4 antibodies to capture the target antigen, followed by the addition of glutaraldehyde-modified silica (SiO_2) particles as the elemental tag. The assay achieved a detection limit of 0.0022 pM, with a clear linear response.

Illustrating the methodological flexibility of Tag-LIBS, Konecna *et al.* introduced a strategy that integrates quantum dot labeling with immunoassay-based LIBS detection to quantify metallothionein (MT), a metal-binding biomarker implicated in cancer biology.[47,86] They utilized Cd-containing QDs (CdTe and CdS) as elemental tags and demonstrated that LIBS can sensitively detect cadmium through its emission at 508.58 nm, even in dried samples on polystyrene microplates, independent of fluorescence. To verify the feasibility of LIBS for immunoassay readout, they showed specific detection of streptavidin-conjugated QDs bound to biotinylated antibodies, with strong LIBS signals maintained even after sample washing, confirming both specificity and robustness. Their results showed that LIBS offers reliable spatial mapping of QD distribution, and in a sandwich-type Tag-LIBS assay, it enabled direct visualization and quantification of MT. Importantly, the authors reported that the LOQ for MT using LIBS was more than 10-fold lower than that achieved by classical ELISA (6.8 ng mL^{-1}), emphasizing LIBS's superior sensitivity.

In a notable expansion of Tag-LIBS into cellular immunolabeling, Pořízka *et al.* applied LIBS-based detection for immunocytochemistry (ICC) of Human Epidermal Growth Factor Receptor 2 (HER2) biomarker on breast cancer cell lines.[49] The authors employed an indirect assay format, in which yttrium-containing UCNPs, conjugated to streptavidin, were bound to HER2-expressing cells *via* a biotinylated secondary antibody. Utilizing the yttrium emission line at Y II 437.49 nm, indirect imaging of cell pellets was achieved with a spatial resolution of 100 μm, enabling clear differentiation between HER2-positive (BT-474) and HER2-negative (MDA-MB-231) cells. The optimal signal-to-background ratio (SBR) of 3.3 was obtained at a UCNP–streptavidin (UCNP–SA) concentration of 140 μg mL^{-1}, while lower concentrations (*e.g.*, 7 μg mL^{-1}) produced minimal signal enhancement (SBR = 1.2),

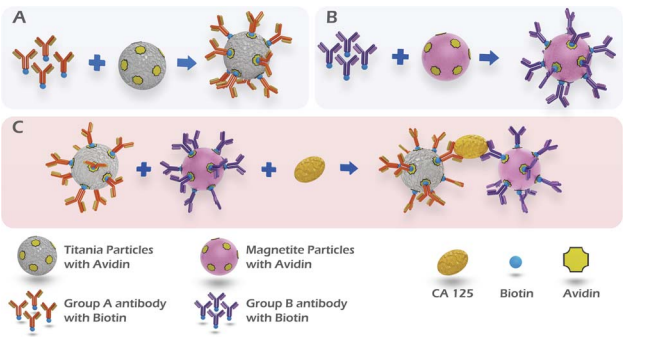

Fig. 3 Schematic of Tag-LIBS assay steps. (A) Group A recognition molecules conjugated to titania tags. (B) Group B recognition molecules conjugated to magnetite tags. (C) CA125 analytes form a sandwich complex bridging the two tagged conjugates for LIBS detection. Reproduced from ref. 44 with permission from Elsevier, copyright [2025].

approaching the LIBS detection limit. In a subsequent study, the same group further improved the sensitivity of the UCNP-based Tag-LIBS immunoassay by incorporating magnetic microbeads (MBs) as the solid phase for the detection of prostate-specific antigen (PSA).[50] LIBS readout was performed by measuring the Y II 360.07 nm line from UCNPs and the Fe I 356.54 nm line from MBs, enabling internal standardization to correct for signal fluctuations and sample handling variability. The optimized DP-LIBS configuration enhanced, achieving an LOD of 4.0 pg mL^{-1} using analyte preconcentration.

Two studies have explored the application of Tag-LIBS for the detection of HSA, a key plasma protein and representative biomarker in clinical diagnostics.[87] In the first study, Modlitbová *et al.* implemented a sandwich-type Tag-LIBS immunoassay using streptavidin-coated silver nanoparticles (AgNPs) as elemental tags, with detection performed *via* nanosecond LIBS in standard 96-well microtiter plates.[43] The assay achieved an LOD of 10 ng mL^{-1}, with an extended dynamic range up to 100 μg mL^{-1}, thus surpassing fluorescence-based readouts that saturated at lower concentrations. In a subsequent study, the same group significantly improved the sensitivity of HSA detection using a UCNP-based immunoassay.[83] Compared to their earlier LIBS assay, the LOD was enhanced by nearly two orders of magnitude: from 10 ng mL^{-1} to 0.29 ng mL^{-1}. This improvement was achieved using a DP-LIBS configuration, which increased the signal-to-noise ratio by up to 30-fold. The resulting LOD was comparable to that of ELISA (0.37 ng mL^{-1}).

Tag-LIBS has also been applied to infectious disease diagnosis. Wu *et al.* developed an LFIA-based Tag-LIBS assay for the detection of interleukin-6 (IL-6), a key inflammatory marker associated with severe COVID-19 cases, enabling rapid and quantitative analysis suitable for point-of-care use.[68] The system utilized lanthanide-complexed polymers (LCPs) conjugated to antibodies as elemental tags, specifically europium (Eu), enabling LIBS-based elemental readout directly from the test lines of LFIA strips. Using a benchtop nanosecond LIBS system, the Eu(II) emission at 420.504 nm was detected and correlated with IL-6 concentration, producing a linear response between 0.01 and 1.2 μg mL^{-1} and an estimated LOD of about 0.23 μg mL^{-1}. The assay achieved readout within 15 minutes and showed potential for use in urgent clinical settings.

5.2 Pathogen detection

Beyond biomarker analysis, Tag-LIBS has also been applied to the detection and identification of bacterial pathogens. In a recent publication, Wu *et al.* developed a hybrid lateral-flow strip (LFS)-based Tag-LIBS biosensor for rapid and ultrasensitive detection of *Staphylococcus aureus*.[59] The assay used Ag_3Au_2 bimetallic nanoparticles (Ag_xAu_yBNPs) conjugated to antibodies as elemental tags, enabling both visual colorimetric readout and quantitative elemental analysis *via* LIBS. Upon immunoreaction on the nitrocellulose membrane of the LFS, the accumulation of Ag_xAu_yBNPs at the test line was detected through Ag(I) emission at 328.0 nm, enabling quantification of bacterial load down to 1.6 CFU mL^{-1} in about 10 minutes. This shows that this approach is more sensitive to standard LFS and ELISA. The authors optimized the nanoparticle composition for dual-mode detection, demonstrating strong specificity, reproducibility, and stability over 13 days.

In a different innovative application of Tag-LIBS for bacterial quantification, Yang *et al.*[42] developed an aptamer-based Tag-LIBS assay for the rapid and specific detection of *Salmonella typhimurium*. Copper nanoparticles were synthesized on a polythymine (poly-T) template covalently conjugated to *Salmonella*-specific aptamers, enabling selective bacterial labeling within 30 minutes. Subsequently, bacteria were captured on silicon nanowire arrays modified with Au@Ag nanoparticles, allowing efficient immobilization. LIBS mapping, analyzing the Cu(I) emission line at 324.75 nm, provided rapid quantitative analysis, yielding a linear detection range of 10^2 to 10^6 CFU mL^{-1} ($R^2 = 0.978$) and a detection limit of 61 CFU mL^{-1}.

Gondhalekar *et al.*[53] developed an LFIA-based Tag-LIBS assay for the selective detection of *Escherichia coli* (*E. coli*). The system used gold nanoparticles as elemental tags, conjugated to antibodies for analyte recognition, with detection of the tagged analyte complexes directly on commercial LFIA test strips. The authors achieved an LOD of 1.03×10^4 CFU mL^{-1} using LIBS, comparable to colorimetric image analysis (8.89×10^3 CFU mL^{-1}). The assay was further optimized for LIBS detection of lanthanide-based elemental tags (Eu, Yb, Nd, and Pr), which exhibited lower LODs than gold on nitrocellulose substrates (*e.g.*, Eu: 1.05 ppm *vs.* Au: 15.97 ppm), suggesting enhanced sensitivity for future multiplexing. Gondhalekar *et al.* also investigated the application of handheld Tag-LIBS systems for sensitive, multiplexed detection of labeled biomolecules, with particular emphasis on LFIAs.[88] Their findings demonstrated the feasibility of handheld Tag-LIBS as a practical tool for rapid and sensitive immunoassay readouts.

6 Comparison with other techniques

In this section, we compare the analytical capabilities of Tag-LIBS in biomedical applications with those of similar bioassay techniques. We focus on this area because most Tag-LIBS research targets biomedicine, especially biomarker detection. While Tag-LIBS has potential beyond biomedicine, including environmental monitoring, more studies are required to facilitate comprehensive comparisons.

Evaluating bioassay techniques involves multiple metrics, including sensitivity, multiplexing capability, speed, matrix tolerance, sample preparation complexity, and portability. Bioassay methods such as ELISA, LFAs, chemiluminescent immunoassay (CLIA), flow cytometry, ICP-MS with tagging, DNA-based biosensors, and nanotechnology-based assays have significantly advanced, providing robust and diverse analytical solutions beyond merely focusing on sensitivity.

Table 1 summarizes the LOD reported across various Tag-LIBS studies. A major challenge in assessing Tag-LIBS is the inconsistent reporting of performance metrics, making direct comparisons across studies difficult. However, the range of LODs differs considerably, influenced by the specific biomarker, the detection method used, and the sample matrix (*e.g.*, blood, urine, or environmental samples). Generally, Tag-

LIBS studies highlight their results in terms of LOD, often demonstrating sensitivities comparable or superior to current methods. However, evaluating assay performance requires a wider approach that considers factors beyond just LOD. Initial Tag-LIBS implementations achieved detection limits in the low ng mL^{-1} range, with early immunoassays for protein biomarkers reaching approximately 30 ng mL^{-1}.[26] Recent advancements, particularly in LIBS excitation/collection schemes and tagging improvements, have significantly enhanced sensitivity. For instance, a 2024 study reported a double-pulse LIBS setup incorporating magnetic microbeads and analyte preconcentration, achieving an LOD of 4.0 pg mL^{-1} for prostate-specific antigen, surpassing conventional enzyme immunoassays and approaching state-of-the-art fluorescence immunoassays.[50] We note that methods like CLIA and digital ELISA provide sensitivities, with digital ELISA variants, that can reach thresholds as low as femtograms per milliliter (fg mL^{-1}).[89] We also note that flow cytometry offers high-throughput and precision for cellular analysis, while CRISPR-based diagnostics provide rapid, highly specific nucleic acid detection.[90,91] Despite recent advances, Tag-LIBS still does not match digital ELISA in single-molecule sensitivity but achieves sensitivity comparable to that of standard immunoassays (sub-ng mL^{-1}). While ICP-MS offers higher sensitivity than LIBS, Tag-LIBS has achieved comparable results to ICP-MS with tagging, a significant milestone in elemental analysis.[16]

LFAs, though less sensitive, offer simplicity, cost-effectiveness, home-based diagnostics (10–15 min), and ease of use.[92] Conversely, ELISA is sensitive and cost-effective but labor-intensive and typically limited to single-target detection.[93] PCR offers unparalleled sensitivity, but requires rigorous sample preparation and is susceptible to contamination.[94]

These trade-offs indicate that no single bioassay universally outperforms others. Ongoing hybridization and optimization efforts, for instance, combining LFAs with PCR or electrochemical methods, seek to merge high sensitivity with portability.[94] Ultimately, the optimal assay choice depends on application-specific priorities, whether detecting ultra-trace analytes in laboratory settings or achieving rapid, field-based diagnostics.

7 Looking ahead

The advances summarized in this review illustrate the progress made in the application of Tag-LIBS, specifically regarding its sensitivity, specificity, and multiplexing capabilities. Tag-LIBS has proven to have potential for innovative applications in oncology, infectious diseases, and bacterial pathogen detection.

Despite these promising advances, most of the approaches presented in this review represent proof-of-concept studies. Several technical and methodological challenges remain, highlighting the need for further research. Some challenges are inherent to LIBS itself, while others stem specifically from the tagging process unique to Tag-LIBS. Reproducibility and quantitative accuracy, for instance, remain challenging because of variability in sample preparation, substrate materials, calibration protocols, and tagging efficiency. Additionally, Tag-LIBS instrumentation typically remains bulky, expensive, and challenging to adapt for point-of-care clinical diagnostics. Another challenge stems from the absence of standardized procedures, making direct comparison between different research groups and studies problematic. However, some researchers have begun to address these limitations. Gondhalekar *et al.* have showcased the feasibility of a handheld Tag-LIBS device, offering a portable and cost-effective alternative for rapid, *in situ* diagnostics.[88] This innovation directly addresses the issues of instrumentation size and expense, bringing Tag-LIBS closer to practical field applications.

Progress in the broader field of LIBS technology, which continues to gain traction in medical and analytical applications, will inevitably benefit Tag-LIBS as well. Although Tag-LIBS is a new and evolving technique, it relies on labeling, a method well-established in techniques such as ELISA, CLIA, and mass spectrometry. Advances in laser design, detectors, and data processing could further improve Tag-LIBS performance and reliability, especially for point-of-care use.

Based on recent progress in Tag-LIBS, it is safe to suggest that the future of Tag-LIBS holds promise, driven by opportunities to integrate it with complementary analytical platforms. Combining Tag-LIBS with techniques such as Raman spectroscopy, fluorescence imaging, or mass spectrometry could yield multimodal diagnostic systems capable of providing both elemental and molecular insights from a single sample. Embedding Tag-LIBS within microfluidic platforms, for instance, could simplify workflows, reduce sample volumes, and enable high-throughput analysis.

While integration with complementary platforms, as discussed, enhances its prospects, Tag-LIBS technology itself continues to evolve. Ongoing research actively addresses key challenges in reproducibility, instrumentation refinement, and standardization. Acknowledging that its intrinsic sensitivity may not always match that of ultra-sensitive benchmarks like digital ELISA, Tag-LIBS often compensates with a unique suite of operational strengths. Specifically, its capacity for rapid, *in situ* analysis, label-based multiplexing, minimal sample preparation requirements, and compatibility with portable devices makes it particularly well-suited for many biomedical applications. These features are especially valuable in contexts like point-of-care testing, where speed, ease of use, and field-readiness can be prioritized alongside analytical sensitivity. Although the technique's partially destructive nature warrants consideration for certain delicate samples, these practical advantages often make Tag-LIBS a compelling option for diverse diagnostic needs. Beyond biomedicine, the adaptability of Tag-LIBS opens avenues in environmental monitoring, food safety, and agriculture. Unlocking the full potential of Tag-LIBS will require careful attention to tagging strategies, further miniaturization of instruments, improved analytical algorithms, and close interdisciplinary collaboration.

Conflicts of interest

There are no conflicts to declare.

Data availability

This review is based on data and findings from previously published studies. No new datasets were generated or analyzed. All data sources are cited in the references section of this article.

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